ISSN 2218-5836 (online)

World Journal of *Orthopedics*

World J Orthop 2015 January 18; 6(1): 1-160

Published by Baishideng Publishing Group Inc

WJO World Journal of Orthopedics

A peer-reviewed, online, open-access journal of orthopedics

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2015-2018

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WJO World Journal of Orthopedics

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NAME OF JOURNAL
World Journal of Orthopedics

ISSN
ISSN 2218-5836 (online)

LAUNCH DATE
November 18, 2010

FREQUENCY
Bimonthly

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World Journal of Orthopedics
Room 903, Building D, Ocean International Center,
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E-mail: editorialoffice@wjgnet.com
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http://www.wjgnet.com

PUBLICATION DATE
January 18, 2015

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-5836/g_info_20100722172650.htm

ONLINE SUBMISSION
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World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.1

World J Orthop 2015 January 18; 6(1): 1-7
ISSN 2218-5836 (online)

EDITORIAL

Rehabilitation in spinal infection diseases

Kemal Nas, Mehmet Karakoç, Abdulkadir Aydın, Kadriye Öneş

Kemal Nas, Department of Physical Medicine and Rehabilitation, School of Medicine, Sakarya University, Korucuk, 54290 Sakarya, Turkey
Mehmet Karakoç, Department of Physical Medicine and Rehabilitation, School of Medicine, Dicle University, 21280 Diyarbakir, Turkey
Abdulkadir Aydın, Orthotics and Prosthetics Center, Dicle University, 21280 Diyarbakır, Turkey
Kadriye Öneş, Istanbul Physical Medicine and Rehabilitation Research and Training Hospital Physical Therapy and Rehabilitation Clinic, 34180 Istanbul, Turkey
Author contributions: Nas K and Aydın A contributed to the concept and design; Karakoç M contributed to the interpretation; Öneş K contributed to the literature review.

Correspondence to: Dr. Kemal Nas, Department of Physical Medicine and Rehabilitation, School of Medicine, Sakarya University, Korucuk, 54290 Sakarya, Turkey. kemalnas@yahoo.com
Telephone: +90-264-2759192
Fax: +90-264-2759192
Received: June 19, 2014
Peer-review started: June 21, 2014
First decision: July 10, 2014
Revised: July 23, 2014
Accepted: October 14, 2014
Article in press: October 16, 2014
Published online: January 18, 2015

Abstract

Spinal cord infections were the diseases defined by Hypocrite yet the absence of modern medicine and there was not a real protocol in rehabilitation although there were many aspects in surgical treatment options. The patients whether surgically or conservatively treated had a lot of neurological, motor, and sensory disturbances. Our clinic has quite experience from our previous researchs. Unfortunately, serious spinal cord infections are still present in our region. In these patients the basic rehabilitation approaches during early, pre-operation, post-operation period and in the home environment will provide significant contributions to improve the patients' sensory and motor skills, develop the balance and proriocaption, increase the independence of patients in daily living activities and minimize the assistance of other people. There is limited information in the literature related with the nature of the rehabilitation programmes to be applied for patients with spinal infections. The aim of this review is to share our clinic experience and summarise the publications about spinal infection rehabilitation. There are very few studies about the rehabilitation of spinal infections. There are still not enough studies about planning and performing rehabilitation programs in these patients. Therefore, a comprehensive rehabilitation programme during the hospitalisation and home periods is emphasised in order to provide optimal management and prevent further disability.

Key words: Spinal infections; Rehabilitation; Exercises

Core tip: Spinal cord infections were not a real protocol in rehabilitation although there were many aspects in surgical treatment options. In these patients the basic rehabilitation approaches during early, pre-operation, post-operation period and in the home environment will provide significant contributions to improve the patients. The aim of this review is to share our clinic experience and summaries the publications about spinal infection rehabilitation. There are very few studies about the rehabilitation of spinal infections. Therefore, a comprehensive rehabilitation programme during the hospitalization and home periods is emphasized in order to provide optimal management and prevent further disability.

Nas K, Karakoç M, Aydın A, Öneş K. Rehabilitation in spinal infection diseases. *World J Orthop* 2015; 6(1): 1-7 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/1.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.1

INTRODUCTION

Spinal infections were first noted in the historical record dating back to 4000 Before Christ when Hippocrates described the symptoms of tuberculous spondylitis. Pott's paraplegia was described by Sir Percivall Pott in the eighteenth century. Infections of the spine and infections of the spinal cord and surrounding structures can directly or indirectly cause damage to the spinal cord with subsequent neurologic compromise[1]. Most common causes in the etiology are osteomyelitis, discitis, tuberculosis of the spine, epidural abscess, arachnoiditis, intramedullary spinal cord abscess, transverse myelitis, spinal cord involvement by the human immunodeficiency virus and other infectious etiologies[2].

Great developments have been achieved in the diagnosis and management of spinal infections. Despite the use of broad spectrum antibiotics and advances in surgical treatment techniques and stabilization methods, spinal infections still keep their importance due to the diagnosis, treatment and rehabilitation of sequelae[3,4]. Therefore, spinal infections should be included in education programs for all physicians who interested in the management of low back pain, especially in developing countries and even in industrialized countries due to the increased incidence of tuberculosis in patients with acquired immune deficiency syndrome.

All patients who admitted with neck and back pain should also be evaluated in terms of spinal infections and rehabilitation, because early diagnosis leads to early treatment and early rehabilitation[5]. Particularly in endemic regions such as undeveloped countries, brucellar and tuberculosis spondylitis should be kept in back pain. An early diagnosis will prevent the development of more severe complications such as spinal cord compression. Delayed diagnosis leads to increased morbidity. As there is almost always a late diagnosis during pharmacological treatment and rehabilitation, there has to start an early rehabilitation in order to diminish mortality and its economic costs. Physical medicine and rehabilitation has a prevailing role in the improvement of the functional prognosis in this disease[6].

Limited information exists in the literature about the nature of a rehabilitation program to be applied for patients treated for spinal infections. Our goal as a rehabilitation concept is to identificate a fast and accurate diagnosis because spinal infection have many signs/symptoms and could be mimicked by various diseases and start to the rehabilitation as possible as early. The goal of rehabilitation is to ensure that the patients can continue his/her daily life and business life independently.

Our clinic has extensive experience and publications about spinal infection rehabilitation. The rehabilitation of patients with spinal infections and our experiences are presented herein. Pediatric spinal cord injury (SCI) patients have not been included in this review; this review is about only adult patients.

REST AND PAIN TREATMENT

Although the treatment varies according to the etiological factors in acute phase plan, combination of antibiotics, drainage (if indicated) and surgical intervention are the main options[2]. Before addressing rehabilitation procedures, we will concentrate on pain and resting that are important in rehabilitation practice. Back pain is the most common clinical manifestation in the patients with spinal infection diseases. Low back pain which related to spinal infections or rehabilitation procedures may have negative influences on the rehabilitation program, so the pain management has critical importance. Non-steroidal anti-inflammatory drugs or analgesics and muscle relaxants can be initiated as required. In the absence of any contraindications, this treatment can be continued up to 2-4 wk. Narcotic analgesics can be initiated when there is no response to this treatment or for early pain management[7]. One of the aspects of the management of low back pain due to spinal infection is resting. Although resting is not recommended except for an acute period of non-infectious low back pain, it is recommended in spinal infections both for pain management and for the maintenance of stability[8]. The resting period in cases without neurologic deficits should be kept minimal (24-72 h); however, it may be prolonged depending on general status, pain severity, and stability in cases with neurologic deficits. Prolonged immobilization will lead to weakness in the trunk and lower extremity muscles and will contribute to the development of complications. Prolonged immobilization may also induce generation of secondary gains[9,10].

NON-TRAUMATIC SPINAL CORD INJURIES

Since spinal infections are generally considered under the heading of non-traumatic spinal cord injuries, it is suggested that the patients should be evaluated as having spinal cord injury. However, the etiologic factors in non-traumatic SCI are tumor, degeneration, infection and vascular etiology, transverse myelitis, spina bifida, syringomyelitis. The differences in the etiological factors of non-traumatic SCI, among different countries, may be due to social, cultural, and genetic differences[11]. The factors such as age, prognosis, the period of illness, the severity of illness, the surgical endicaton and response to treatment effect the rehabilitation (spinal kord eclipse ifadesi bence çıkarılmalıdır). Due to spinal cord infections are different, their rehabilitation are different as well. The infections should be handled differently. When the complications at the times of hospital admissions were assessed, the number of complications in the non-traumatic SCI group was found to be less than the number of complications in the traumatic SCI group. In one study, it has been reported that complications such as

spasticity, pressure ulcers, deep venous thrombosis, and autonomic dysreflexia in non-traumatic SCI patients had been found to be less often when compared to traumatic SCI patients[11,12]. These complications are typically observed in cases with severe neurologic damage and instability[13,14].

Non-traumatic spinal cord lesions represent a significant proportion of individuals with spinal cord lesions who admitted in rehabilitation clinics, and it is important to further evaluate their demographic, neurological presentation and functional outcome[15,16]. A plethora of literature is available on the medical complications as well as on the neurological and functional outcome of traumatic spinal cord lesions, but very few studies have focused on medical complications[17,18], etiology[19-21], neurological[22,23] and functional[15,16] outcomes after non-traumatic spinal cord lesions. However, very few studies are present related with neurological and functional rehabilitation in spinal disease infections[7,24,25]. Irrespective of the etiology, severity and extent of insult to the cord, patients with spinal cord lesions perform better in activities of daily living, including self-care, personal toilet, transfer and locomotion by whatever means, in a much better way after rehabilitation intervention and show significant neurologic recover[22,23].

A previous study have reported significant functional recovery in patients with non-traumatic spinal cord lesions after rehabilitation intervention[26].

In studies evaluating the complications in patients of non-traumatic SCI, it was found that urinary tract infection was the most common complication. Pressure ulcers were the second most common complication in the non-traumatic SCI[11,27]. Both the neurological and functional status of non-traumatic SCI patients were better than the patients in the traumatic SCI group[11,26,27,28].

Functional status was better at the time of the hospitalization in the non-traumatic SCI group *vs* the traumatic group, however functional gain and functional efficiency have been found to be low in the non-traumatic group. In other words, response to rehabilitation therapy has been found to be better in the traumatic SCI group. The prognosis for neurologic recovery is affected mainly by SCI severty and etiology, and is usually more ameliorative in non-traumatic SCI patients than traumatic SCI patients[29]. The little that is known about recovery rates following non-traumatic SCI patients mentioned in a few studies about spinal tuberculosis[28,30-32]. Total recovery rate was 90% in patients with spinal cord tuberculosis following drug therapy and rehabilitation[33].

NEUROLOGICAL EVALUATION

The clinical status of the patients should be evaluated in addition to the detailed physical examination and system questioning before initiation of the rehabilitation program. Factors; including the general status of the patient, the presence of paresis, the level of the lesion in cases of neurologic involvement, the presence of incontinence, and cardiopulmonary and psychological status should be evaluated in detail. The evaluation of functional status scales is also necessary for optimal rehabilitation programs. It should be taken into consideration that the rehabilitation program requires teamwork and consultation of related clinics with multidisciplinary approach. Brucellosis and tuberculosis are the most frequent chronic infections involving the spine and also our clinical experiences mostly include the rehabilitation of complications caused by these infections in the spine.

COMPLICATIONS IN SPINAL INFECTION

Patients with spinal infections are bedridden for certain period, which is longer in those with neurologic deficits or those who were recommended surgical operation. These patients should be monitored closely in terms of complications and treated accordingly. Failure to detect and treat complications, such as hypertension, hypotension, deep venous thrombosis, pulmonary infections, urinary retention, urinary infections, spasticity, contractures, decubitus ulcers, depression, and osteoporosis increase morbidity and mortality[34].

Spinal deformity and paraplegia are the significant complications of spinal tuberculosis both of which occur more often in cases of delayed diagnosis and management[35]. Patients with an initial kyphotic angle of 30 degrees or less should be treated with antituberculous medications, with close monitoring for progression of deformity[36]. Rehabilitation programs of patients with neurologic deficits or those who had surgical operation due to spinal infections should be conducted with more care. Complications are observed more frequently and the response to treatment is delayed because of the longer immobilization period.

REHABILITATION PROGRAMME

The most important factor in SCI rehabilitation programme is early rehabilitation. The positioning in the acute phase, early starting of passive, active-assisted and active exercises will greatly contribute standing of the patient earlier and to mobilize. Standing and mobilization are not recommended in the acute period for these patients. Generally, standing and ambulation are recommended during the subacute period. Patients with spinal tuberculous, bracing with a conforming orthosis (plaster or molded thermoplastic) has been used in combination with antituberculous drugs as initial treatment. Bracing is continued 3 mo after the first radiologic sign of bony fusion[37].

The onset of pain or increase in pain during exercise programs in the early period should be evaluated carefully. Pain aggravating exercises should be avoided and the exercise program should be discontinued if there is a significant increase in pain intensity disturbing the patient following the rehabilitation program. The patient should not be exhausted during exercise and mobilization and should have adequate resting after exercise. High calorie diet regimens should be provided since metabolic requirements are increased during both disease and the rehabilitation period.

In general, there are very few studies concerning

spinal infection rehabilitation[7,24,25]. Our clinic has significant experiences with these issues. The rehabilitation program is applied with respect to the neurologic status of patient. For this purpose, the levels in which the spinal cord injury may occur and the involved segments are determined before implementation of the program. Following a detailed physical and neurologic assessment, determination of the region that lesion affects the type of paralysis, the urologic and neurologic status, concomitant diseases, the age of patient, and the involved region is crucial to establish a realistic and optimal rehabilitation program. Following this assessment, patients should be monitored closely in terms of maintaining good posture, bed care, and positioning during early rehabilitation. The presence of instability and the type of surgical procedure are important for the implementation of rehabilitation program. Musculoskeletal problems and secondary problems as a result of immobilization should be monitored and prevented[5].

REHABILITATION IN PATIENT WITH NON-NEUROLOGICAL FINDINGS

In patients with mild neurologic findings, active or active assistive range of motion and isometric exercises should be applied in all joints of the lower extremity during the acute phase. Accordingly, ambulation of the patient is targeted in the early period. During the subacute period, isotonic exercises for the low back, hip, and lower extremity muscles and mobilization exercises (using corset according to the status of patient as necessary) are performed. Also, balance problems, if exist, are tried to be improved. In the chronic stage, isotonic and strengthening exercises are prescribed for atrophic muscles of patient and mobilization is continued. The patient is discharged by providing a home exercise regimen and followed up at regular intervals[7,24].

REHABILITATION IN PATIENT WITH NEUROLOGICAL FINDINGS

In patients with severe neurologic findings due to spinal cord compression, the rehabilitation program differs according to acute, subacute, and chronic stages. In cases with spinal infections, medical treatment should be considered at first, even in cases with spinal cord compression due to paravertebral abscess[38]. However, both surgery and medical treatments are necessary in cases of neurologic involvement.

ACUTE STAGE

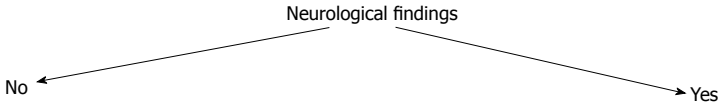
The most important factor in the acute rehabilitation period is to determine the patient's physical capacity. According to the degree of infection, the muscles weakness can be seen in varying degrees in lower, upper extremity and trunk muscle. Bed positioning in appropriate with dermatomal areas, passive joint movements and breathing exercises are important in the acute phase of flastisity. Each group of muscles must be evaluated separately if there is muscle weakness. Isometric, passive, active-assisted, active exercises are performed to improve the functional capacity of muscles. This should be done at least daily, which will help to prevent contractures. The shoulder, elbow, hip flexors, and ankles are most important to range, because contractures are most frequently observed in these joints in the acute rehabilitation unit. The most important aspects in the acue period include bowel, bladder, and pulmonary management, deep venous thrombosis, and gastrointestinal prophylaxis and proper positioning in bed with turning at least every 2 h. The trunk and extremities should be properly positioned and the feet should be supported in a neutral position. If the level of spinal infection is in thoracic vertebrae, respiratory exercises are added. The pressure must be reduced in order to prevent decubitus ulcers. While in the supine position, the patient is turned from one side to the other every 2 h to reduce pressure and monitored constantly for erythema formation[4]. An indwelling catheter is placed if urinary incontinence is present.

In the acute stage, isometric exercises are initiated during the pre-operative period and continued during the early post-operative period. The patient is assisted to be mobilized within the bed by turning from one side to the other. Isometric contraction is sustained by isometric compression of the lumbar, thoracic, and sacrospinal muscles towards the bed. Isometric exercises are performed in cervical, thoracic, and sacrospinal muscle groups and all lower extremity muscles; patient in the supine position continues to elevate head and shoulder until the toes are visible. Gluteal muscles are contracted and relaxed bilaterally and isometric contraction of the pelvic muscle group is provided[7,24].

SUBACUTE STAGE

Subacute period is the out of bed ambulation period of the patients. According to the width of the localization of infection and the patient with appropriate assistive devices bodice and on the edge of the bed before backing out of bed by then, with crutches or walker is focused on mobilization. Also bearing exercises quadriceps exercises in addition to the side of the mattress is required to be done in an active way. Standing on the edge of the bed and standing proper ways are taught.

Active and active assisted exercises are performed during the subacute stage. Feet are raised straightly and contraction of hip flexors and lumbar extensors is performed by raising the bilateral quadriceps muscles about 20 cm. The patient is assisted by the corset to sit on the bed (supported or unsupported). Balance exercises are performed at this position. The patient is assisted to walk by cane or walker. Mobilization is repeated up to 3 or 4 times daily. The patient is left to rest after the onset of signs of fatigue. Assistive equipment is withdrawn following the successful independent mobilization of the patient[7]. Clean intermittent catheterization is performed instead of continuous indwelling catheter to prevent



Acute stage	Subacute stage	Chronic stage
Active exercises Active-assistive exercises Isometric exercises The ambulation	Isometric exercises Mobilization exercises Balance exercises Mobilization The ambulation	Isometric exercises Strengthening exercises Balance exercises Mobilization The ambulation

Acute stage	Subacute stage	Chronic stage
Bed positioning Breathing exercises Passive exercises Isometric exercises Active assistive exercises Active exercises Exercises in bed	Active-assistive exercises Active exercises Balance exercises Strengthening exercises Breathing exercises Standing The ambulation	Mobilization Standing Trunk and pelvic active isotonic strengthening exercises The ambulation Home exercises Daily living exercises

Figure 1 Rehabilitation programme according to the presence of neurological findings.

urinary infections. The patient should be examined at certain intervals for urinary infection, should drink enough water and should be ambulated continuously. The patient should be fed by high-fiber food to prevent constipation which might be a significant problem. The patient should be taken to the rest room once or twice a day to stimulate defecation[4]. If the upper extremities are preserved, active strengthening exercises should be performed for all upper extremity joints.

CHRONIC STAGE

The chronic period is a term that the patients return back to his previous life and regain maximum independence. For this purpose, the patients should be awayed from bed. Mobilization should be done independently supported or unsupported. Lying down, sitting and standing exercises should include active and resistive exercise. The balance and gait exercises assets should be studied in parallel bars. Climbing stairs, squat, sit on the ground activities like lifting should be done. The patients are assisted to walk by using crutches or orthotics during the chronic stage. Patients who achieve trunk and pelvic stabilization are taken to the parallel bar by wearing corset for standing exercises. In standing position, forward, backward and sideways stepping exercises, as well as neutral position exercises such as forward flexion, are performed. Cat-camel stretching exercises are performed to strengthen abdominal and dorsal muscles. These exercises may also be performed in bed without wearing corset[7,24].

Decubitus ulcers are significant health problems in patients with paraplegia. Decubitus ulcer should be considered during the chronic stage as well. Depression may occur in patients with spinal cord compression, therefore psychological support should be provided for these patients[4].

HOME EXERCISE PROGRAMME

Home exercise program based on the patient's capacity should be designed in such a way that she or he can understand. The home evaluation is an important aspect of the rehabilitation process, to allow the patients to return home. The main areas of concern in the home evaluation include the entrances, bedroom, bathroom, kitchen, and general safety issues. The maximum ergonomic changes should be made as possibly in the patient's home environment (toilet, bathroom, bedroom, hallway, *etc.*) in order to ensure the patient's independancy. Patients' check-up and general condition should be evaluated at regular intervals. Recommendations should be done specificly to facilitate the patient's activities of daily living in the late stages where the patients can return back to the work

After the completion of the rehabilitation programme in hospital, the patient is then discharged with a home exercise program and followed up at regular intervals. In addition to the exercises performed during the subacute and chronic stages, hand and wrist joint exercises, full abduction, extension and flexion exercises for abdominal, sacrospinal, iliopsoas, gluteus maximus, gluteus minimus, hamstring, and quadriceps muscles, and resistive exercises for oblique abdominal muscles are recommended to be performed at home. Exercises to increase respiratory capacity are continued. Cardiovascular endurance exercises are prescribed after complete improvement of vertebral bones[7]. According to the presence of neurological findings, rehabilitation programme was indicated (Figure 1). A neurologic examination and laboratory tests are performed at the follow-up visits. A multidisciplinary follow-up program is performed together with infectious diseases, pulmonary diseases, neurosurgery, and/or orthopedics clinics when necessary.

We determined significant improvements in discharge scores of the patients with tuberculosis and brucella after their admission to hospital when we evaluated motor scores for lower limbs and modified barthel index (MBI). At the end of the rehabilitation program patients experienced less pain and were able to perform their daily work with fewer complications. In the final radiological examinations of every patient, degenerative alterations at the pathologic

disc space were found to be less than we had expected[7,24]. Yen *et al*[25] evaluated MBI and determined significant improvements in discharge scores of patients with respect to their admission scores. They also found significant improvements in discharge scores of the same patients in terms of the motor scores for the lower limbs.

CERVICAL SPONDYLODISCITIS

In general, Cervical spondylodiscitis published reports on the outcome of rehabilitation have been very limited[34,39,40]. Cervical spondylodiscitis is a rare localization of spinal infection, and also may be associated with a higher incidence of devastating neurological complications, and an overall worse prognosis. Thus, the cervical spine was immobilized with a hard neck collor. Neck mobility returned to normal, and the hard neck collar changed to a soft one[34,39]. Neck isometric exercise must start in acute pain stage during that cervical collar was being applied. The cervical corset is applied for immobilization at least for one month due to severity of acut neck pain. Range of motion exercise must start in subacute stage. In the chronic phase, exercise must start to improve the function of the neck muscles, and isotonic was started[38,39].

CONCLUSION

Whether traumatic or non-traumatic SCI rehabilitation includes quite difficult and a long process for both patients, patients' relatives and for the rehabilitation team. It is based on multidisciplinary studies as with spinal cord injury. Patients and their relatives are the most important elements of this team. Patient compliance will ensure the success of rehabilitation by simplifying the work of the rehabilitation team. The best rehabilitation target for these patients is to be independent like their past life and be able to rotate without limits. For this purpose the whole medical team must handle the rehabilitation of patients with spinal infection and they should identify the assessment and rehabilitation program as possible as early. The patient should be informed with the idea that success comes with his/her own efforts at the end of a long process.

A successful rehabilitation program should assist patients to return their daily living activities by providing early mobilization with pain reduction, strengthening of weak muscles or prevention of muscle weakening, stabilization, maintenance correct posture and trunk mobilization. Long-term follow up with the spinal cord injury specialist is extremely important. This allow for monitoring of medical issues, reevaluating the therapy program and setting updated goals, and prescribing equipment.

ACKNOWLEDGMENTS

We thank Dr. Volkan ŞAH for his support for review of the manuscript and for insightful comments.

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P- Reviewer: Hyun SJ, Lakhdar F, Lin YW **S- Editor**: Gong XM
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.8

World J Orthop 2015 January 18; 6(1): 8-16
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

Kemal Nas, MD, Professor, *Series Editor*

Rehabilitation of spinal cord injuries

Kemal Nas, Levent Yazmalar, Volkan Şah, Abdulkadir Aydın, Kadriye Öneş

Kemal Nas, Department of Physical Medicine and Rehabilitation, School of Medicine, Sakarya University, Korucuk, Sakarya, 54290 Turkey
Levent Yazmalar, Department of Physical Medicine and Rehabilitation, School of Medicine, Dicle University, 21280 Diyarbakir, Turkey
Volkan Şah, Department of Phsyical Treatment and Rehabilitation, Erzincan University Mengucek Gazi Training and Research Hospital, 24100 Erzincan, Turkey
Abdulkadir Aydın, Orthes and Prothes Center, Dicle University, 21280 Diyarbakır,Turkey
Kadriye Öneş, Istanbul Physical Medicine and Rehabilitation Research and Training Hospital Physical Therapy and Rehabilitation Clinic, 34718 Istanbul, Turkey
Author contributions: Nas K, Yazmalar L and Öneş K contributed to the concept and design; Şah V contributed to the interpretation; Aydın A contributed to the literature review.

Correspondence to: Kemal Nas, MD, Professor, Department of Physical Medicine and Rehabilitation, School of Medicine, Sakarya University, Korucuk, Sakarya, 54290 Turkey. kemalnas@yahoo.com
Telephone: +90-264-2759192
Fax: +90-264-2759192
Received: February 14, 2014
Peer-review started: February 14, 2014
First decision: April 4, 2014
Revised: May 24, 2014
Accepted: June 14, 2014
Article in press: June 16, 2014
Published online: January 18, 2015

Abstract

Spinal cord injury (SCI) is the injury of the spinal cord from the foramen magnum to the cauda equina which occurs as a result of compulsion, incision or contusion. The most common causes of SCI in the world are traffic accidents, gunshot injuries, knife injuries, falls and sports injuries. There is a strong relationship between functional status and whether the injury is complete or not complete, as well as the level of the injury. The results of SCI bring not only damage to independence and physical function, but also include many complications from the injury. Neurogenic bladder and bowel, urinary tract infections, pressure ulcers, orthostatic hypotension, fractures, deep vein thrombosis, spasticity, autonomic dysreflexia, pulmonary and cardiovascular problems, and depressive disorders are frequent complications after SCI. SCI leads to serious disability in the patient resulting in the loss of work, which brings psychosocial and economic problems. The treatment and rehabilitation period is long, expensive and exhausting in SCI. Whether complete or incomplete, SCI rehabilitation is a long process that requires patience and motivation of the patient and relatives. Early rehabilitation is important to prevent joint contractures and the loss of muscle strength, conservation of bone density, and to ensure normal functioning of the respiratory and digestive system. An interdisciplinary approach is essential in rehabilitation in SCI, as in the other types of rehabilitation. The team is led by a physiatrist and consists of the patients' family, physiotherapist, occupational therapist, dietician, psychologist, speech therapist, social worker and other consultant specialists as necessary.

Key words: Spinal cord; Injury; Tetraplegia; Paraplegia; Rehabilitation

Core tip: Spinal cord injury (SCI) leads to serious disability and complications. The treatment and rehabilitation process of SCI is long, expensive and requires a multidisciplinary approach. Early rehabilitation is important to prevent disability and complications.

Nas K, Yazmalar L, Şah V, Aydın A, Öneş K. Rehabilitation of spinal cord injuries. *World J Orthop* 2015; 6(1): 8-16 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/8.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.8

INTRODUCTION

Spinal cord injury (SCI) is the injury of the spinal cord from the foramen magnum to the cauda equina which occurs as a result of compulsion, incision or contusion. As a result of the injury, the functions performed by the spinal cord are interrupted at the distal level of the injury. SCI causes serious disability among patients[1]. Every year, about 40 million people worldwide suffer from SCI. Most of them are young men, typically aged from 20 to 35, although 1% of this population are children[2]. In children, motor vehicle accidents are the most common mechanism of injury. Sports-related injuries are responsible for the largest number of spinal injuries after children begin school and start participating in organized sports. Among all sports, football causes the greatest number of injuries[3]. Sixty to eighty percent of spinal injuries in children occur in the cervical region. The remaining 20%-40% are evenly split between the thoracic and lumbar region. Boys are more likely to experience spinal trauma than girls[4]. The most common causes of SCI in the world are traffic accidents, gunshot injuries, knife injuries, falls and sports injuries. Diving was reported to be the most common sport inury. Injury is usually caused by flexion, compression, hyperextension or flexion-rotation mechanisms. This is called "primary damage" that occurs as a result of these mechanisms. The responses of the body in order to overcome the primary damage, such as hemorrhage, inflammation and the release of various chemicals, are described as secondary damage[5].

Spinal cord injuries are classified by the American Spinal Injury Association (ASIA) by considering the motor and sensory functions. The last revision of the ASIA Disorder Scale was made in 2011. The term of "deep anal sense" is replaced by "deep anal pressure". The term skeleton level was not included in the latest "International Standards for Neurological Classification of Spinal Cord Injury (ISNCSC)" contents as it is not always present in spinal cord lesions[6]. The ASIA scale is listed in Table 1.

There is a strong relationship between functional status and whether the injury is complete or not complete, as well as level of the injury. A complete injury means full loss of motor and sensory functions at the distal level of injury[7]. Incomplete injury defines partial preserving of sensory and motor functions below the neurological level and in the lower sacral segments. With this lesion, deep anal sensation and/or anal mucocutaneous superficial sense is expected to be preserved. The status of the lesion could be unclear until the end of the spinal shock period. Although the signs indicating the end of this period are disputed, an increase in reflex activity is known to be a positive indicator.

Tetraplegia (preferred to "quadriplegia")

This term refers to impairment or loss of motor and/or sensory function in the cervical segments of the spinal cord due to damage of neural elements within the spinal canal. Tetraplegia results in impairment of function in the arms as well as typically in the trunk, legs and pelvic organs, *i.e.,* including the four extremities. It does not include brachial plexus lesions or injury to peripheral nerves outside the neural canal.

Paraplegia

This term refers to impairment or loss of motor and/or sensory function in the thoracic, lumbar or sacral (but not cervical) segments of the spinal cord, secondary to damage of neural elements within the spinal canal. With paraplegia, arm functioning is spared but the trunk, legs and pelvic organs may be involved depending on the level of injury. The term is used in referring to cauda equina and conus medullaris injuries, but not to lumbosacral plexus lesions or injury to peripheral nerves outside the neural canal.

Tetraparesis and paraparesis

Use of these terms is discouraged as they describe incomplete lesions imprecisely and incorrectly imply that tetraplegia and paraplegia should only be used for neurologically complete injuries. Instead, the ASIA Impairment Scale (AIS) provides a more precise approach to description of severity (*i.e.*, completeness) of the SCI[6].

In that case, also called quadriplegia, all extremities and trunk are affected by neurological damage. Tetraplegia occurs in cases of injury at C1-C8 segments. Injuries of the brachial plexus and the nerves outside the neural canal are not included in the definition of tetraplegia. The previous definition of tetraplegia is no longer used and incomplete tetraplegia is preferred instead. The term paraplegia indicates the paralysis of lower extremities and part of the trunk resulting from injury of thoracic, lumbar and sacral segments. This concept encompasses lesions of the cauda equina and conus medullaris but it does not include peripheral nerve and lumbosacral plexus lesions outside the neural canal. Paraplegia is sometimes called diplegia. The body and/or extremities may not be affected depending on the level of the lesion. In many cases of paraplegia, sensory loss and urinary and anal sphincter dysfunction would be detected in the distal levels of injury, in addition to loss of motor function[8].

The most common form of spinal cord injury in the neck is the posterior ligament rupture and dislocation that causes severe neurological pathologies, especially as it is related to damage and ischemia of the gray part in the cord. Ischemia occurs due to direct injury of the circulatory system or neurogenic shock caused by vasospasm. Results of the SCI vary according to the size and localization of the injury[9].

The results of SCI bring not only damage to independence and physical function, but also cause many

Table 1 American Spinal Injury Association scale for spinal cord injury

ASIA-A	Complete. There is no sensory or motor function preserved in the sacral segments of S4-S5
ASIA-B	Sensory incomplete. Motor deficit without sensory loss below the neurological level, including the sacral segments of S4-S5 (light touch, pin sensation or deep anal pressure at S4-S5), and there is no protected motor function from three levels below the motor level at each half of the body
ASIA-C	Motor incomplete. Motor function is preserved below the neurological level[1] and more than half of the muscles below this level have strength lower than 3/5 (0, 1 or 2)
ASIA-D	Motor incomplete. Motor function is preserved below the neurological level[1] and at least half of the muscles (half or more) below this level have strength higher than 3/5
ASIA-E	Normal. Sensory and motor function as assessed by ISNCSC in all segments are normal and in patients with pre-existing deficits there is "E" degree of ASIA. Initially one without a spinal cord injury does not have an ASIA degree

[1]To have a degree of American Spinal Injury Association (ASIA) C or D so to be motor incomplete, the patient must have voluntary contraction of the anal sphincter or protection of motor function at more than three levels below motor level on the same side of the the body with sacral sensory protection. These standards permit the use of muscle function except the key muscles more than three levels below the motor level in discrimination of ASIA B and C. Motor levels in both sides are used to distinguish between ASIA B and C. Single neurological level is used to distinguish between ASIA C and D.

complications. Neurogenic bladder and bowel, urinary tract infections, pressure ulcers, orthostatic hypotension, fractures, deep vein thrombosis (DVT), spasticity, heterotrophic ossification, contractures, autonomic dysreflexia, pulmonary and cardiovascular problems, and depressive disorders are frequent complications after SCI. These complications are directly related to the patient's life expectancy and quality of life. Bladder infections, pressure ulcers and autonomic dysreflexia especially isolate the patient from society[10,11]. Negative changes occur in the patient's perception of health due to complications resulting from SCI. Pressure ulcers, spasticity, contractures, bladder and bowel problems especially cause delay of integration with society and psychosocial distress for patients. SCI patients are hospitalized for a long period of time and experience a variety of limitations in daily living activities due to these complications. Low self-esteem can also occur as a result of the decrease in sexual dysfunction, negatively affecting the patient's body image[12].

During the growth period, diabetes and metabolic diseases are potentially serious diseases in patients who have suffered spinal cord injury in childhood. Spasticity, insulin resistance, dyslipidemia, reduced glucose transfer and obesity are common childhood complications. Passive, active-assisted, active and resistive exercises, cycling and water exercises have to be compatible with the level of SCI and the complications. These exercises will reduce muscle atrophy, decubitus ulcers, inactivity, obesity and bone fractures[13].

The treatment and rehabilitation process for trauma caused by SCI is long, expensive and exhausting, which brings biophysical, psychosocial and economic problems[14]. Treatment of patients with spinal cord injury treatment is an ongoing process for many years and starts shortly after the injury with acute care and early surgical interventions; thereafter, sensory, motor and autonomic dysfunction treatment in the chronic phase and finally, life long treatment in the home environment. Therefore, it is difficult to calculate the cost of treatment in spinal cord injury for many reasons, such as not recording the treatment regularly and not calculating the total cost of the patient as a whole. DeVivo *et al*[15] reported that overall mean first year costs were $222,087 and that mean annual cost after 1 year were $68815 (2009 US $). Mean initial acute care costs of $76711 and mean rehabilitation costs of $68543 (2009 US $) have been reported. Munce *et al*[16] reported that both the average per patient and total direct costs of health care utilization for traumatic SCI increased between 2003 and 2005. The average patient cost rose from $102900 in 2003/04 to $123674 in 2005/06.

The treatment and rehabilitation process of SCI is long, expensive and requires a multidisciplinary approach. Therapeutic strategies and results of clinical studies related to the rehabilitation of patients with spinal cord injury are summarized in Table 2.

Functional goals

Short and long term functional targets are determined by the calculation of the patients' ASIA scale, taking into consideration medical and social status and the individualized rehabilitation plan. Expected functions of motor complete injury patients at the end of the first year according to the level of the injury are given below[28-30].

C1-C4 levels

Patients with C3 and higher level injuries need ventilator support. C4 level patients can manage spontaneous respiration. The patients in this level are completely dependent. Mouth bars can be used for some activities such as page turning and writing. Wheelchairs must have high back supports and a safety belt which is able to stabilize the body and is available for a reclining or tilting position. Battery powered wheelchairs must have a head, tongue, breath or jaw control. Elbow flexion and deltoid muscles are moderately powerful in C4 level patients and thus they can use balanced forearm orthosis in personal care. Static wrist orthosis can be used to maintain the normal position of the hand and wrist and reduce the risk of contractures and deformities.

C5 level

There is enough elbow flexion muscle strength at this level. Range of motion (ROM) and stretching exercises are important in the acute stage to prevent elbow flexion and supination contractures. Static positioning of the hand orthosis preserves the wrist extensors against overstretching.

Table 2 Therapeutic strategies and results of clinical studies related to the rehabilitation of patients with spinal cord injury

Ref.	Therapeutic strategy	Results
Mehrholz *et al*[17]	Locomotor training for walking after spinal cord injury	There is insufficient evidence from RCTs to conclude that any one locomotor training strategy improves walking function more than another for the patients with SCI. The effects of robotic-assisted locomotor training are not clear, therefore research in the form of large RCTs, particularly for robotic training, is needed. Specific questions about which type of locomotor training might be most effective in improving walking function for the patients with SCI need to be explored
Berlowitz *et al*[18]	Respiratory muscle training for cervical spinal cord injury	Inspite of the relatively small number of studies included in this review, meta-analysis of the pooled data indicates that RMT is effective for increasing respiratory muscle strength and perhaps also lung volumes for people with cervical SCI. Further research is needed on functional outcomes following RMT, such as dyspnea, cough efficacy, respiratory complications, hospital admissions, and quality of life. In addition, longer-term studies are needed to ascertain optimal dosage and determine any over effects of RMT on respiratory function, quality of life, respiratory morbidity and mortality
Domingo *et al*[19]	A systematic review of the effects of pharmacological agents on walking function in people with spinal cord injury	There is limited evidence that pharmacological agents tested so far would facilitate the recovery of walking after SCI. More studies are needed to better understand the effects of drugs combined with gait training on walking outcomes in people with SCI
Wessels *et al*[20]	Body weight-supported gait training for restoration of walking in people with an incomplete spinal cord injury: a systematic review	Subjects with subacute motor incomplete spinal cord injury reached a higher level of independent walking after over ground training, compared with body weight-supported treadmill training. More randomized controlled trials are needed to clarify the effectiveness of body weight-supported gait training on walking, activities of daily living and quality of life for subgroups of persons with an incomplete spinal cord injury
Taricco *et al*[21]	Pharmacological interventions for spasticity following spinal cord injury	There is insufficient evidence to assist clinicians in a rational approach to antispastic treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care
Hitzig *et al*[22]	Randomized trial of functional electrical stimulation therapy for walking in incomplete spinal cord injury: effects on quality of life and community participation	The present study provides insight into the perceived benefits acquired by participating in an RCT comparing exercises to FES therapy and serves as a model for pinpointing domains of well-being that could be targeted for assessment in future SCI trials
Astorino *et al*[23]	Effect of chronic activity-based therapy on bone mineral density and bone turnover in persons with spinal cord injury	Chronic activity-based therapy did not reverse bone loss typically observed soon after injury, yet reductions in BMD were less than the expected magnitude of decline in lower extremity BMD in persons with recent SCI
Sadowsky *et al*[24]	Lower extremity functional electrical stimulation cycling promotes physical and functional recovery in chronic spinal cord injury	FES during cycling in chronic SCI may provide substantial physical integrity benefits, including enhanced neurological and functional performance, increased muscle size and force-generation potential, reduced spasticity, and improved quality of life
Gorgey *et al*[25]	Neuromuscular electrical stimulation attenuates high skeletal muscles atrophy but not trunk muscles after spinal cord injury	NMES can delay the process of progressive skeletal muscle atrophy after chronic SCI However, the effects are localized to the trained high muscles and do not extend to the proximal trunk muscles
Karimi *et al*[26]	Robotic rehabilitation of spinal cord injury individual	Although various types of orthotic systems have been developed for paraplegic subjects for walking and rehabilitation, there is not enough research in this regard. It is not easy to determine the therapeutic influence of robotic orthosis on the health status of paraplegic subjects There is a huge gap for a randomized clinical trial research to determine the effect of robotic system on the health status of the SCI subjects
Karimi *et al*[27]	Functional walking ability of paraplegic patients: comparison of functional electrical stimulation *vs* mechanical orthoses	FES and hybrid orthoses offer considerable potential for restoring standing and walking abilities in persons with SCI. However, improvements in their designs and operation with subsequent objective evaluations are required to demonstrate that the systems enable users to improve their performance over that currently possible with passive, mechanical orthoses

SCI: Spinal cord injury; FES: Functional Electrical Stimulation; RCTs: Randomized controlled studies.

Patients can use a battery powered wheelchair with a joystick modification and can push a manual wheelchair with special gloves. Transferability is completely dependent. Most of these patients need assistance for daily living activities although they may eat with a special splint.

C6 level

Active wrist extension is possible and hand grip can be achieved with a tenodesis effect. These patients are usually independent in activities like nutrition, care and hygiene and dressing the upper body. A dynamic triceps-driven orthosis is helpful for reading books, eating, teeth and hair care activities in the cases of weak proximal muscles and strong distal muscles. The driven hand/wrist brace can be used for the function of the hand grip. Transfers are achieved by the assistance of transfer board. A manual wheelchair can be used by adding a knob to the circle but a battery powered wheel chair is needed for long distances. While men are independent in bladder care with some modifications such as clean intermittent catheterization,

women often need help.

C7-C8 levels

The elbow extension in C7 level and finger flexor muscle strength in C8 level is sufficient. Patients are independent in most daily living activities and transfers. They may need some help in lower extremity dressing. A manual wheelchair is accessible and wheelchair transfer is successful. Specially equipped cars can be used.

T11-T12 levels

Patients are independent in daily living activities, bowel-bladder care, using a manual wheelchair and transferring. The target is therapeutic ambulation in upper thoracic injury patients. They can not socially ambulate. Body control is present in lower thoracic injury patients and they may be ambulant at home with lower extremity orthoses and a walker.

L1-L2 levels

They are fully independent in activities of daily living and personal care. They may be ambulatory with long leg walking device for short distances but they need a wheelchair for a long distance.

L3-L4 levels

Patients can lock the knee fully and dorsiflexion of the ankle can be partly made. Patients can ambulate socially with elbow crutches and ankle foot orthoses. They are independent in bowel and bladder care.

L5 and lower

They are independent in all activities.

ACUTE AND SUBACUTE REHABILITATION IN THE SCI

This period begins with admission to hospital and stabilization of the patient's neurological state and is a 6-12 wk bed period. The aim of rehabilitation in this period is to prevent complications that may occur long term. Passive exercises should be done intensively to resolve contractures, muscle atrophy and pain during the acute period of hospitalization in patients with complete injury. Positioning of the joints is important in order to protect the articulary structure and maintain the optimal muscle tonus. Sand bags and pillows can be useful in positioning. If the pillows and sandbags are not able to provide positioning, it can be achieved with plaster splints or more rigid orthotics. Ankle foot orthosis, knee-ankle foot orthosis or static ankle foot orthosis, *etc*. are mainly used for this purpose[31].

The most common and important complication is the development of joint contractures and stiffness during this period. At least one joint contracture (43% shoulder, 33% elbow, 41% forearm and wrist, 32% hip, 11% knee, 40% foot and ankle) has been reported in about 66% of patients within 1 year. If the patient is paraplegic or tetraplegic, intensive passive ROM exercises must maintain the lower extremities to be compatible with the level of the injury. ROM exercises prevent contractures and maintain functional capacity. These exercises should be done in a flaccid period at least once a day and at least 2-3 times a day in the presence of spasticity. Damage level, awareness and cooperation with the state determine the places that must be protected by passive EHA. Shoulder ROM exercises are important to prevent pain in all levels of damage. Passive ROM exercises should be done for both upper extremities in C1-C4 level tetraplegia. In injuries of C5 and C6 levels, ROM exercises should be done to prevent the development of contractures, especially contractures of elbow flexion and supination[32].

Stretching should be done to protect the tenodesis effect in patients without active wrist extension and fingers that are not fully stretched. Muscles are flaccid during the spinal shock period. Exercises can be done more easily with flaccid muscles. Flaccidity is replaced with spasticity after the period of spinal shock. Despite the positive effects of spasticity, it has negative effects on mobility, daily living activities and transferring. The severity and type of the other complications of SCI affects spasticity and the precipitating factors should be eliminated for the treatment of spasticity. Isometric, active or active-assisted truncal exercises should be done in the patient's bed if partial movements are present, depending on the injury level. Recent studies have shown that early mobilization plays an important role in prevention of pulmonary function decline and in the development of muscle strength. Breathing exercises should be carried out and taught and its importance should be explained to complete or incomplete paraplegic and tetraplegic patients during the acute phase in order to protect lung capacity. During this period, the number of exercises should be kept at the maximum level depending on the patient's tolerance. If the physiotherapist or allied health staff in the clinic are not present or are not sufficient, the patient's family should be included in the rehabilitation team from the initial days and the importance and necessity of the rehabilitation must be shared with patients and their relatives[33].

The most important point is strengthening of the upper extremities to the maximal level in the acute period of rehabilitation in patients with complete paraplegia. Enpowering exercises for shoulder rotation are proposed for using crutches, swimming, electric bicycles and walking[34]. At the end of the acute phase, strong upper extremities are needed for the independent transfer from bed. For this purpose, active and resistance exercises to strengthen the muscles of the upper extremity should be initiated at the earliest possible period. Weight and resistance exercises can be applied with dumbbells in bed depending on the patient's muscle strength. Electrical stimulation may be a useful alternative if extreme fatigue occurs while strengthening the muscles. Shoulder exercises performed with elastic bandages were found to be effective to reduce shoulder pain[35].

In order to prevent decubitus ulcers, the patient's position should be changed every 2-3 h. Decubitus ulcers

occur most frequently on the sacrum, ischium, trochanter and superior aspect of the heel. Flexion contractures of the hip may develop due to continuous lying on the side and sitting in the wheelchair. Flexor muscle tension can be reduced with a prone position at regular intervals and ROM exercises in all directions. The ankle ROM exercises are useful to prevent contractures of the foot as well as the proper positioning of the foot while sitting in a wheelchair. Patients should be asked to change position and actively participate. In addition, attention should be paid to keeping the skin clean and preventing the formation of decubitus ulcers[36].

Corsets are used for fixation and supporting the spine while moving on to a sitting position after the end of the bed interval. Hyperextension corsets or plaster plastic body jackets are used in treatment of thoracic and upper lumbar region fractures. A knight-type corset would be more appropriate to support the fractures at the lower of L2 vertebrae. Knight-Taylor type corsets restrict flexion and extension of the trunk but have no restriction on rotation. Plaster or plastic body jacket corsets should be used to restrict movements in all directions[37].

Orthostatic hypotension is likely to be found in patients with a long period of lying in bed. Syncope can be seen in these patients while sitting and being lifted up due to low blood pressure. A tilt table may be useful for patients with this condition, starting from 45 degrees for 30 min a day. The degree is increased according to the patient's complaints or state. Standing upright stimulates the blood pressure reflexly to a sufficient and persistent limit. The patients adapt to sit and stand and are prepared to transfer and balance. When the patient comes to the upright position with a tilt table, the patient should be in a sitting position on the edge of the bed 3-4 times a day and balance exercises should be done to maintain this position. Independent sitting on the edge of the bed is very important for wheelchair use, enabling wheelchair transfer. The purpose of this rehabilitation period should focus on stability and strength education for sitting and transportation. Functional goals must prepare the patient for movements such sitting up in bed or a wheelchair, dressing and transfers. Initially, the goal is for successful bed movements. ROM and stretching exercises are used for functional activities. Exercises for sitting, balance and strengthening of the upper extremities should be done at the beginning. Patients who can tolerate sitting can begin to push up, with static and dynamic balance training to transfer to the wheelchair[38].

Wheelchairs, walkers and crutches are used for out of bed transferring of patients. The wheelchair is the most important tool for SCI patients to be mobile and participate in social life. Ideally, wheelchairs must allow for optimal mobility, protect skin integrity and maintain the normal anatomical posture. A battery assisted wheelchair is appropriate for injuries at the upper segments, whereas a manual wheelchair is preferred at lower levels. Wheelchair dimensions such as the height, pelvic width, seat length, backrest, seat and arm support should be specifically prescribed for each patient[39].

The success of splints or other attempts for functional ambulation depends on whether the injury is complete or incomplete and the injury level. An incomplete SCI patient has the potential to walk, irrespective of level. The beginning of functional ambulation level is considered to be T12. Truncal and pelvic stabilization must be provided to stand and mobilize in the parallel bars. Mobilization in the parallel bars, standing and balance training exercises should be started and the patient could be supported by a posterior shell in the parallel bars during this period. A long and locked knee joint walking device is utilized, ensuring the integrity and stability of the lower extremity joints in patients after the upright standing with a posterior shell. The benefits of standing are a reduction in spasticity and the risk of DVT, bowel and bladder function recovery, prevention of pressure ulcers and osteoporosis, and reduction in depression[40]. Functional neuromuscular stimulation (FNS) is based on innervating nerve fibers of intact muscles. If the muscles are denervated, FNS stimulates the muscle fibers. A study suggests that suitable activation to specific muscles of the trunk and lower extremity can enable patients with SCI to alter their standing postures with minimal upper body effort and subsequently increase the muscle volume[41].

CHRONIC REHABILITATION PERIOD OF SCI

The most important goal is realization of the independent mobilization for both complete and incomplete paraplegic patients during the chronic period. Ambulation can be social, domestic and aimed at exercise. The patient must be able to walk 50 m unaided or with assistive devices for social ambulation. Those who ambulate domestically can walk independently or with partial assistance and need a little help or can be independent at home. Those who ambulate for exercise need advanced help for walking or transferring. Factors such as injury level, age, weight, general health status, motivation and spasticity affect the ambulation potential. Generally, patients with an injury of T10 and above can be ambulated for exercise. Patients with T11-L2 injuries can ambulate in the home (domestic) and the patients of more distal injuries can ambulate socially[42].

Walkers, crutches and orthoses are important to provide chronic stage ambulation. Patients with pelvic control can walk with an orthosis or crutches outside the parallel bars. If the muscle strength of quadriceps femoris is normal, patients can walk with elbow crutches and orthosis without needing a wheelchair. In patients with complete injury of C8-T12, ambulation can be achieved by a parawalker (hip guidance orthosis), both in the house and outside. Walking devices used in spinal cord injury are becoming more and more lightweight and easy to move. However, the devices with advanced technological features are also more expensive. Oxygen consumption, energy expenditure and walking speed can vary significantly depending on the shape, type and weight of material of

devices used by the patients. One of them is the RGO (Reciprocating Gait orthosis)[43]. For effective use, patient's excess weight reduction and increased aerobic capacity must be maintained and muscle mass must be increased. RGO has been further developed and is more complicated and more expensive than ARGO[44]. ARGO also leads to an excessive waste of energy like RGO[45]. Hybrid walking devices were created by adding Functional Electrical Stimulation to orthosis. Walking is becoming better within the hybrid devices[46]. Robotic training is a new approach and is developing day by day. A case report showed that upper extremity function has been improved by robotic assistance over four weeks. After training, manual muscle test scores of wrist extensor, finger flexor and finger abductor are significantly increased[47]. Another study demonstrated that the robotic-assisted gait training using the locomat system improved the functional outcome of subacute SCI patients[48].

The most important expectations in the chronic phase or phase to return home are ensuring the maximum independence related to the level of the patient's injury, integration of the patient to society and teaching the importance of the family's role.

In addition, house modifications are important for patients with SCI in order to have independent activities of daily living. Door width should be 81.5 cm for manual wheelchair access and 86.5 cm for battery assisted wheelchairs. The height of electric switches should be 91.5 cm. Adequate insulation and heat must be provided at home. Door handles must be the "leverage shaped" type and the height of the door sills should not impede the passage of a wheelchair for tetraplegic patients. Carpets should be removed and the surface should be hard in order to maneuver the wheelchair. Bath tubs should be mounted on the wall and must have handles. The height of kitchen apparatuses should be accessible to the patient[49]. There must be a ramp at the entrance to the house[50].

One of the important features of this period is restoring the patient's psychological and emotional state again because of the high incidence of depression in patients (the incidence is about 1/3 in the first six months). Depression is not a natural process experienced after SCI but is a complication that needs to be treated. Suicide is the most common cause of death after SCI among patients under the age of 55. Frequency of posttraumatic stress disorder is 17% and usually occurs in the first 5 years. Consultation with a psychiatrist is needed if there is psychotic behavior and depression[51]. Occupational therapy and finding the patient's role in society are most important factors in restoring the psychological state. Social and psychological problems in the absence of daily activities have been reported. Suicide attempts have been reported due to a lack of daily activity, depression, alcohol dependence and emotional distress. Occupational therapy allows SCI patients to be more social, to use their own functions for creative jobs and to deal with psychological problems like depression[52].

Occupational therapy is an important part of the rehabilitation process. In developed countries, occupational therapy is carried out by the occupational therapist in the rehabilitation team. Occupational therapists assess the patient's limitations and plan the occupational activities. Occupational therapy is planned and implemented depending on the social and cultural characteristics of individuals, level of education, personality traits, interests, values, attitudes and behaviors before and after the injury. Pictures, music, crafts, ceramic work and a variety of activities (for example, sports) and entertainment are implemented and planned to focus on the purpose in the occupational treatment[53].

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P- Reviewer: Zaminy A, Zhang M **S- Editor**: Wen LL
L- Editor: Roemmele A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.17

World J Orthop 2015 January 18; 6(1): 17-23
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

Kemal NAS, Professor, *Series Editor*

Acute complications of spinal cord injuries

Ellen Merete Hagen

Ellen Merete Hagen, Spinal Cord Injury Centre of Western Denmark, Department of Neurology, Regional Hospital of Viborg, 8800 Viborg, Denmark
Ellen Merete Hagen, Department of Clinical Medicine, University of Bergen, 5020 Bergen, Norway
Ellen Merete Hagen, Institute of Clinical Medicine, Aarhus University, 8200 Aarhus, Denmark
Author contributions: Hagen EM solely contributed to this paper.

Correspondence to: Dr. Ellen Merete Hagen, Spinal Cord Injury Centre of Western Denmark, Department of Neurology, Regional Hospital of Viborg, Heibergs Alle 4, 8800 Viborg, Denmark. e-mhagen@online.no
Telephone: +45-78-446177
Fax: +45-78-446159
Received: October 24, 2013
Peer-review started: October 25, 2013
First decision: November 12, 2013
Revised: December 24, 2013
Accepted: May 28, 2014
Article in press: May 29, 2014
Published online: January 18, 2015

Abstract

The aim of this paper is to give an overview of acute complications of spinal cord injury (SCI). Along with motor and sensory deficits, instabilities of the cardiovascular, thermoregulatory and broncho-pulmonary system are common after a SCI. Disturbances of the urinary and gastrointestinal systems are typical as well as sexual dysfunction. Frequent complications of cervical and high thoracic SCI are neurogenic shock, bradyarrhythmias, hypotension, ectopic beats, abnormal temperature control and disturbance of sweating, vasodilatation and autonomic dysreflexia. Autonomic dysreflexia is an abrupt, uncontrolled sympathetic response, elicited by stimuli below the level of injury. The symptoms may be mild like skin rash or slight headache, but can cause severe hypertension, cerebral haemorrhage and death. All personnel caring for the patient should be able to recognize the symptoms and be able to intervene promptly. Disturbance of respiratory function are frequent in tetraplegia and a primary cause of both short and long-term morbidity and mortality is pulmonary complications. Due to physical inactivity and altered haemostasis, patients with SCI have a higher risk of venous thromboembolism and pressure ulcers. Spasticity and pain are frequent complications which need to be addressed. The psychological stress associated with SCI may lead to anxiety and depression. Knowledge of possible complications during the acute phase is important because they may be life threatening and/ or may lead to prolonged rehabilitation.

Key words: Spinal cord injuries; Autonomic dysreflexia; Cardiovascular disease; Orthostatic hypotension; Bradycardia; Thromboembolism; Respiratory insufficiency

Core tip: The paper provides an overview of acute complications of spinal cord injury. Frequent complications in the acute phase of are bradyarrhythmias and hypotension. Other complications are instability of temperature (hypothermia and hyperthermia), pain, spasticity and autonomic dysreflexia (AD). AD is associated with an abrupt, uncontrolled sympathetic response, elicited by stimuli below the level of injury, and it can cause severe hypertension, cerebral haemorrhage and death. All personnel caring for the patient should be able to recognize the symptoms and intervene promptly. Knowledge of possible complications during the acute phase is important because they may be life-threatening and/or may lead to prolonged rehabilitation.

Hagen EM. Acute complications of spinal cord injuries. *World J Orthop* 2015; 6(1): 17-23 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/17.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.17

INTRODUCTION

Traumatic spinal cord injury (SCI) may cause long-lasting dysfunction in many organ systems, and together with permanent change of function, lead to a higher morbidity together with a lower quality of life[1,2]. The management of acute SCI has changed significantly during the past decades due to increased knowledge about the pathophysiology of SCI together with new diagnostic methods and treatment methods. The spinal cord is affected by both the immediate physical effects of trauma, and secondary pathologic processes. Especially ischemia and oedema may worsen the injury during the first few hours after an injury.

Knowledge of possible complications during the acute phase is important because they may be life-threatening and/or may lead to prolonged rehabilitation.

DEFINITION

Traumatic spinal cord injury is defined as an acute injury of the spinal cord which results in a varying degree of paralysis and/or sensory disorder[3]. Injury to the cauda equina is usually included in the definition, while other isolated injuries to nerve roots are excluded[4].

Based on pathophysiological changes the early acute phase is defined to be 2-48 h after the injury, the subacute phase from 2 d to 2 wk, and the intermediate phase from 2 wk to 6 mo[5]. Based on timing of surgery studies have found that early decompression either < 24 h or < 72 h resulted in statistically better outcomes compared to delayed decompression[6]. However, the clinically acute phase is usually defined as the first 4-5 wk after the injury.

ANATOMY

An acute traumatic SCI starts with an abrupt, injury to the spine leading to fractures or dislocations of vertebrae. Displaced bone fragments and disc material causes the immediate injury leading to irreversible damage of axons and broken neural cell membranes. Ruptured blood vessels may cause bleeding in the spinal cord, and thereby increase the damage during the subsequent hours. Several mechanisms contribute to the total injury of the spinal cord tissue.

Goals in the management of SCI-patients include minimizing the primary neurological damage, and preventing secondary cord injury due to hypoperfusion, ischemia, and apoptotic, biochemical and inflammatory changes[7].

An acute injury above the sixth thoracic (Th6) vertebra disturbs the descending pathways to neurons of the sympathetic trunk (in the intermediolateral cell column) from the first thoracic (Th1) to the second lumbar (L2) vertebrae. The consequences are abolished supraspinal control of the sympathetic nervous system, and lack of inhibition of the parasympathetic nervous system resulting in an increased sympathetic activity below the injury level. Along with motor and sensory deficits, instabilities of the cardiovascular, thermoregulatory and broncho-pulmonary system are common after a SCI. Disturbances of the urinary and gastrointestinal systems are typical as well as sexual dysfunction[8,9]. Patients with injury below Th6 will have intact sympathetic and parasympathetic control of the heart and lungs. Thus, the responses from the organ systems will differ between patients with tetraplegia and patients with paraplegia[10].

SURGERY

After a traumatic SCI, the number of complications during the acute phase hospitalization, depends on the timing of surgery, with less complications when surgery is performed soon after the injury[11]. It's proposed that patients with traumatic SCI should be operated within 24 h following injury to reduce complications. If impossible to operate within 24 h, efforts should be made to perform surgery earlier than 72 h after a the injury[11].

ACUTE COMPLICATIONS

Neurogenic shock

Neurogenic shock is due to severe hypotension and bradycardia in cervical injuries due to drop in blood pressure in relation to an acute SCI[12,13]. Hypotension is defined as systolic blood pressure < 90 mmHg in supine position, and is due to low intravascular volume (*e.g.*, blood loss, dehydration)[8]. Because of an intact parasympathetic influence *via* the vagal nerve and a loss of sympathetic tone due to disruption in supraspinal control, neurogenic shock develops as a result of imbalance of the autonomic control[12]. Depending on the severity of the SCI, prolonged and severe hypotension, requiring vasopressive therapy may last up to 5 wk after injury[12].

In the Trauma Audit and Research Network database, the percentages of neurogenic shock was 19.3% in cervical injuries[14]. In thoracic and lumbar injuries the reported incidence was 7.0% and 3.0%, respectively[14].

Cardiovascular disease

Injuries to the autonomic nervous system are the cause of many of the cardiovascular complications following a SCI. Cardiovascular dysfunction in patients with cervical and high thoracic SCI may be life-threatening and may exacerbate the neurological impairment due to the spinal cord injury. Patients have higher morbidity and mortality as a result of the autonomic dysfunction[15-17]. A Canadian study found that SCI is associated with an increased odds of heart disease (OR = 2.72) and stroke (OR = 3.72) compared to ablebody[18].

In the acute phase many irregularities of the cardiac rhythm may occur; sinus bradycardia and bradyarrhythmias

(14%-77%)[19] including escape rhythm, supraventricular ectopic beats (19%)[19], ventricular ectopic beats (18%-27%)[19,20], orthostatic hypotension (33%-74%)[21,22], increased vasovagal reflex, vasodilatation and stasis[20]. Sidorov *et al*[23] found that orthostatic hypotension persisted during the first month following SCI in 74% of cervical and 20% of upper thoracic motor complete SCI patients. Following cervical injuries both sinus bradycardia and arterial hypotension frequently arise[8,24-26]. Bradycardia is reported in 64% to 77% of cervical SCI[20]. Studies have found a peak in incidence four days post-injury, then a gradual decline in incidence[27]. Arterial hypotension is reported in 68% of patients with motor complete cervical SCI (ASIA A and B) who develop bradycardia. Of these will 35% require vasopressors, and 16% will have a cardiac arrest[28]. In the acute phase arterial hypotension in the acute phase can be misunderstood as loss of volume. This may lead to over hydration in the acute phase.

Common autonomic disturbances after 4 to 5 wk post-injury are autonomic dysreflexia, orthostatic hypotension (also in sitting position), reduced cardiovascular reflexes (which regulate blood pressure, blood volume and body temperature) and the absence of cardiac pain[20]. The prevalence of autonomic dysreflexia in patients with SCI with injury above Th6 is 48%-90%[28,29]. Krassioukov *et al*[30] found an incidence of early AD of 5.2% in a population of acute SCI, the earliest episode of AD occurred on the 4th post-injury day. Patients with cervical or thoracic injuries above Th4 may have disrupted the sympathetic afferent fibres including cardiac pain fibres; their sensation of ischemic cardiac pain may be changed (referred pain) or absent[31].

Secondary cardiac changes in patients with tetraplegia, are loss of muscle mass in the left ventricle (due to physiological adaptation to reduced myocardial load[32]) and pseudo infarction - a rise in Troponin with or without ECG changes[25,33].

TEMPERATURE REGULATION

Abnormal temperature control is another well-known clinical phenomenon after SCI, especially in patients with cervical and high thoracic injuries. This is largely due to reduced sensory input to thermo-regulating centres and the loss of sympathetic control of temperature and sweat regulation below the level of injury[34]. A number of temperature regulation disorders following SCI have been described. Some patients have poikilothermia-an inability to maintain a constant core temperature irrespective of the ambient temperature. Injuries above Th8 are often associated with fluctuating temperature, hypothermia and hyperthermia[25].

SWEAT SECRETION

The sweat glands are largely sympathetically innervated in the upper part of the body from Th1-Th5, and in the lower part of the body from Th6-L2. Supraspinal control of sweat excretion is located in regions of the hypothalamus and amygdala[34]. Changes in sweat secretion often occur after SCI, and excessive sweating (hyperhidrosis), absence of sweating (anhidrosis) and diminished sweating (hypohidrosis) may all occur.

Excessive sweating is a common problem in persons with SCI[35,36]. In most individuals, episodic hyperhidrosis is usually associated with other autonomic dysfunctions such as autonomic dysreflexia and orthostatic hypotension, or with post-traumatic syringomyelia. Most common symptoms are minimal/abolished sweating under the level of injury and profuse sweating over the level of injury. This is due to compensatory increase in sweat secretion above the level of injury due to the loss of sympathetic stimulation below the level of injury, which results in reduced sweat production[37]. Sweating may also occur exclusively below the level of injury. This type of sweat is reflex sweating, and is usually a symptom of a massive autonomic response that occurs particularly with cervical and high thoracic injuries (above Th8-Th10).

Respiratory complications and dysphagia

Cervical injury has major effects on the pulmonary system, and respiratory difficulties are one of the major complications and a frequent cause of death, both in the acute and chronic phase after injury[38]. Studies have found that 67% of acute SCI patients experience severe respiratory complications within the first days after the injury; atelectasis (36.4%), pneumonia (31.4%), and respiratory failure (22.6%)[39].

In the acute phase 84% of patients with injuries above C4 and 60% of patients with injuries from C5 to C8, will experience respiratory problems[40], and 75%-80% of tetraplegia above C4 and 60% of tetraplegia caudal to C4 will need invasive mechanical ventilation[41]. Close surveillance of respiration is important. In addition a total of 65% of patients with injuries at levels from Th1 to Th12 may have severe respiratory complications[42]. A 30%-50% reduction of vital capacity is described during the first week post injury in patients with injuries at C5-C6. It is recommended that vital capacity and arterial blood gases should be measured until the patient is stable[41-43].

Thromboembolism

Individuals with SCI have a higher risk of coagulation disorders and venous stasis due to physical inactivity, altered haemostasis with reduced fibrinolytic activity and increased factor Ⅷ activity[44]. They are therefore predisposed to thromboembolism[45,46]. During the first year post-injury, the incidences of deep vein thrombosis and pulmonary embolism are estimated to be 15% and 5%, respectively[47]. The incidence is highest 2-3 wk after the injury, followed by a small peak three months after the injury[48]. During the chronic phase, the incidence of clinically significant thromboembolism is less than 2%[44].

Pressure ulcers

Pressure ulcers are a common complication following SCI. Good prevention requires identifying the individuals at risk for developing pressure ulcers[49]. Pressure ulcer is the

most common long term complication in SCI. Meticulous surveillance in the acute phase and in the operating theatre to prevent pressure ulcers is vital[50].

Heterotopic ossification

Heterotopic ossification (HO) is a frequent, irreversible complication after SCI[51], and involves para-articular formation of mature lamellar bone in soft tissues[52]. The incidence varies between 10% to 53% in different studies[51,53]. The development of HO starts usually within the first 2-3 wk post injury below the level of injury[51,53]. The most common joints affected are hip (70%-97%) and knee[51,53]. Substantial HO, the patients present with a reduction in range of motion of the joint in 20%-30%[53], whereas ankylosis develops in only 3% to 8%[53].

BLADDER

SCI interrupts control of the bladder[54]. Immediately after SCI, the bladder and sphincter are frequently hypotonic. In the chronic phase the bladder dysfunction is classified as either an upper or lower motor neuron syndrome.

Upper motor neuron syndrome (reflex bladder) involves loss of cortical inhibition of sacral reflex arcs due to disturbance of descending spinal tracts, leading to detrusor hyperactivity often in combination with detrusor sphincter dyssynergia[55]. Inhibition of the stretch reflex by the pontine storage centre is abolished. A minor amount of stretch will give a contraction of the bladder wall, the external urethral sphincter lacks voluntary control, resulting in recurrent, spontaneous voiding.

Lower motor neuron syndrome is due to injury to the sacral (S2-S4) part of the autonomic nervous system resulting in a diminished motor stimulation of the bladder and reduced or absent contractility of the detrusor and subsequently an enlarged bladder[56,57].

BOWEL

Between 27% and 62% of patients with SCI report having problems with their bowel, the most frequent symptoms are obstipation, distension and abdominal pain[58]. Other symptoms are rectal bleeding, haemorrhoids, incontinence and autonomic dysreflexia[58]. Spinal shock leads to loss of all activities, under the level of injury, including autonomic function and reflexes. During the first four weeks, 4.7% of patients experienced acute abdominal symptoms, while 4.2% reported acute gastro duodenal ulceration and haemorrhage[58,59].

Spasticity

Patients with an acute complete SCI present with spinal shock associated with muscle paralysis, reduced muscle tone and absent tendon reflexes under the level of injury[60]. Spasticity is usually established after 2-6 mo post injury with exaggerated tendon reflexes, increased muscle tone, and muscle spasms[61,62]. Up to 70% of patients with SCI develop spasticity[63].

Pain

In the acute phase the patients encounter a range of sensory experiences following the trauma. Acute pain commonly accompanies the injury and recedes as healing occurs. Chronic pain is a frequent, disabling complication of SCI. Up to 80% of patients with SCI are reported to suffer from pain[64]. Patients with SCI may have nociceptive or neuropathic-type of pain or a combination of the two[65].

In order to reduce the evolution of chronic pain, it is important to minimize the primary neurological damage, and prevent secondary injury due to hypoperfusion, ischemia, and apoptotic, biochemical and inflammatory changes of the cord[66].

MUSCULOSKELETAL AND METABOLIC COMPLICATIONS

Musculoskeletal pain is common in chronic SCI[67]. The muscles atrophy in response to reduced activity[61]. Studies have found that all patients with complete SCI have some extent of deterioration of muscle, joints and ligaments[61]. Therefore, the patients with SCI experience a period of "metabolic chaos", *i.e.*, an strong catabolic process, which is generated by the loss of physical pressure on muscle, joints and ligaments[61]. This results in bone demineralization leading to hypercalciuria, renal urolithiasis and bladder stones, which may lead to renal failure[61].

IMMUNOLOGICAL MEDIATED NEURO-INFLAMMATION

Excessive activity of matrix metalloproteinases (MMP) in the cord immediately after the injury lead to break of the blood-spinal cord barrier, entering of leukocytes into the injured cord, and disintegration of cells[68]. Studies have shown that MMP-9 and MMP-2 both are important in the regulation of inflammation and neuropathic pain after peripheral nerve injury. They may also contribute to the SCI-induced pain[68]. By blocking the effects of MMP early using pharmacologic agents, an improvement in long-term neurological recovery may be possible, together with reduced glial scarring and neuropathic pain[68].

SEXUALITY

Immediately after a SCI, most patients are focused on the physical improvement. However, when they manage to accept their injury, dealing with sexuality is an important step in the physical and psychological rehabilitation process[69].

ANXIETY AND DEPRESSION

Many patients with SCI experience psychological stress. Patients with a good mental health are usually capable of coping with stress, but the patients response is affected

by the cause and extent of injury, and the patients current life situation[70]. Proper attention and care for each patient's way of dealing with their injury psychologically are important. To prevent or minimize the problems physical, pharmacological or psychological interventions should be available. Interventions will be pain relief, avoidance of sensory and/or sleep deprivation, providing a familiar atmosphere, as well as giving the patient careful explanations and reassurance[70,71]. If possible the patient should have access to psychotherapy and pharmacological treatment during their rehabilitation[70,71].

ASSOCIATED INJURIES

Many patients with SCI have associated injuries to other body parts and organ systems, which may affect negatively affect rehabilitation outcome. The most commonly associated injuries include extremity fractures (29.3%), loss of consciousness (28.2%), pneumohemothorax (17.8%), and traumatic brain injury affecting cognitive or emotional functioning (11.5%)[72].

SPECIALIZED CARE OF PATIENTS WITH SCI

Patients with acute traumatic SCI should be managed at a trauma centre with SCI experience, particularly patients with concomitant injuries[73]. The first European centre specializing in SCI was established in 1944 at Stoke Mandeville Hospital in England. The objective of specialized SCI centres is to advance the care for patients with SCI and thereby improve the neurological recovery. In a recent review Parent *et al*[74] found that early transfer to a specialized SCI centre, lead to a reduced length of stay and decreased mortality.

FUTURE RECOMMENDATIONS

Frequent complications in the acute phase after SCI are arrhythmias, bradycardia, hypotension, pain and spasticity. Knowledge of possible complications during the acute phase is important because they may be life-threatening and/or may lead to prolonged rehabilitation. There is still a need for increased knowledge about the acute cardiovascular complications following SCI as well as temperature regulation, pain and spasticity.

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P- Reviewer: Gorgey AS, Kasai Y, Nas K, Panchal RR
S- Editor: Ma YJ **L- Editor**: A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.24

World J Orthop 2015 January 18; 6(1): 24-33
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

Kemal Nas, MD, Professor, *Series Editor*

Chronic complications of spinal cord injury

Nebahat Sezer, Selami Akkuş, Fatma Gülçin Uğurlu

Nebahat Sezer, Selami Akkuş, Department of Physical Medicine and Rehabilitation, Yıldırım Beyazıt University, Faculty of Medicine, Atatürk Training and Research Hospital, 06800 Bilkent-Ankara, Turkey
Fatma Gülçin Uğurlu, Department of Physical Medicine and Rehabilitation, Atatürk Training and Research Hospital, 06800 Bilkent-Ankara, Turkey
Author contributions: Sezer N and Akkuş S contributed equally to this work; they performed the literature research, designed and wrote the paper; Uğurlu FG performed the literature research.

Correspondence to: Nebahat Sezer, MD, Associate Professor, Department of Physical Medicine and Rehabilitation, Yıldırım Beyazıt University, Faculty of Medicine, Atatürk Training and Research Hospital, 06800 Bilkent-Ankara, Turkey. nsezer1994@yahoo.com
Telephone: +90-312-2912525
Fax: +90-312-2912726
Received: October 24, 2013
Peer-review started: October 25, 2013
First decision: December 13, 2013
Revised: January 2, 2014
Accepted: April 25, 2014
Article in press: April 29, 2014
Published online: January 18, 2015

Abstract

Spinal cord injury (SCI) is a serious medical condition that causes functional, psychological and socioeconomic disorder. Therefore, patients with SCI experience significant impairments in various aspects of their life. The goals of rehabilitation and other treatment approaches in SCI are to improve functional level, decrease secondary morbidity and enhance health-related quality of life. Acute and long-term secondary medical complications are common in patients with SCI. However, chronic complications especially further negatively impact on patients' functional independence and quality of life. Therefore, prevention, early diagnosis and treatment of chronic secondary complications in patients with SCI is critical for limiting these complications, improving survival, community participation and health-related quality of life. The management of secondary chronic complications of SCI is also important for SCI specialists, families and caregivers as well as patients. In this paper, we review data about common secondary long-term complications after SCI, including respiratory complications, cardiovascular complications, urinary and bowel complications, spasticity, pain syndromes, pressure ulcers, osteoporosis and bone fractures. The purpose of this review is to provide an overview of risk factors, signs, symptoms, prevention and treatment approaches for secondary long-term complications in patients with SCI.

Key words: Spinal cord injury; Chronic complications; Management of complications; Long-term morbidity; Secondary morbidity of spinal cord injury

Core tip: Spinal cord injury (SCI) is a important clinical condition that can lead to lifelong disability. Additionally, the secondary complications following SCI, especially long-term complications, increase morbidity and decrease community participation and health-related quality of life. Improving functional level and quality of life are essential goals of rehabilitation in patients with SCI. Therefore, it is important to be aware of chronic complications of SCI and learn how to manage these complications for the recovery and rehabilitation process. The purpose of this review is to provide an overview of chronic complications of SCI.

Sezer N, Akkuş S, Uğurlu FG. Chronic complications of spinal

cord injury. *World J Orthop* 2015; 6(1): 24-33 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/24.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.24

INTRODUCTION

Spinal cord injury (SCI) is a serious medical condition that causes functional, psychological and socioeconomic disorder[1]. Long-term, secondary medical complications are common and play an important role in the continuum of care for patients with SCI[2,3]. Complications are a frequent cause of morbidity and mortality and lead to increased rates of rehospitalization, loss of employability and decreased quality of life[3].

The purpose of this review is to provide an overview of chronic complications of SCI, whether due to trauma or different conditions.

RESPIRATORY COMPLICATIONS

Respiratory complications associated with SCI are the most important cause of morbidity and mortality in both acute and chronic stages[4,5]. The extent of respiratory complications depends on the level of SCI and the degree of motor impairment[4]. Linn and colleagues presented a large investigation assessing pulmonary function in 222 adult outpatients with chronic SCI. They reported that forced vital capacity and forced expired volume (FEV_1) were normal in patients with low-level paraplegia who had never smoked but they found that both decreased with rising SCI level more prominently in patients with tetraplegia[6].

Besides these essential determinants, the effect of duration of injury, smoking history, age and body mass index (BMI) on pulmonary function were also evaluated in various studies in patients with SCI[6,7]. For example, Stepp and colleagues reported that they found a significant decrease in all lung volumes with increasing BMI[7]. Similar results were reported for duration of injury[6,7].

As seen through the literature, SCI often leads to respiratory dysfunction[6,8-10], including insufficiency of respiratory muscles, reduction in vital capacity, ineffective cough, reduction in lung and chest wall compliance and excess oxygen cost of breathing[10]. Due to these problems, atelectasis, pneumonia and respiratory failure are the most common respiratory complications in patients with SCI[4,9].

Pleural effusion, pneumothorax and hemothorax are less common respiratory complications of SCI[9]. Additionally, it is reported that SCI patients have a high prevalence of sleep-related respiratory disorders, particularly obstructive sleep apnea syndrome, which can adversely affect quality of life and rehabilitation[4]. The number of studies of patients with SCI have shown that the syndrome occurs in 25%-45% of those with long-term follow-up[4,11,12].

Patients with cervical and high thoracic SCI are at higher risk for developing atelectasis and pneumonia due to paralysis of the respiratory muscles below the level of injury, resulting in a weak cough mechanism and difficulty mobilizing lung secretions[13].

Respiratory failure occurs most frequently in the acute period. Atelectasis and pneumonia are mainly seen in the acute stage of SCI but they also can appear as an important chronic respiratory problem in SCI. Chen *et al*[14] reported that individuals with complete tetraplegia are clearly at greatest risk for the development of atelectasis/pneumonia. McKinley *et al*[13] reported that the incidence of atelectasis and/or pneumonia at the first annual follow-up year was 3.5% and there was no significant decrease in follow-up years 2, 5, 10, 15 and 20. Pneumonia/atelectasis was also seen more frequently in persons older than 60 years of age in same model analysis study[3]. Pneumonia is also cited as the primary cause of death during chronic SCI[13,15,16].

In the literature, various recommendations were reported about the management of respiratory complications associated with SCI. They include positioning and postural changes, breathing techniques, spontaneous cough and cough assistance, suctioning, respiratory muscle training, ventilation techniques and education, vaccination agents for influenza and pneumococcal infections and pharmacological interventions. Furthermore, the modifiable risk factors (obesity, smoking, *etc*.) must be addressed, particularly in patients with tetraplegia and of older age[3,7,8,10].

CARDIOVASCULAR COMPLICATIONS

Individuals with SCI have a high risk of cardiovascular complications and their long-term effects such as thromboembolism and autonomic dysreflexia[17]. Common cardiovascular complications in the chronic stage of SCI are orthostatic hypotension (OH), autonomic dysreflexia, impaired cardiovascular reflexes, reduced transmission of cardiac pain, loss of reflex cardiac acceleration, cardiac atrophy with tetraplegia due to loss of left ventricular mass and pseudo-myocardial infarction[17-19].

Orthostatic hypotension

OH is usually seen in both acute and chronic stages following SCI[20,21]. It is defined as a decrease in systolic blood pressure of 20 mmHg or more, or a reduction in diastolic blood pressure of 10 mmHg or more, when the body position changes from supine to upright, regardless of whether symptoms occur[22].

Krassioukov *et al*[23] reported that the low level of efferent sympathetic nervous activity and the loss of reflex vasoconstriction after SCI are among the major causes of OH. OH is particularly common in cervical and high thoracic lesions[24-26]. It is also reported that the prevalence of orthostatic hypotension was 21% and cervical injuries had the highest prevalence in a large cohort study with incomplete SCI[27].

The symptoms associated with orthostatic hypotension include dizziness, light headedness, headache, pallor, yawning, sweating, muscle weakness, fatigue and occasionally syncope[23,28,29]. It is reported that management of OH includes application of pressure stockings and abdominal

binders, adequate hydration, gradual progressive daily head-up tilt and administration of pharmacological agents (salt tablets, midodrine, fludrocortisone, dihydroergotamine, ephedrine or L-DOPS)[23,29].

Autonomic dysreflexia

Autonomic dysreflexia (AD) is a well-known medical emergency. It generally occurs in patients with SCI at levels of T_6 and above[30]. AD is characteristic for the chronic stage but may appear any time after SCI[28]. It is reported that the life time frequency among patients with SCI is 19%-70%. It is more common in patients with cervical and complete lesions[17].

AD is caused by spinal reflex mechanisms initiated by a noxious stimulus entering the spinal cord below the level of injury. This afferent stimulus generates a sympathetic overactivity leading to vasoconstriction below the neurological lesion, along with involvement of splanchnic circulation that causes vasoconstriction and hypertension. The excessive parasympathetic activity (and lack of sympathetic tone) leads to vasodilation above the level of the lesion and is thought to be responsible for headache, flushing, sweating and nasal congestion. The reflex bradycardia is secondary to vagal stimulation[31,32].

Bladder distension is the most common triggering factor for AD. The distension can result from urinary retention or catheter blockage and accounts for up to 85% of cases[33]. The second most common triggering for AD is bowel distension due to fecal impaction. Other potential factors include hemorrhoids and anal fissures, gastrointestinal precipitants (appendicitis, cholecystitis, *etc*.), pressure ulcers, ingrown toenails, heterotopic ossification, fractures, menstruation, pregnancy or labor, deep vein thrombosis, pulmonary embolism and sexual activity. Medications, especially nasal decongestants and misoprostol, may also induce AD[31].

An important part of the succesful management of AD is prevention. It is reported that education of the patient, caregivers and family members regarding autonomic dysreflexia is vital to prevent AD and to recognize its occurrence without delay[34]. If AD occurs, the initial management involves non-pharmacological therapeutic interventions. These interventions include placing the patient in an upright position to take advantage of any orthostatic reduction in blood pressure. The next step must be to loosen tight clothing and/or constrictive devices. Blood pressure is controlled at least every 5 min until the patient is stable. It is also necessary to find and eliminate the triggering stimulus which in 85% of patients is related either to bladder distension or bowel impaction[30,35]. These steps will resolve the problem in most patients. It is reported that if non-pharmacological measures fail and arterial blood pressure is 150 mmHg or greater, pharmacological management should be initiated[35]. In general, the predominant medications are antihypertensive agents that have a rapid onset and short duration of action. Nifedipine and nitrates appear to be the most commonly used medications[31]. Additionally, various pharmacological agents (*e.g*., captopril, terazosin, prazosin, phenoxybenzamine, Prostaglandin E2 and Sildenafil) have been proposed for the management of AD episodes[30,35]. The management goals are normalization of the heart rate and blood pressure and clearing the symptoms of AD[19].

URINARY AND BOWEL COMPLICATIONS

One of the most important complications following SCI is the loss of genitourinary and gastrointestinal function[36].

Bladder dysfunction

As with other complications, urological dysfunctions after SCI also increase the risk of long-term complications and decrease psychological and social well-being of the patient[19]. SCI may lead to disturbances of the urinary system. It especially causes bladder dysfunction, often referred to as the neurogenic bladder.

Bladder function is mainly controlled by three areas of the central nervous system: the cerebral cortex, the pontine micturition center and the sacral micturition center[19]. Central lesions can interrupt the pontine and sacral micturition centers. Peripheral lesions also can affect the parasympathetic supply to the detrusor muscle or the sympathetic supply to the bladder neck as well as somatic innervation to the external urethral sphincter in SCI[36].

There are different types of clinical conditions in terms of detrusor and sphincter activity in neurogenic bladder in patients with SCI: (1) hypereflexia of detrusor and sphincter with involuntary contractions, sphincter dyssynergia, reflex incontinence and residual urine; (2) detrusor areflexia with sphincter areflexia. Patients experience stress incontinence and residual urine due to injury to sacral (S2-S4) anterior horn cells or their associated axons, which leads to impaired motor output to the bladder and decreased or absent detrusor contractility (flaccidity); (3) detrusor areflexia with sphincter hyperreflexia with overflow incontinence and urinary retention; and (4) detrusor hyperreflexia with sphincter areflexia with reflex incontinence[36].

It has been reported that the ultimate goals of bladder management after SCI are to preserve upper tract function with low intravesical pressure through adequate bladder drainage and to maintain urinary continence. In patients with SCI, it is generally agreed that urodynamic evaluation is essential to provide a precise diagnosis and treatment options for bladder dysfunction[37]. The urodynamic evaluation is also strongly recommended according to the Autonomic Standards Assessment Form[38]. Time-dependent changes are seen in the level of bladder dysfunction after SCI. Because of that, detailed therapy management should be individualized to the type of voiding dysfunction, level of injury, extent of disability and level of care available to the patient[37].

Treatment methods for neurogenic bladder can be categorized into two groups: therapy to facilitate bladder emptying and therapy to facilitate filling or storage of urine[39].

Weld and Dmochowski reported clean intermittent

catheterization (CIC) as the safest bladder emptying method for SCI patients in terms of urological complications[40]. It was also shown to be the optimal method for assisted bladder voiding after SCI by Shen *et al*[41]. CIC requires education and support, particularly during the initial stages and follow-up. Patients with sufficient hand function using CIC are able to empty the bladder regularly, with a lower urinary tract infection rate and good continence between catheterization[39].

Emptying the bladder with a permanent indwelling urethral or suprapubic catheter or reflex voiding may be an option for some patients with SCI[19]. Indwelling urethral catheters are used in the acute phase of injury but they are not recommended for long-term use because of the high risk for urinary complications (*e.g.*, urinary tract infection, calculi, urethral damage, renal dysfunction and bladder cancer)[42]. Singh *et al*[43] reported an indwelling catheter as the most prevalent risk indicator of urinary tract infection in SCI patients. The risk of urinary tract infection increases with the increasing duration of catheterization.

In spite of the risks, there are times when the use of an indwelling catheter is necessary. For example, it may be used transiently to assist wound healing and prevent contamination in patients with stage 3 or 4 perineal pressure ulcers. Long-term indwelling catheterization may be used for tetraplegic patients who do not have adequate upper limb function and assistance of a caregiver[37,42].

The Crede maneuver is not recommended for bladder emptying in the long-term because it raises intravesical pressures against a closed bladder outlet, raising the risk of vesicoureteral reflux, hernia, rectogenital prolapse and hemorrhoids[42]. Reflex voiding is not recommended in SCI patients with AD, voiding with high pressure, incomplete emptying and in female patients[37]. It may be a viable option for tetraplegic men who are unable to self-catheterization[42].

The other treatment options for bladder management in SCI include pharmacological interventions (anticholinergic medications, α-blockers, botulinum toxin) and surgical procedures (urethral stents, transurethral sphincterotomy, electric stimulation and posterior sacral rhizotomy, bladder augmentation, continent urinary diversion, cutaneous ileovesicostomy)[2].

Regular monitoring and suitable management for bladder dysfunction are important to prevent long-term complications (*e.g.*, infections, vesicouretheral reflux, renal failure, renal calculi, bladder cancer) and provide a better quality of life in patients with SCI.

NEUROGENIC BOWEL

Neurogenic bowel (NB) is a major problem in terms of physical and psychological aspects for people with SCI[44]. Liu *et al*[45] reported NB as a very common complication in patients with SCI, affecting nearly half of those with SCI (46.9%). It has also been shown that a high level of cord lesion, completeness of cord injury and longer duration of injury (≥ 10 years) can predict the severity of NB in patients with SCI[46].

A neurogenic bowel occurs when there is a dysfunction of the colon due to lack of nervous control[36,44]. Two main types of neurogenic bowel presented as upper motor neuron (UMN) bowel syndrome and lower motor neuron (LMN) bowel syndrome, reported by Stiens *et al*[47].

The UMN bowel syndrome or hyperreflexic bowel results from a lesion of the spinal cord above the conus medullaris. The defecatory maneuver cannot be performed due to lack of functioning abdominal musculature. There is increased colonic wall and anal tone. The voluntary control of the external anal sphincter is interrupted and the sphincter remains tight, thereby retaining stool. The UMN bowel syndrome leads to constipation and fecal retention, at least in part due to the external sphincter activity. The LMN bowel syndrome or areflexic bowel results from a lesion affecting parasympathetic cell bodies at the conus, cauda equina or the pelvic nerve. This syndrome is characterized by the lack of spinal cord-mediated reflex peristalsis and slow stool propulsion. There is an increased risk of incontinence because of the denervated external anal sphincter. The LMN bowel syndrome is correlated with constipation and a significant risk of incontinence due to the atonic external anal sphincter and lack of control over the levator ani muscle[36,44,47,48].

It is reported that bowel dysfunction caused major restrictions in social activities and in the quality of life in 39% of patients with SCI. The management of this problem is fairly important because it can be a greater problem than both bladder and sexual dysfunction[45].

There are various interventions used for management of bowel dysfunction in patients with SCI. The non-surgical treatment methods include high dietary fiber intake[49], abdominal massage[50], digital rectal stimulation[51], manual evacuation[52], oral laxatives[52], transanal irrigation[53], rectal suppository[54] and other pharmacological agents (stool softeners, colonic stimulants, contact irritants, bulk formers)[46] and functional electrical and magnetic stimulation of skeletal muscles[44].

Conservative or pharmacological interventions are successful in the management of neurogenic bowel dysfunction in 67% of the SCI population and when conservative management is ineffective, surgical interventions provide an option. Surgical treatments include sacral nerve stimulation with implantation of electrical stimulation systems, colostomy and Malone antegrade continence enema[44].

SPASTICITY

Spasticity is a common secondary impairment after SCI characterized by hypertonus, increased intermittent or sustained involuntary somatic reflexes (hyperreflexia), clonus and painful muscle spasms[55]. Spasticity affects 70% of patients with SCI and causes considerable disability for many[56,57].

The pathogenesis of spasticity in patients with SCI remains uncertain. An alteration in the excitability of various supraspinal inhibitory nerve paths used to be the

main explanation[57]. Although spasticity has often been viewed as a factor that can negatively affect functional level after SCI[56], light to moderate spasticity may have a positive impact on functional activities, including standing, transfers and ambulation. Additionally, it contributes to better peripheral circulation, thereby avoiding edema and reducing the risk of deep vein thrombosis[56,57].

Severe spasticity may contribute to increased functional impairment, contractures, ulcers, posture disorders and pain. Treatment should start as soon as possible to prevent such negative effects [57].

Management options of spasticity involve the elimination of exacerbating factors (such as urinary tract infection, constipation, ingrown nails, pulmonary infection, pressure ulcers, *etc.*) and the use of physical agents (heat, cold) and physical techniques, systemic medications, chemical neurolysis, intrathecal agents, electrical stimulation and surgical interventions[13,57,58].

Commonly used antispastic medications are baclofen, tizanidine, botulinum toxin, benzodiazepine, dantrolene sodium, gabapentin and pregabalin. Baclofen is a gamma-aminobutyric acid (GABA) agonist. It inhibits the excitatory activity at the spinal reflexes. In addition to an oral form, baclofen has been reported to effectively manage spasticity when used intrathecally. The use of baclofen can be limited because of its adverse effects (*e.g.*, sedation, fatique, drowsiness, ataxia and mental confusion)[55,59].

Tizanidin is a centrally acting α_2-adrenergic agonist involved in presynaptic inhibition[13]. Mirbagheri *et al*[60] reported that tizanidine acts to reduce reflex mechanical responses substantially without inducing comparable changes in intrinsic muscle properties in individuals with SCI.

Botulinum toxin is an injectible medication that acts on the neuromuscular junction to inhibit the release of acetylcholine. A chemical denervation occurs with botulinum toxin in intrafusal and extrafusal muscle fibers and its effect is reversible. The major side effect is excessive weakness of the treated muscle. Another antispastic medication is benzodiazepine. The presumed action mechanism of benzodiazepines is to enhance the binding efficacy of $GABA_A$ receptors. Dantrolene sodium is a unique agent that affects the level of skeletal muscles directly but it tends to cause generalized weakness of muscles, which can affect the patient's participation in a rehabilitation program[55].

Gabapentin and pregabalin were developed for the treatment of epilepsy but are widely used for the treatment of neuropathic pain. Their mechanisms of action require the binding to the high affinity α_2- delta subunit protein of the voltage gated Ca^{2+} channels, thereby decreasing release of excitatory neurotransmitters in the central nervous system[55].

Chemical neurolysis is usually used for localized spasticity. In this intervention, phenol or ethanol solution is used to constitute a nonselective destruction of the nerve axon or motor point that can decrease spasticity. Poor localization of the nerve or an inadequate dose causes treatment failure[13,58].

Surgical approaches include many orthopedic procedures (*e.g.*, tendon extension, tendon plasty or osteotomy) and the ablation of motor nerves and/or rhizotomy of sensory spinal roots. Surgical treatment of spasticity leads to irreversible changes and can often be avoided if other methods are used at an early stage[57,58].

PAIN SYNDROMES

Chronic pain is one of the frequent secondary complications for individuals with SCI, with up to 80% of patients with SCI reported to suffer from it[61]. Chronic pain may lead to functional disability and emotional discomfort and may impact negatively on community participation and quality of life[13,62].

The International Association for the Study of Pain has proposed a taxonomy of pain with a tiered classification of pain related to SCI in which pain types are divided into two main groups: nociceptive (musculoskeletal or visceral) and neuropathic (either above level, at level or below level of injury)[63].

Nociceptive pain

After SCI, chronic musculoskeletal pain, a type of nociceptive pain, may occur with abnormal posture, gait and overuse of structures such as the arm and shoulder. For example, using a manually operated wheelchair increases the risk of developing shoulder pain. Carpal tunnel syndrome and ulnar nerve entrapment at the cubital tunnel and Guyon canal are also seen. Muscle spasm pain is another type of musculoskeletal pain that is often seen in patients with incomplete SCI[2,13,61,63].

Visceral pain is a less distinct category of SCI-related pain. It arises from damage, irritation or distention of internal organs. This type of pain is reported in 15% of patients with chronic SCI[2,13].

Neuropathic pain

Neuropathic pain can occur above the level, at the level or below the level of injury. Above the level neuropathic pain may arise from complex regional pain syndromes and compressive mononeuropathies. At the level neuropathic pain may be due to damage to either nerve roots or the spinal cord itself. In the presence of late onset neuropathic pain, post-traumatic syringomyelia must be considered[61,63].

Below the level neuropathic pain is also referred to as central dysesthesia syndrome or deafferentation pain and often presents diffusely caudal to the level of SCI. It is generally characterized as a burning, aching, tingling or stabbing sensation[63].

Identifying the characteristic features of pain is important for determining suitable treatment.

Pain treatment

The use of simple analgesics, non-steroidal anti-inflammatory drugs and opioids are frequently reported for treatment of patients with musculoskeletal pain after SCI[2,61,63,64]. Pain relief medication combined with non-pharmacological

Table 1 Classification of pressure ulcers[76]

Category/stage Ⅰ: Non-blanchable erythema
Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area. The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Category I may be difficult to detect in individuals with dark skin tones. May indicate "at risk" persons
Category/stage Ⅱ: partial thickness
Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanginous filled blister. Presents as a shiny or dry shallow ulcer without slough or bruising[1]. This category should not be used to describe skin tears, tape burns, incontinence associated dermatitis, maceration or excoriation
Category/stage Ⅲ: Full thickness skin loss
Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling. The depth of a Category/Stage Ⅲ pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and Category/Stage Ⅲ ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage Ⅲ pressure ulcers. Bone/tendon is not visible or directly palpable
Category/Stage Ⅳ: Full thickness tissue loss
Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often includes undermining and tunneling. The depth of a Category/Stage Ⅳ pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and these ulcers can be shallow. Category/Stage Ⅳ ulcers can extend into muscle and/or supporting structures (*e.g.*, fascia, tendon or joint capsule) making osteomyelitis or osteitis likely to occur. Exposed bone/muscle is visible or directly palpable
Additional categories/Stages for the United States
Unstageable/unclassified: Full thickness skin or tissue loss - depth unknown
Full thickness tissue loss in which actual depth of the ulcer is completely obscured by slough (yellow, tan, gray, green or brown) and/or eschar (tan, brown or black) in the wound bed. Until enough slough and/or eschar are removed to expose the base of the wound, the true depth cannot be determined but it will be either a Category/Stage Ⅲ or Ⅳ. Stable (dry, adherent, intact without erythema or fluctuance) eschar on the heels serves as "the body's natural (biological) cover" and should not be removed
Suspected deep tissue injury - depth unknown
Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue. Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed. The wound may further evolve and become covered by thin eschar. Evolution may be rapid exposing additional layers of tissue even with optimal treatment

[1]Bruising indicates deep tissue injury.

treatment such as physiotherapy is also reported[61].

Neuropathic pain relief in patients with SCI can be complex and requires a multifaceted approach. Medications, surgical interventions, the use of modalities and psychotherapy are included in this approach[2].

In the literature, the use of anticonvulsants[65-67], antidepressants[68,69], opioid and other analgesics[64,70-72] and antispasticity medications[73] were reported with different effects on neuropathic pain relief of SCI patients. It is also reported that nonpharmacological treatment such as transcutaneous electrical nerve stimulation, acupuncture, spinal cord stimulation and surgical procedures may be effective for some patients with SCI-related neuropathic pain[63].

PRESSURE ULCERS

Pressure ulcers are an important and potentially life-threatening secondary complication of SCI. They can lead to further functional disability and fatal infections and surgical interventions can be required[74]. Diseases of skin (including pressure ulcers) were reported as the second most common etiology for rehospitalization at most time intervals (years 1, 10, 15, 20) in a multicenter analysis with SCI patients[75].

Pressure ulcers have been defined as a localized injury to the skin and/or underlying tissue, usually over a bony prominence, as a result of pressure or pressure in combination with shear[76].

A common classification system for pressure ulcers has been developed by the National Pressure Ulcer Advisory Panel (NPUAP) and European Pressure Ulcer Advisory Panel (EPUAP). They have agreed on four levels of injury which range in severity from category/stage I (intact skin with non-blanchable erythema) to category/stage Ⅳ (full thickness tissue loss). Recognizing that the terms unclassified/unstageable and deep tissue injury are generally graded as "Ⅳ" in Europe, NPUAP has agreed to put them separately (Table 1)[76].

It is reported that the most common locations for pressure ulcers after 2 years of SCI are the ischium (31%), trochanters (26%), sacrum (18%), heel (5%), malleolus (4%) and feet (2%)[3]. Hoff *et al*[77] also reported that risk factors for pressure ulcers are immobility, reduced activity, lack of sensibility, moisture due to urinary and fecal incontinence, muscle atrophy, prolonged time since injury, depression, smoking and poor nutrition.

Prevention of pressure ulcers begins at the time of injury and is a lifelong commitment for those living with SCI or their caregivers[74]. Pressure ulcer management includes daily inspection of skin, keeping skin clean and dry, avoidance of excessive pressure or shearing, proper pressure relief techniques, individually prescribed equipment (*e.g.*, wheelchair cushions), well-balanced nutrition, early recognition and treatment[74,75].

A treatment plan for pressure ulcer following SCI outlined in the Consortium Guideline includes cleansing, debridement (autolytic, enzymatic, mechanical, sharp,

surgical), dressing (transparent films, hydrocolloids, hydrogels, foams, alginates, gauze dressings), nutritional support, management of tissue loads (bed positioning, using pressure-reducing bed and wheelchair support surfaces, avoiding the individual's postural alignment) and surgery[78].

Furthermore, Regan *et al*[74] reported that there was level 1 evidence to support the use of electrical stimulation, ultrasound/ultraviolet light C and non-thermal pulsed electromagnetic energy treatment as adjunctive therapies to standard wound management.

OSTEOPOROSIS AND BONE FRACTURES

Osteoporosis, a condition characterized by low bone mass and deterioration of the skeletal microarchitecture, is a well-known complication of SCI[79]. It occurs rapidly in the first 12-18 mo but continues for several years[62]. A significant decrease in bone mineral density has been reported in chronic SCI patients[80-82].

The mechanism involved in the development of SCI-induced osteoporosis is complex and multifactorial. Disuse may play an important role in the pathogenesis of osteoporosis but non-mechanical factors also appear to be important. These factors may include insufficient nutritional support, disordered vasoregulation, hypercortisolism (either therapeutic or stress-related), alterations in gonadal function and other endocrine disorders[79].

Bone loss after SCI leads to increased risk of low impact fractures (those occurring spontaneously or from a transfer from bed to chair)[83]. The most common fracture sites appear to be those around the knee, such as the distal femur or proximal tibia[82-85]. A number of factors appear to have an influence on bone mass in patients with SCI. The level of the lesion, the extent of functional impairment, muscular loading of the bones, the duration of injury and aging are included in these factors. The degree of bone loss may be more severe in patients with complete SCI than with incomplete SCI[79,84]. The bone mass tends to reduce with increasing time post-injury and age in patients with SCI[79,86]. Muscular loading of the bones has been considered to play a role in the maintenance of bone density[79].

There is generally no standardized treatment guidelines for management of osteoporosis in patients with SCI[83,87]. In the literature, pharmacological and rehabilitation-oriented approaches were reported[79,84].

Pharmacological interventions for osteoporosis after SCI have focused on reversing bone resorption[88]. The bisphosphonates, the most studied pharmacological agents in the treatment of SCI-induced osteoporosis. They strongly inhibit bone resorption (79). The efficacy of bisphosphonates to decrease bone loss has been reported in both the acute and chronic period[85].

Gilchrist *et al*[88] concluded that alendronate 70 mg orally per week for 1 year initiated soon after acute SCI prevents bone loss. Zehnder *et al*[89] also reported that SCI bone loss was stopped at all measured cortical and trabecular infralesional sites over 2 years with alendronate 10 mg daily in a group of paraplegic men.

In a recent study, zoledronic acid, the newest generation of bisphosphonates, was reported to be an effective and well-tolerated treatment to prevent bone mineral density loss at the total hip and trochanter for up to 1 year following SCI[90].

Non-pharmacological treatment methods such as standing-up, orthotically aided walking, weight-bearing physical exercises, functional electrical stimulation and low-intensity pulsed ultrasound have been studied in the literature. Charmetant et al reported that mechanical and rehabilitational approach aimed at stimulating sublesional bone segments may be a useful adjunct to drug treatment. In various studies standing-up and orthotically-aided walking seem to have a favorable effect during the early phase of SCI[79,84,91,92].

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P- Reviewer: Lykissas MG, Mori K **S- Editor**: Ma YJ
L- Editor: Roemmele A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.34

World J Orthop 2015 January 18; 6(1): 34-41
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

Kemal Nas, MD, Professor, *Series Editor*

Current and future surgery strategies for spinal cord injuries

Sedat Dalbayrak, Onur Yaman, Tevfik Yılmaz

Sedat Dalbayrak, Department of Neurosurgery, Neurosurgery, Neuro Spinal Academy, Istanbul 34940, Turkey
Onur Yaman, Clinic of Neurosurgery, Tepecik Education and Training Hospital, Izmir 35110, Turkey
Tevfik Yılmaz, Department of Neurosurgery, Faculty of Medicine, Dicle University, Diyarbakır 21280, Turkey
Author contributions: Dalbayrak S, Yaman O and Yılmaz T contributed equally to this work; Dalbayrak S, Yaman O and Yılmaz T designed and performed research; Dalbayrak S, Yaman O and Yılmaz T analyzed data and wrote the paper.

Correspondence to: Dr. Onur Yaman, Clinic of Neurosurgery, Tepecik Education and Training Hospital, Yenisehir, Izmir 35110, Turkey. dronuryaman@yahoo.com
Telephone: +90-23-24696969
Fax: +90-23-24696969
Received: October 24, 2013
Peer-review started: October 25, 2013
First decision: December 2, 2013
Revised: April 8, 2014
Accepted: May 13, 2014
Article in press: May 14, 2014
Published online: January 18, 2015

Abstract

Spinal cord trauma is a prominent cause of mortality and morbidity. In developed countries a spinal cord injury (SCI) occurs every 16 min. SCI occurs due to tissue destruction, primarily by mechanical and secondarily ischemic. Primary damage occurs at the time of the injury. It cannot be improved. Following the primary injury, secondary harm mechanisms gradually result in neuronal death. One of the prominent causes of secondary harm is energy deficit, emerging from ischemia, whose main cause in the early stage, is impaired perfusion. Due to the advanced techniques in spinal surgery, SCI is still challenging for surgeons. Spinal cord doesn't have a self-repair property. The main damage occurs at the time of the injury primarily by mechanical factors that cannot be improved. Secondarily mechanisms take part in the following sections. Spinal compression and neurological deficit are two major factors used to decide on surgery. According to advanced imaging techniques the classifications systems for spinal injury has been changed in time. Aim of the surgery is to decompress the spinal channel and to restore the spinal alinement and mobilize the patient as soon as possible. Use of neuroprotective agents as well as methods to achieve cell regeneration in addition to surgery would contribute to the solution.

Key words: Spinal cord injury; Surgery; Classification; Mechanism; Management

Core tip: Spinal cord trauma is a prominent cause of mortality and morbidity. In developed countries a spinal cord injury (SCI) occurs every 16 min. Due to the advanced techniques in spinal surgery, SCI is still challenging for surgeons. Spinal compression and neurological deficit are two major factors used to decide on surgery. Aim of the surgery is to decompress the spinal channel and to restore the spinal alinement and mobilize the patient as soon as possible. Use of neuroprotective agents as well as methods to achieve cell regeneration in addition to surgery would contribute to the solution.

Dalbayrak S, Yaman O, Yılmaz T. Current and future surgery strategies for spinal cord injuries. *World J Orthop* 2015; 6(1): 34-41 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/34.htm DOI: http://dx.doi.

org/10.5312/wjo.v6.i1.34

EPIDEMIOLOGY

Every year more than 1 million spinal cord trauma cases and more than 50000 spinal trauma related spinal cord injuries occur in the United States[1]. The incidence of spinal cord injuries amounts to 7500-10000 annually. In developed countries, 32000 new cases occur every year, which means, a spinal cord injury (SCI) occurs every 16 min. Spinal cord trauma may occur due to a number of reasons, which usually include motor vehicle accidents, falls and gunshot wounds[2]. Damage to the spinal column usually occurs at the cervicothoracic or thoracolumbar region. Studies revealed that SCI incidence is frequent at ages 16 to 30[3].

PATHOPHYSIOLOGY OF THE SCI

A lot of tissues in the human body are capable of self-repair. However, it is not the case for the central nervous system. SCI occurs due to tissue destruction, primarily by mechanical and secondarily ischemic[4,5]. Primary damage occurs at the time of the injury. It cannot be improved[6]. Following the primary injury, secondary harm mechanisms gradually result in neuronal death[7]. One of the prominent causes of secondary harm is energy deficit, emerging from ischemia, whose main cause in the early stage, is impaired perfusion[4,7]. Following the local infarction, caused by ischemia, grey matter becomes damaged, especially because of its high metabolic requirements. Ischemia leads to insufficient glucose and oxygen transfer to tissues, energy deficit and reduction in adenosine triphosphate store. As a result, the system starts to perform anaerobic respiration. Ischemia and subsequent anaerobic respiration induce many pathological processes.

Another important mechanism, in the process of secondary damage, is post-traumatic over synthesizing of nitric oxide. Nitric oxide (NO) plays a part in continuing the transmission starting with glutamate, in the central neural system. Besides its physiological function, as a result of its high production, NO becomes neurotoxic and plays an important role in the process of secondary damage as a free radical[8]. Over production of nitric oxide causes necrosis with peroxynitrite development, protein damage, increase in lipid peroxidation, cellular energy loss, mitochondrial diaphoresis and deoxyribonucleic acid replication inhibition[9].

Macrophages assume the main role for giving an immune response to the damage occurring in cells other than those of the central nervous sytem (CNS). They activate lymphocytes by releasing cytokines while trying to get rid of the toxic elements. Macrophages act as the antigen presenting cell (APC) for lymphocytes. Cytokines and growth factors are released by the activated macrophages and lymphocytes.

The microglia in the CNS are weak in their APC function. Microglia may have destructive effects in addition to their repair function. Even if the lymphocytes arrive at the location of damage, they lack the APC to activate them.

CLASSIFICATION OF SCI

SCI can be classified into two groups, notably the complete and the incomplete[10]. Complete SCI cannot be diagnosed before the spinal shock regresses. Once the bulbocavernosus reflex (BCR) is back, the injury is diagnosed as complete damage if there is no motor or sensory function. Once the BCR is back, if there is a sensation below the level of injury, it is diagnosed as sensory incomplete SCI. If there is some preserved motor and sensory function below the level of injury, the case is diagnosed as incomplete motor and sensory incomplete SCI. There are 4 types of incomplete SCI syndromes. Anterior spinal cord syndrome is observed as a result of the trauma in the anterior of spinal cord. The damage usually occurs as a result of flexion compression. Posterior spinal cord syndrome is relatively rare. The motor function is preserved below the level of injury, but there is decreased sensory function. Central cord syndrome is more common. It occurs in old patients with cervical spondylosis due to extension injury. Loss of function is more severe in the upper extremities compared to the lower extremities. Brown-Sequard Syndrome is characterized by the lateral hemisection of the spinal cord. Patients with Brown-Séquard syndrome suffer from ipsilateral motor paralysis and loss of proprioception, and as well as contralateral loss of pain and temperature sensation. It is very difficult to reverse this syndrome.

MECHANISM OF INJURY

Majority of the classifications suggested for the spinal trauma are structured along how the damage occurred[11-15]. Spinal injury occur due to flexion, extension, lateral rotation, axial loading, or the combination of these forces. Majority of SCI classifications aim at evaluating the acute phase of trauma. Holdswort explained spinal cord injuries with suggested treatment methods[16]. Denis suggested three column theory built on this classification[17]. Allen Ferguson presented another classification about lower cervical trauma[11]. AO proposed a new classification system for thoracolumbar traumas, which was found suitable by McCormack *et al*[18] according to the load-bearing theory[16-18]. The classification is intended to identify whether the fracture is stable or not. However, there are certain drawbacks in the current classification system. Damage occurs due to the impact of the majority of the abovementioned mechanisms. The results of the modern imaging methods are not taken into account in many classification systems. One can determine the posterior-ligamentous complex in thoracolumbar traumas where instability plays an important role, and the status of the disco-ligamentous complex in cervical traumas through magnetic resonance imaging (MRI) images. Many

systems are not sufficient to decide on the treatment of the existing trauma. Spine Trauma Study Group (STSG) proposed Subaxial Injury Classification (SLIC) for the subaxial cervical traumas in order to eliminate the current gaps[14,15]. The current system took into account the disco-ligamentous complex and the neurological status in addition to the mechanism of injury. The compression forces, distraction and translation forces were also taken into consideration in determining the mechanism of injury. Injury morphology of the disco-ligamentous complex is divided into intact, indeterminate (interspinous spreading, or soft tissue T2 hyperintensity) or disrupted (facet dislocation or disc space widening). Neurological status is classified as (1) intact; (2) radiculopathy; (3) incomplete SCI; and (4) complete SCI. Patients with a score equal to or higher than 4 and above as a result of the classification require surgery.

On the other hand, the classification system proposed by the STSG to address the thoracolumbar injuries is the Thoracolumbar Injury Classification and Severity Score[15]. This system is easier to use and has a high standardization.

SURGERY

Spinal compression and neurological deficit are two major principles used to decide on surgery. However, the surgical approach-either anterior, posterior or combined-varies depending on each patient. As a general principle, the main approach for the patients without the presence of any pathology causing compression in the canal is the posterior stabilization and fusion. Anterior compression and fusion as well as posterior stabilization are required for the patients with certain pathologies causing compression in the canal. In some cases, anterior or posterior surgical approach does not cause any difference. Brodke *et al*[19] operated some of 52 SCI patients with subaxial cervical traumas with anterior approach and some with posterior approach and there was no difference wound between two groups with respect to fusion rates, sagittal alignment and neurological recovery.

Anterior decompression

Anterior decompression is preferred to address the anterior compression[13,20]. Surgery alone can be preferred with posterior approach to remove the compression in the lower cervical spine whereas anterior decompression and stabilization can be achieved with anterior approach in certain cases affected by an anterior disc or bone.

Anterior surgery is usually needed after the posterior compression to treat the lumbar and thoracic injuries since it often achieves indirect decompression. In more than 50% of the compression cases, anterior surgery is required.

The benefit of decompression in thoraclumbar traumas with neurological deficit is still controversial[21-23]. Reduction and stabilization in patients with incomplete neurological injury was demonstrated to be effective in neurological recovery[24,25]. Stabilization in patients with complete neurological damage was reported to decrease the hospital stay, rehabilitation need and complications[26,27]. It was also demonstrated that the pressure removed by anterior decompression later accelerated the neurological recovery of the patients[27,28]. The pressures in the conus and cauda equine decompressed at later a phase were also reported to be beneficial[29].

Despite different views, it is stated that there is not any relation between the stenosis in the canal and the neurological deficit[21]. There is a direct association between the spinal cord contusion rates and neurological injury. Neurological deficit in stenosis of patients with burst fractures is likely to increase by 35% at T11 and T12 levels, by 45% at L1, and by 55% at L2[30].

The studies conducted to determine whether anterior or posterior surgery is more effective showed that anterior decompression was more effective than the posterior approach to treat the patients with incomplete injury. Neurological recovery was found to be better in patients operated with anterior approach according to the urine and stool examinations[25]. Difference was not found between anterior and posterior surgery in 60 SCI patients with compression in the canal by more than 20%[21]. In another study, it was observed that anterior decompression was easier to apply for patients with burst fractures whereas no difference was found between the groups in terms of sagittal alignment[30].

Surgical approaches for spinal decompression

Decompression should achieved by posterior, posterolateral and anterior approaches. Posterior laminectomy for thoracolumbar fractures should be avoided as it will further increase the instability[31,32]. Posterior laminectomy can only be performed to repair the dural tear, to decompress a posterior fracture, and in the presence of epidural hematoma[25]. Posterolateral approach should only be performed with costotransversectomy, lateral extracavitary decompression and lateral extrapleural parascapular decompression[33].

INDICATIONS AND OPERATIVE TECHNIQUES FOR THORACOLUMBAR INJURIES

Compression fractures

Injury of the posterior elements with the presence of 30 degree-kyphosis due to the compression fracture and more than 50% loss in the vertebrae height is indicated for surgery. Posterior approach would be appropriate for such patients. Reduction and stabilization should be performed in distraction mode[34]. Lateral flexion-compression fractures should be stabilized in distraction mode on the damaged side and in compression mode on the non-damaged side.

Burst fractures

Surgical treatment of thoracolumbar burst fractures is controversial. Anterior decompression and stabilization would be appropriate for the instable burst fractures in

the thoracolumbar junction with neurological deficit[35]. Anterior decompression is more effective than posterior indirect decompression approach[36]. The reconstructive technique to be applied following decompression should be determined depending on the shape of the deformity. If the posterior elements remain intact, anterior and medial middle columns should be supported[36]. Parker reported that he performed anterior decompression and fusion for 150 patients who had thoracolumbar burst fractures with neurological deficit and 72% of patients had recovery in their neurological deficits[37]. Posterior instrumentation should be supplemented to the treatment of patients with posterior injury. Short segment pedicle screws lead to high rates of insufficiency in instable thoracolumbar fractures due to the rigidity of the posterior pedicles[12]. 360 degree fusion surgery would be appropriate for the patients with serious injury in the anterior column rather than anterior approach alone[38].

Flexion-distraction injuries

Interspinous ligaments, posterior longitudinal ligament (PLL) and disc that are damaged due to the flexion-distraction injury cause instability in adults[38]. If the middle column remains intact, one level above and one level below the damaged level should be stabilized in compression mode. If the middle column is not intact, the system should be stabilized by distraction to prevent the fracture fragments from entering into the canal.

Fracture-dislocations

Fracture-dislocation fractures are instable, and postural reduction is not effective on the bilateral facet dislocations[39]. In this case, decompression and stabilization by anterior surgical approach should be performed after the posterior surgery[39].

Distraction-extension injuries

Distraction-extension injuries are instable and accompanied by neurological deficit. Posterior reduction can achieve spinal stability and sagittal alignment.

Cervical injuries: Indications and options for surgery

The basic principle of surgery is to perform decompression and restore stability in order to reverse the neurological deficit. To this end, anterior, posterior or combined surgery can be chosen. In some cases, halo and traction may be needed. The objective is to make the patient mobile again as soon as possible and provide rehabilitation to the patient.

Anterior decompression and stabilization

Decompression can be achieved between C3 and C7 with anterior approach[40-42]. Anterior approach may also be applied to the C1-2 junction, though rarely. It is possible to access upper pathologies by transoral approach. There are methods available where stabilization with transoral approach has been defined[42].

Posterior decompression and stabilization

It is also possible to access the entire cervical spine by posterior approach. It would be suitable to use the traction device for patients with fracture dislocation. As correction of the dislocation in such patients eliminates the main problem which causes stenosis in the canal, it would also exclude the need for laminectomy. Fusion should be performed after correcting the dislocated vertebrae.

Cervical fractures

Atlas (C1): SCI is less likely to occur as the canal diameter at C1 and C2 is larger than the subaxial cervical canal. Results of the direct radiographies have been used to determine whether surgery is required for the fractures of the anterior and posterior arches, which are commonly known as Jefferson fractures. The stability of the fracture depends on the lateral displacement of the fracture. If the lateral displacement is greater than 7 mm, it is good for transverse ligament damage and a sign for instability[43,44]. Since MRI is now used on a daily basis, it is possible to clearly identify any damage in the transverse ligament. Spence divided atlas fractures into two categories by assessing the MRI images, which are transverse ligament damage without fracture in the bone (Type Ⅰ) and transverse ligament damage accompanied by avulsion in the bone (Type Ⅱ). Authors suggest that the instability of C1-2 in case of Type I injuries should be stabilized surgically.

McGuire *et al*[45] reported that they fixed and fused the instable atlas burst fractures with C1-2 transarticular screws. Halo should be used for 12-16 wk by patients for whom posterior wiring was performed at C1-2 level[20].

Axis (C2) [odontoid (dens) fracture]: They occur due to the flexion or extension mechanisms. Classification is done depending on the location of the fracture. Type Ⅰ fractures are in the apex of the dens. They can be treated with rigid neck collars. Separation of 4 to 5 mm in Type Ⅱ fractures might not be probably fused[43]. C1-2 wiring can be performed for patients without posterior arch fracture. Lateral mass or transarticular screwing can be an option in the presence of a posterior fracture. Alternatively, odontoid screws may also be used[20]. The advantage of the odontoid screw is that it does not restrict rotation. Julien et al. reported 89% fusion in Type Ⅱ fractures and 100% in Type Ⅱ fractures where they used odontoid screws[46]. Moon *et al*[47] reported to have achieved fusion in all cases for whom he used odontoid screws.

Traumatic spondylolisthesis (Hangman's fracture): It is a fracture caused by C2 sliding onto C3. Type Ⅰ fractures are stable and can be treated by collars whereas Type Ⅱ fractures are displaced more than 3 mm and have an angulation more than 11 degrees. Dislocation is low in Type ⅡA but angulation is higher. Type Ⅲ fractures have a displacement greater than 3.5 mm, angulation more than 11 degrees and bilateral facet dislocation. Type ⅡA, Ⅲ fractures are instable. Fixation and surgery are required for the cases with failed fusion by rigid immobilization. Moon *et al*[47] reported to have achieved fusion in all instable patients treated with anterior C2-3 interbody fusion.

Vaccaro achieved fusion through surgical fixation in Type Ⅱ A patients with failed fusion by immobilization[38]. Xu *et al*[48] reported to have achieved fusion in all patients treated by anterior discectomy and fusion. Posterior surgery is one of the alternatives to treat the Hangman fractures. El milgui reported that they achieved fusion in all patients that stabilized by transpedicular screws[49]. Dalbayrak *et al*[50] reported successful fusions in all patients stabilized with pars screws.

Subaxial spine (C3 to C7): SCI is more likely to occur in subaxial cervical traumas with more stenotic spinal canal compared to subaxial[41-43]. Decompressive surgery is usually needed due to the compression in the anterior side. Posterior fusion might also be needed more in patients with PLL tear.

Bilateral facet dislocation occurs after high energy traumas. PLL, disc and facet capsule are ruptured. This type of trauma with double column damage is instable and requires surgery. Posterior reduction and fusion and also anterior compression might require anterior decompression. PLL might remain intact in unilateral facet dislocations, in this case the fracture is stable and fuses itself. Unilateral facet dislocations which are not reduced might cause pain and radiculopathy in later stages[40]. To prevent this, posterior reduction and fusion should be performed. In some cases, compression may be caused by the disc. In this case, anterior decompression fusion is needed before reduction. Posterior surgery would increase the likelihood of fusion in later stages[20].

Depressed fractures might occur in the vertebrae due to the compression forces. If 1/3 of the fracture is in the anterior, if the displacement is not greater than 3.5 mm den and angulation is not greater than 1 degree, the fracture is considered to be stable[32]. If the fracture also affects the middle column, the fracture is considered to be stable and requires surgery[13]. Decompression should also be performed for the disc and bone fragments pressing into the canal.

TIMING OF SURGERY

Urgent surgery is indicated in the presence of compression in the canal and progressive neurological deficit. In all other cases, timing of the surgery is still debated[13]. Some authors suggests surgery as soon as the vital functions of the patient become stable whereas some other authors claim that surgery would be appropriate in 4-5 d following the trauma. Some clinical studies reported that decompression within 24 h would be effective for neurological recovery[51]. Early decompression was demonstrated to be effective for the neurological recovery in the animal tests conducted to reverse the neurological deficit caused by SCI[4]. In the controlled study conducted by Delamarter on canines, he stated that surgery within the first hour following the trauma achieved neurological recovery[1]. He also reported that decompression surgery at hour 6 could not achieve neurological recovery. In another study, decompression within 1-3 h was reported to be effective on neurological recovery[52].

IN THE FUTURE

Many tissues in human body have a self-repair property. However, central nervous system does not have such property. Aguayo demonstrated that the CNS axonal regeneration could be achieved by grafts obtained from peripheral nerves.

The response of the immune system to the damage in the spinal cord is different from the response of the immune system to the damages in other tissues. The initial response of the nervous system except in central nervous system is mediated by the macrophages in the blood. Macrophages move to the damaged area and try to keep the toxic elements away. Macrophages activate the lymphocytes. Immune response is primarily mediated by the microglia cells to the spinal cord injuries rather than rather than the macrophages in the blood. The first reaction of the microglia cells is to increase the existing damage. The spinal cord cells cannot respond to the existing damage following the trauma. The main objectives of the strategies that are being developed is to provide the cells which can mediate the immune response to the damaged area[53].

Macrophages are known to transform into antigen-presenting cell-like cells by incubation with the peripheral nerves that have the regeneration capability [bomstein]. MHC-Ⅱ responsible in the delivery of antigens and also the auxiliary molecules (CD80, CD86 and Intercellular Adhesion Molecule 1) were observed to increase in the incubated macrophages. Macrophages release IL-1β IL-6, brain-derived neurotrophic factor.

Macrophages which are co-intubated with peripheric nerve system (PNS) cause increase in the myelin clearance and axon regeneration and continuity when transected optical nerve is injected[54]. In the mice tests, motor recovery was observed in 15 out of 22 mice in their spinal cord transaction models injected by macrophages which were co-intubated with PNS[55]. Neurological recovery was observed in the spinal transaction models of the mice injected with skin-cointubated macrophages.

Contusion model of mouse spinal cord is a frequently used method for the spinal cord damages. It mimics the spinal cord damages in humans[56]. When skin-coincubated macrophages were injected to mice on different days following contusion, motor recovery was observed to be at the highest level on the 8^{th}-9^{th} day. This period corresponds to the peat time when the number of T cells increases. Lower number of cysts was observed in the mice injected with the macrophages within a few months following contusion[57]. Motor recovery as well as much lower number of cyst formation were also reported in mice injected with dendritic cells[53].

Treatment with macrophages is indicated for the human spinal cord damages. Neurological recovery was reported in 5 of 14 patients with complete spinal cord damages in a study in which autoologous skin incubated macrophages were injected within 2 wk following the

spinal cord damage.

Lu *et al*[58] found that U0126 inhibited extracellular signal-regulated kinase (ERK) phosphorylation and the migration of astrocytes across a wound and showed to. Mitogen-activated protein kinase (MAPK)/ERK (MEK) phosphorylation activates ERK. Lin *et al*[59] showed that MEK inhibition reduces glial scar formation and promotes the recovery of sensorimotor function in rats following SCI. Walker *et al*[60] showed the neuroprotective effect of phosphatase and tensin homolog (PTEN)/phosphatidylinositol 3-kinase and mitogen-activated protein kinase signaling cascades and they improved neurological outcome after injury to the spinal cord.

Wu *et al*[61] demonstrated functional restoration of injured spinal cord by self-assembled nanoparticles composed of ferulic acid modified glycol chitosan (FA-GC). And their histological analysis revealed that FA-GC treatment significantly preserved axons and myelin and also reduced cavity volume, astrogliosis, and inflammatory response at the lesion site[61]. In another study it was shown that the selective inhibition of signal transducer and activator of transcription 1 (STAT1) reduces SCI in mice[62]. Wang *et al*[63] demonstrated that curcumin, a natural product inhibited the activation of signal transducer and activator of transcription-3 and NF-kappa B in the injured spinal cord and reduced the astrogliosis in SCI mice.

CONCLUSION

For almost 4000 years since the first introduction of SCI in the written documents of Edwin Papyruses, it is still debated. Progress could not be achieved much except the attempts to surgically eliminate the pathology causing the compression. The studies to correct SCI are ongoing. Use of neuroprotective agents as well as methods to achieve cell regeneration in addition to surgery would contribute to the solution.

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P- Reviewer: Grote S, Tokuhashi Y **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.42

World J Orthop 2015 January 18; 6(1): 42-55
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

Kemal NAS, Professor, *Series Editor*

Current and future medical therapeutic strategies for the functional repair of spinal cord injury

Tevfik Yılmaz, Erkan Kaptanoğlu

Tevfik Yılmaz, Department of Neurosurgery, Faculty of Medicine, Dicle University, Diyarbakır 21280, Turkey
Erkan Kaptanoğlu, Department of Neurosurgery, Faculty of Medicine, Near East University, Nicosia 99138, North Cyprus
Author contributions: Yılmaz T and Kaptanoğlu E contributed equally to this work; Yılmaz T and Kaptanoğlu E designed and performed the research, analyzed the data and wrote the paper.

Correspondence to: Tevfik Yılmaz, Assistant Professor, Department of Neurosurgery, Faculty of Medicine, Dicle University, the East of Diyarbakır, Diyarbakır 21280, Turkey. kartaltevfik@hotmail.com
Telephone: +90-412-2488001
Fax: +90-412-2488440
Received: October 24, 2013
Peer-review started: October 25, 2013
First decision: December 13, 2013
Revised: February 15, 2014
Accepted: April 25, 2014
Article in press: April 29, 2014
Published online: January 18, 2015

Abstract

Spinal cord injury (SCI) leads to social and psychological problems in patients and requires costly treatment and care. In recent years, various pharmacological agents have been tested for acute SCI. Large scale, prospective, randomized, controlled clinical trials have failed to demonstrate marked neurological benefit in contrast to their success in the laboratory. Today, the most important problem is ineffectiveness of nonsurgical treatment choices in human SCI that showed neuroprotective effects in animal studies. Recently, attempted cellular therapy and transplantations are promising. A better understanding of the pathophysiology of SCI started in the early 1980s. Research had been looking at neuroprotection in the 1980s and the first half of 1990s and regeneration studies started in the second half of the 1990s. A number of studies on surgical timing suggest that early surgical intervention is safe and feasible, can improve clinical and neurological outcomes and reduce health care costs, and minimize the secondary damage caused by compression of the spinal cord after trauma. This article reviews current evidence for early surgical decompression and nonsurgical treatment options, including pharmacological and cellular therapy, as the treatment choices for SCI.

Key words: Spinal cord injury; Treatment; Pharmacological treatment; Trauma; Cellular treatment; Management

Core tip: In recent years, various pharmacological agents have been tested for acute spinal cord injury (SCI). Today, the most important problem is ineffectiveness of nonsurgical treatment choices in human SCI that showed neuroprotective effects in animal studies. A number of studies on surgical timing suggest that early surgical intervention is safe and feasible, can improve clinical and neurological outcomes and reduce health care costs. This article reviews current evidence for early surgical decompression and nonsurgical treatment options, including pharmacological and cellular therapy, as the treatment choices for SCI.

Yılmaz T, Kaptanoğlu E. Current and future medical therapeutic strategies for the functional repair of spinal cord injury. *World J Orthop* 2015; 6(1): 42-55 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/42.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.42

INTRODUCTION

Currently, the management of patients with acute spinal cord injury (SCI) includes pharmacological agents, surgical intervention and cellular therapies. There is still no commonly accepted pharmacological agent used in the treatment of SCI but some clinical studies have been carried out to reveal an effective agent. The timing of surgery is another controversial issue. However, studies about cellular therapies give hope for the future. Various clinical studies using pharmacological agents, cellular therapies and surgical intervention for SCI are discussed and summarized in this review.

EPIDEMIOLOGY

The incidence of acute SCI has been reported as 15 to 40 in a million in the world[1]. The common causes of SCI are motor vehicle accidents, sport injuries, work-related accidents, assaults and falls[2]. It is more common in young men. The incidence of traumatic SCI was reported as 12.7 in a million in a study conducted in Turkey in 1992. The most common causes of these injuries are motor vehicle accidents (48.8%), falls (36.5%), cutting injuries (3.3%), gunshot wounds (1.9%) and jumping into the water (1.2%). Male/female ratio has been reported as 2.5:1[3]. The most common causes of non-traumatic SCIs are spinal vascular diseases (25%), tumors (25%), inflammatory diseases (20%) and spinal stenosis (19%)[4].

PATHOPHYSIOLOGY

The concept of a two-step mechanism for SCI was introduced in the early 1900s after progressive damage was shown in spinal cord injured animals by Allen[5]. It has been reported that the first step is primary mechanical damage that occurs within minutes as a result of mechanical SCI. The second step is the secondary injury triggered by the primary damage, resulting in microvascular damage, edema, demyelination, ischemia, excitotoxicity, electrolyte imbalances, free radical production, inflammation and late apoptotic cell death where many more factors are involved[6,7] (Table 1). The pathology behind these mechanisms includes ischemia arising from degenerative spinal cord perfusion and a cellular energy deficiency[8,9]. For this reason, in order to minimize the damage caused by spinal cord injuries, oxygen should be provided and blood pressure should be kept under control. Following an acute SCI, vascular injuries lead to a number of serious changes in the spinal cord which in turn result in a progressive spinal cord ischemia accompanied by a perfusion anomaly, ultimately causing both hemorrhagic and ischemic injuries[10,11]. The area around irreversible injury is the ischemic penumbra. If the ischemia exceeds beyond a critical level, the infarct area expands and irreversible injury occurs. Function can be restored in the case of regenerated blood flow before the beginning of injury[12] (Figure 1). SCIs may also lead to a petechial hemorrhage in the spinal cord following rupture of postcapillary venules or sulcal arteries. This rupture may result from a mechanical break triggered by the direct effect of the trauma or from an intravascular coagulation which is caused by venous stasis or distention[8,13].

In spinal cord injuries, excessive free radicals lead to insufficient antioxidant systems as well as cell death[14]. These antioxidants are general occurrences in normal cells and their function is to keep harmful entities under control. However, the number of free radicals outdoes the number of these oxidants in severe pathological situations such as SCI. The free radicals may react to any cell constituent but lipids are the most delicate among the constituents. The destruction of the cell membrane that contains high amounts of polyunsaturated fatty acids is the very first step in the neuronal damage caused by free radicals[15]. Kaptanoglu *et al*[16-18] reported that melatonin, erythropoietin, thiopental and propofol can inhibit lipid peroxidation following SCI. SCI may also lead to the release of opioids as well as neurotransmitters. In turn, these opioids may obstruct the course of microcirculation by activating kappa opioid receptors. Therefore, studies focusing on the opioid receptors that have a selective effect on kappa receptors have yielded more successful results[8,19]. Following SCI, the lesions may contain a large amount of glutamate. In the early period, the glutamate receptor activation may increase intracellular sodium which in turn may lead to cytotoxic edema, intracellular acidosis and lysis[10]. Glutamate neurotoxicity triggers a chain of events which results in aggravated neuronal death and the development of reactive oxygen and nitrogen products[10].

Neuronal protection is highly important since the spinal neurons cannot achieve regeneration[20]. Apoptotic cell death is likely to happen in any cellular component of the spinal cord (neurons, astrocytes, oligodendrocytes and microglia). In conclusion, understanding the injuries secondary to neuronal death in SCIs remains the most vital issue for the implementation of advanced treatment methods[21] (Figure 2).

TIMING OF SURGERY

Eventually, the ideal management of acute SCI is a combination of pharmacological therapy, early surgery, aggressive volume resuscitation and blood pressure elevation to maximize spinal cord perfusion, early rehabilitation and cellular therapies. A number of investigations were done before the 1970s to both clarify the secondary mechanisms of SCI and find evidence that early surgical decompression affords a better neurological outcome. However, the timing for surgery in spinal cord injuries is not clear yet in terms of neuronal recovery. Partial reversibility of complete cord injury is reported in a limited time interval[22]. A number of pre-clinical studies[1,23-25] suggest no benefit of early surgical intervention to achieve spinal cord decompression on outcomes; however, several others[13,26-28] indicate that longer spinal cord compression before surgery is associated with detrimental outcomes in animal SCI

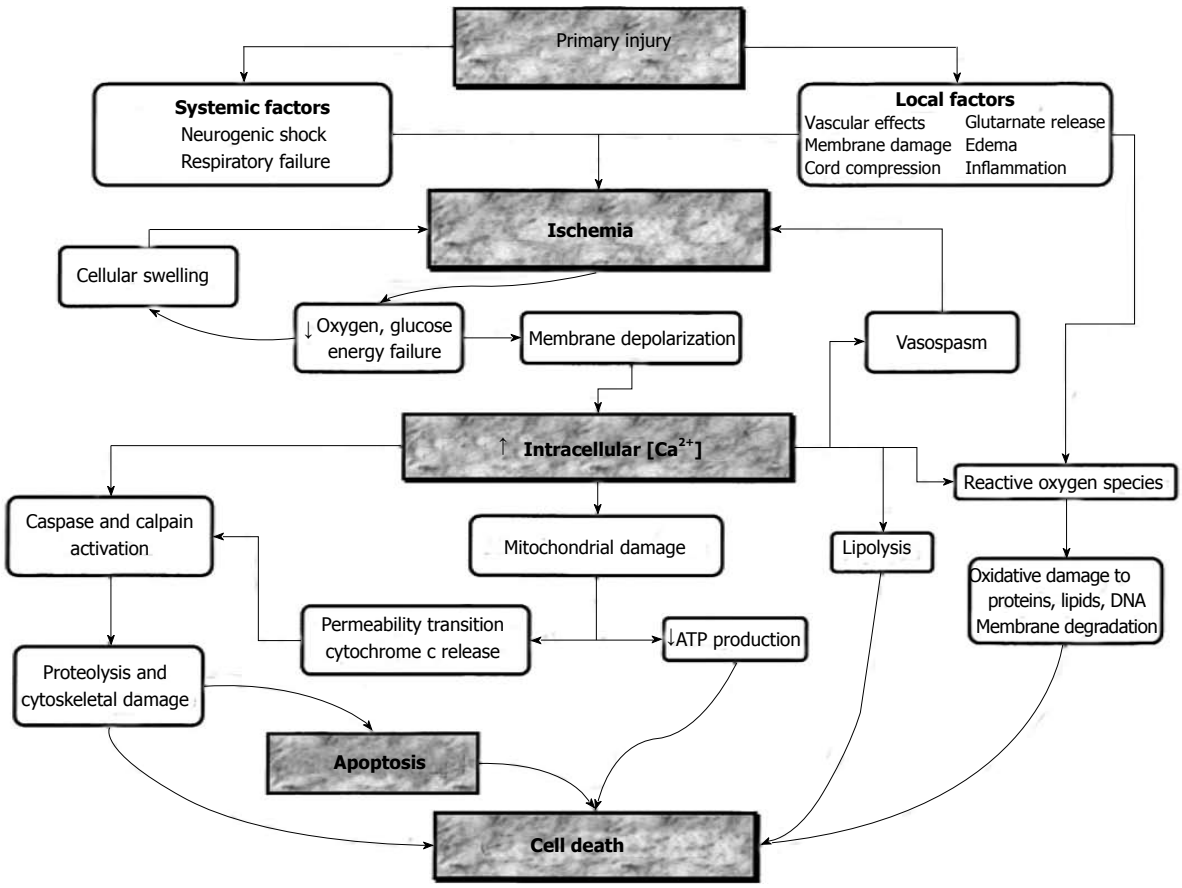

Figure 1 Major mechanisms of cell death are ischemia, intracellular calcium deposition, apoptosis. Pharmacological agents may intervene in these mechanisms at different stages shown in boxes (From Dumont RJ).

models. Animal models suggest that early decompression directly correlates with improved neurological outcome. Dimar *et al*[29] used a rat model with a different time range of extradural compression up to 72 h and demonstrated that animals with shorter compression times showed better neurological recovery. There are no class I clinical trials to guide the timing of surgery. Several class Ⅱ and class Ⅲ studies have been carried out; they demonstrate that early surgery (decompression/reconstruction) is safe and should be strongly considered in patients without life-threatening polytrauma and without major medical co-morbidities. Urgent surgical decompression should be carried out in patients with early neurological deterioration. It is important to avoid intra-operative hypotension to minimize the intraoperative risks with early intervention[30]. Many surgeons advocate early surgery for maximum restoration of neural tissues and rehabilitation and early mobilization of the spinal column. A number of authors defined appropriate early surgery in a range from 8 to 72 h[31-33]. Some authors also report that early surgery results in reduced medical complications and length of stay and cost[32-35].

In a systematic review, Furlan *et al*[36] evaluated 22 clinical studies examining either the feasibility and safety or efficacy of early surgical intervention to stabilize and align the spine and for decompression of the spinal cord. Some of these studies indicated that patients who undergo early surgical decompression can have similar outcomes to patients who received a delayed decompressive operation. However, there is evidence to suggest that early surgical intervention is safe and feasible and that it can improve clinical and neurological outcomes and reduce health care costs. In another systematic review of the current evidence for surgical decompression as a treatment for SCI, Cadotte *et al*[30] demonstrated emerging evidence and a growing consensus among surgeons who support early surgical intervention to help minimize the secondary damage caused by compression of the spinal cord after trauma. In a randomized controlled study by Cengiz *et al*[37], postoperative ASIA score (Table 2) significantly increased in the early surgery group and late surgery group compared to the pre-operative ASIA score. In addition to this finding, the post-operative ASIA score of the early surgery group was significantly better than the late surgery group. Patients in the early surgery group showed a 83.3% improvement in ASIA score, whereas the ASIA score of 26.6% patients in the late surgery group improved. Cadotte *et al*[30] suggested that early surgery is safe and strongly recommended in patients without life-threatening polytrauma and without major medical co-morbidities, according to findings in class Ⅱ and class Ⅲ studies. Urgent surgical decompression should be carried out in patients with deteriorating neurology.

In addition, another level-2b evidence study suggested

Table 1 Secondary ınjury mechanisms involved in the pathophysiology of spinal cord injury

Systemic effects
Heart rate - brief increase then prolonged bradycardia
Blood pressure - brief hypertension then prolonged hypotension
Peripheral resistance - decreased
Cardiac output - decreased
Local vascular damage of the cord microcirculation
Mechanical disruption of capillaries and venules
Hemorrhage - especially gray matter
Loss of microcirculation - mechanical, thrombosis, vasospasm
Biomechanical changes
Excitotoxicity - glutamate
Neurotransmitter accumulation
Catecholamines - noradrenaline, dopamine
Arachidonic acid release
Free radical production
Eicosanoid production
Prostaglandins
Lipid peroxidation
Endogenous opioids
Cytokines
Electrolyte shifts
Increased intracellular calcium
Increased intracellular potassium
Increased intracellular sodium
Inflammatory response
Free radical generation
Macrophages
Axonal breakdown, removal of myelin debris
Release of cytokines
Glial cell activation
Cytotoxic effects on oligodendrocytes
Wallerian degeneration
Edema
Apoptosis
Loss of energy Metabolism
Decreased ATP production

SCI: Spinal cord injury.

that compared to surgical intervention from 72 h to 5 d after thoracolumbar SCI, stabilization of spinal and cord surgical decompression in less than 8 h would result in better neurological outcome, shorter duration of hospitalization, shorter duration of stay in the intensive care unit and lower frequency of secondary complications[37].

No complications were seen in the early surgery group, whereas three cases of respiratory failure and one case of sepsis were seen in the late surgery group[37]. It was reported that early surgery results in reduced LOS, less secondary complications, early mobilization and transfer to rehabilitation and should be considered in all SCI patients.

Finally, the authors declare that as there is strong pre-clinical evidence for biological benefits of early surgical decompression in animal SCI models, surgical decompression of the injured spinal cord should be performed within 24 h when medically feasible. The optimal timing of surgical decompression in patients with a central cord injury remains unclear and there are clinical, neurological and functional benefits of early spinal cord decompression[36].

PHARMACOLOGICAL TREATMENT

A lot of pharmacological treatment methods have been studied by considering the pathophysiological mechanisms in SCI (Table 3). These methods are now mentioned.

Steroids

Corticosteroids have been used to reduce spinal cord edema in acute SCI for over 30 years due to their anti-inflammatory features[38]. Although the exact mechanisms of the neuroprotective effects of corticosteroids are not completely understood, it has been suggested that these include inhibition of lipid peroxidation, modulation of inflammatory and immune responses with inflammatory cytokines, the healing of the vascular perfusion and prevention of calcium entering into the cell[39,40].

Methylprednisolone

Methylprednisolone is a synthetic glucocorticoid and has been used in SCI and brain edema for a long time. Today, the widespread use of methylprednisolone results from three large-scale, prospective, randomized, double-blind, multi-center clinical studies called the National Acute Spinal Cord Injury Studies (NASCIS) Ⅰ, Ⅱ and Ⅲ. In NASCIS Ⅰ, the effects of ten day doses of 100 mg or 1000 mg of methylprednisolone started in patients with SCI within 48 h were evaluated[41]. No motor and sensory differences were found between the two regimes. As a result of animal experiments, it has been suggested that a 1000 mg dose is far below the required dose for effective neuroprotection and that after the initial dose of 30 to 40 mg/kg it would be more appropriate to continue with an intravenous maintenance dose[39].

Therefore, in the next NASCIS Ⅱ trial, after an initial bolus of methylprednisolone 30 mg/kg, 5.4 mg/kg infusion per hour for 23 h was given[42]. All 487 patients in the study in the first 12 h after injury were randomized into one of the groups of methylprednisolone, naloxone or placebo. Statistically, significant sensory and motor improvements were reported when methylprednisolone was given in the first 8 h after injury in both full and partial SCI. NASCIS Ⅱ verified that, besides being the first clinical study showing that methylprednisolone is an effective pharmacological agent for the treatment of SCI, it also provided the widespread use of it and confirmed its relationship with secondary damage and its effective pharmacological strength. Then, NASCIS Ⅲ was performed to evaluate the efficacy of tirilazad mesylate as well as to compare methylprednisolone treatment in different time windows[43]. Because of the antioxidant properties, several complications of steroid use were intended to be avoided. Thirty milligrams per kilogram of methylprednisolone in the form of a bolus was given to all 499 patients in the study after the first 8 h after trauma and then either a 24 or 48 h infusion of methylprednisolone or 48 h of tirilazad mesylate were administered randomly. Of all treatment actions, the motor and sensory recovery was found to be similar in the first 3 h after trauma. In these patients, a 24 h

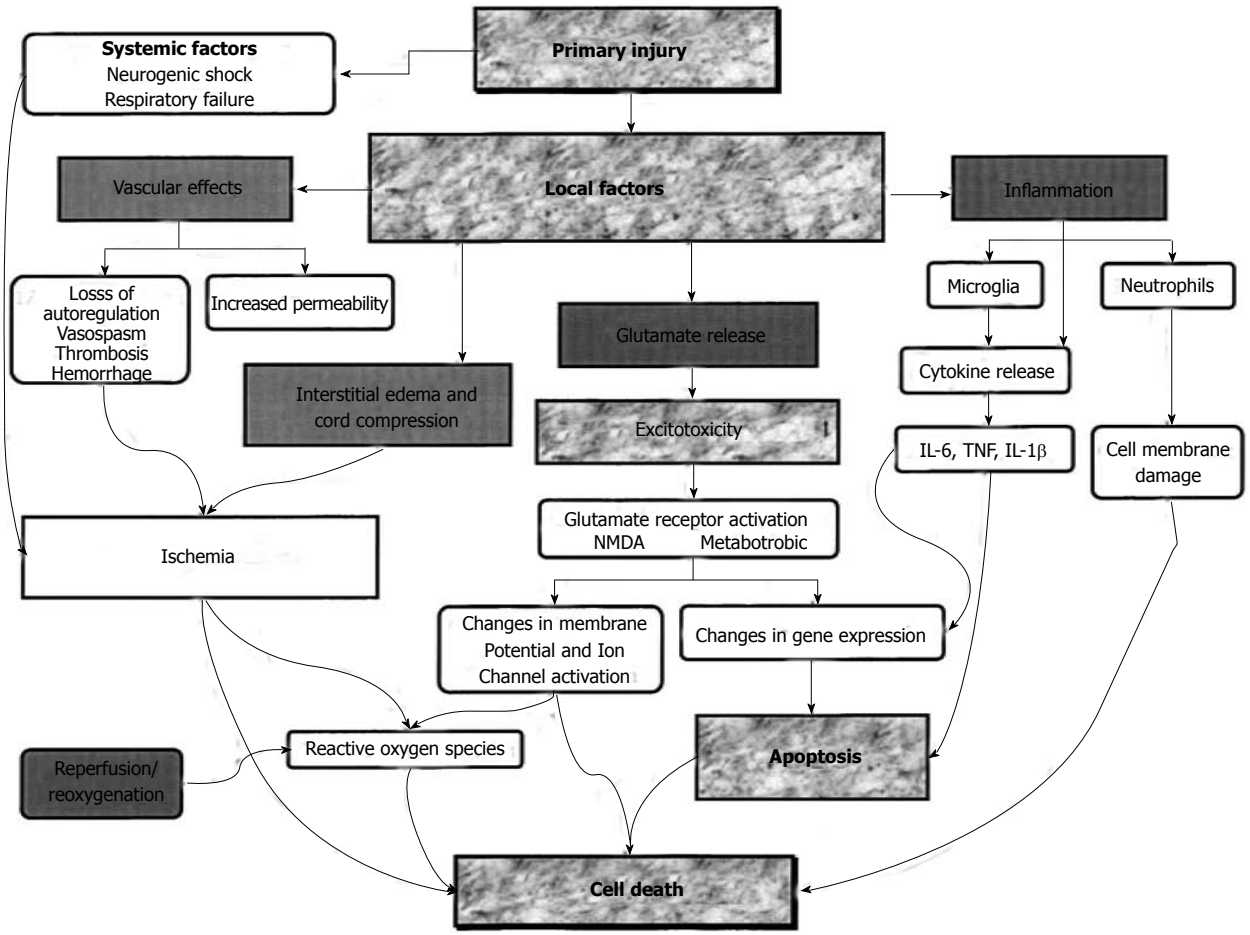

Figure 2 Role of vascular effects, inflammation, interstitial edema, glutamate release, cord compression and reperfusion which underlie the spinal cord injury are shown. Pharmacological agents may be useful at foci which are demonstrated in boxes (From Dumont RJ).

infusion of methylprednisolone has been suggested to be sufficient. However, when methylprednisolone is started between 3 and 8 h, prolonging the infusion to 48 h has been proposed as more beneficial. Improvement in motor function was statistically significant at 6 mo and even after 1 year in the MP group compared with the controls (17.2 and 12.0 points improvement respectively, $P = 0.030$)[42].

Although NASCIS Ⅱ and Ⅲ have led to the establishment of clinical standard application of methylprednisolone in acute SCI in North America, there has been a lot of criticism regarding the results and comments of these studies recently. This situation has led to some centers giving up the application. Many researchers have published their in-depth analysis of NASCIS Ⅱ and Ⅲ trials[44,45]. It has been reported that especially the application of NASCIS Ⅲ in 48 h had minimal effectiveness in neurological healing and increased wound infection rates, pulmonary embolism, severe pneumonia, sepsis and that it even increased secondary deaths due to respiratory complications with the use of steroids. The argument about whether to use this agent in acute SCI still continues[12].

Ganglioside GM-1

Gangliosides are glycosphingolipids that are in the outer lipid layer of the cell membrane and contain sialic acid. Potential effects in neuroprotective and neuronal function restoration were found in experimental studies[46]. By increasing cell regeneration in tissue, they reduce the neurotoxicity of the excitatory amino acids. Promising clinical results with GM1 were obtained in a single center prospective randomized clinical trial with 37 patients with SCI in 1991[47]. In the subsequent experimental studies of SCI with systemic administration of GM1, neuroprotective effects such as neurite outgrowth, plasticity strengthening, prevention of apoptosis and inhibition of excitotoxicity were obtained[47,48]. These positive results led to the realization of a multicenter randomized clinical trial published in 2001[49]. In this clinical trial between 1992 and 1997, over 750 patients were randomly divided into treatment arms, such as placebo, low-dose and high-dose GM1 ganglioside. In the 26th week, at least a two-degree increase was determined in the motor/sensory function of the patients who experienced a significant improvement in a modified Benzel classification with respect to the American Spinal Injury Association (ASIA) scores. Sensory and motor scores in patients treated with GM1 ganglioside and in many parameters including bowel and bladder function in partially paralyzed patients showed an improvement compared to placebo. However, there was no effect on the complete patients but the

Table 2 American spinal ınjury association ımpairment scale

A = Complete: No motor or sensory function is preserved in the sacral segments
B = Incomplete: Sensory but not motor function is preserved below the neurological level and includes sacral segments
C = Incomplete: Motor function preserved below the neurological level; more than half the key muscles below the neurological level have a muscle grade less than 3
D = Incomplete: Motor function preserved below the neurological level; at least half the key muscles below the neurological level have a muscle grade of 3 or more
E = Normal: Motor and sensory function

Table 3 Pharmacotherapy of acute spinal cord injury and mechanism(s) of action

Methylprednisolone
Inhibition of lipid peroxidation/antioxidative/anti-inflammatory Properties decrease ischemia, support energy metabolism, inhibit neurofilament degradation, decrease intracellular Ca, decrease PG F/TxA, increase spinal neuron excitability, decrease cord edema
Ganglioside GM-1
Stimulate neurite regrowth/regeneration
Opioid receptor antagonists
Antagonize the increase in endogenous opioid levels after SCI (opioid receptor activation can contribute to excitotoxicity)
TRH and its analogs
Antagonize endogenous opioids, platelet-activating factor, peptido-leukotrienes and excitatory amino acids
Nimodipine
Decrease intracellular Ca^{2+} accumulation, attenuate vasospasm
Gacyclidine (GK11)
Antagonism of glutamate receptors
Magnesium
Replace Mg^{2+} depletion that is common after SCI, diminish intracellular Ca^{2+} accumulation, block N-methyl-D-aspartate receptor ion channel, modulate binding of endogenous opioids
Hypothermia
Reduce extracellular glutamate, vasogenic edema, apoptosis, neutrophil and macrophage invasion and activation, and oxidative stress
Minocycline
Inhibition of microglial activation, inhibition of cytochrome c release
Erythropoietin
Reduced apoptosis and lipid peroxidation
Estrogen
Not clearly known
Progesterone
Reduce the production of inflammatory cytokines
Cyclooxygenase inhibitors
Prevents/antagonizes decreased blood flow/platelet aggregation from production of arachidonic acid metabolites
Riluzole
Blockade of voltage-sensitive sodium channels and antagonism of presynaptic calcium-dependent glutamate release
Atorvastatin
Prevents neuronal and oligodendrocytic apoptosis
Antioxidants
Antagonize deleterious effects of free radicals (lipid eroxidation, reperfusion injury, *etc.*)

PG F: Prostaglandin F; SCI: Spinal cord injury.

results of the study were promising for the incomplete patients.

Opioid receptor antagonists

After SCI, dynorphin A, an endogenous opioid, is allowed to flow and neurotoxic effects occur. Moreover, it decreases spinal cord blood flow with non-opioid mechanisms[50]. Naloxone is a nonspecific opiate receptor antagonist. In the experimental animal models of SCI, the application of naloxone leads to functional and electrophysiological improvement. Moreover, it reverses the spinal shock and improves the blood flow to the spinal cord[51,52]. It was extensively studied in the early 1980s and in the 1980s the opioid antagonist naloxone was examined in a Phase I SCI trial in humans[53-55]. However, beneficial effects of naloxone that were thought to be due to antagonization of the increase of the endogenous opiates observed after SCI were not confirmed. In NASCIS Ⅱ, the first results obtained from the studies related to naloxone, one of three treatment arms that has not shown any significant neuroprotective benefit over placebo[41].

Thyrotropin releasing hormone and its analogs

Secondary injury mediators such as endogenous opioids, excitotoxic amino acids, leukotrienes and platelet activating factor have been shown to be antagonized by TRH. Functional improvement in rats after experimental SCI by TRH has been shown[56]. The only clinical trial which was ever performed with TRH in acute SCI was published in 1995. Pitts *et al*[57] showed that TRH is effective in increasing the blood flow, reducing lipid degradation, in ionic hemostasis and improving neurological function.

Nimodipine

It has been reported that calcium channel blockers improve the post-traumatic spinal cord blood flow with the regulation of microvasculature. Nimodipine has been shown to increase the blood flow of the spinal cord in experimental SCI[58]. In other animal experiments, however, no significant neurological improvement was observed with nimodipine treatment after spinal cord trauma or ischemia[59]. The SCI trial for humans was carried out in France in 1996[60]. The trial involved 100 patients in 4 treatment arms: nimodipine, MPSS (NASCIS Ⅱ protocol), both agents and placebo. Although it is possible that the study was weak in showing a therapeutic effect, benefit over placebo was not shown in any treatment group. Because of the potential that systemic hypotension develops in impaired spinal cord blood flow autoregulation conditions, it may become detrimental so their usage causes concerns.

Gacyclidine (GK11)

Glutamate is the main excitatory amino acid in the central nervous system and plays an important role in the secondary SCI. Like gacyclidine (GK11), NMDA also has shown that receptor antagonists have significant neuroprotective effects after SCI in animal studies[61]. With the distribution of glutamate into each side of the central nervous system in humans, significant adverse effects of

the systematic treatment may be seen. In previous studies, glutamate receptor antagonists had significant cognitive side effects, including agitation, sedation, hallucinations and memory deficits, even with competitive antagonists such as Selfotel[62]. Therefore, the development of clinical treatment of NMDA antagonists has become difficult. Besides considerably better tolerability than other N-methyl-D-aspartate antagonists, gacyclidine has improved function, histology and electrophysiology in a rat model[61,63].

Magnesium

Magnesium is a well known neuroprotective agent and plays a key role in free radical and glutamate damage in the vascular structure after SCI. Magnesium provides vasoprotection by reducing free radical generation in neural structures. It also stimulates the release of endothelial prostacyclin and provides dilation of the blood vessels supplying the spinal cord. It is believed that magnesium decreases lipid peroxidation by-products with the indirect effect arising from glutamate antagonism[64]. In a study conducted to demonstrate the vascular protection after SCI, Kaptanoglu *et al*[65] showed that magnesium reduced edema and vascular permeability in SCI ultrastructurally[65].

Hypothermia

Hypothermia has a neuroprotective effect with the reduction of brain edema and intracellular calcium, the increased release of gama aminobütirik asit (GABA) and the inhibition of glutamate release[66,67]. Additionally, moderate hypothermia has been reported to be effective in reducing apoptotic neuronal death[68]. Systemic cooling methods used to cool the spinal cord are intravenous fluid infusions and the local cooling is with a cold saline infusion through epidural or intrathecal catheters. To cool a long cord segment is technically difficult[69]. Clinical application of hypothermia in patients with SCI cannot be recommended to be used in neuroprotection because of complications, such as hypotension, bradycardia and infection, unless it becomes safe and applicable[69,70].

Minocycline

It has been shown that minocycline inhibits excitotoxicity, reduces apoptosis with caspase-1 and has neuroprotective effects in Parkinson's disease with possible inhibition of microglial activation and autoimmune encephalomyelitis, amyotrophic lateral sclerosis, ischemic brain injury models in adults and newborns[71-73]. After acute SCI, minocycline has been reported to reduce the size of the lesion. It has also been shown that minocycline can pass the blood-brain barrier easily and effectively reduces functional deficits and secondary spinal tissue loss in mitochondrial cytochrome c in experimental SCI[74].

Cethrin

This agent facilitated axonal growth and promoted functional recovery in a mouse model. The researchers observed an early neurological improvement and reduced apoptosis rates[75].

Erythropoietin

There have been many comprehensive studies for erythropoietin (EPO) in acute SCI. Erythropoietin and its derivatives are the endogenous cytokine mediators in the central nervous system with tissue protective effects. Kaptanoglu *et al*[17] showed that erythropoietin inhibits lipid peroxidation after SCI and provides ultrastructural neuroprotection. A dramatic decrease was shown in the volume of cavitation after rhEPO therapy according to the results of histological examination 7 d after spinal contusion. They contribute to inhibition of erythropoietin apoptosis, inflammation reduction, excitability modulation and proliferation and modulation of neuronal stem cells[76-78]. Improved white and grey matter sparing, reduced apoptosis and lipid peroxidation, reduced ERK phosphorylation, and decreased inflammatory cytokine release and neutrophil invasion were involved in non-behavioral results. The efficacy of EPO in acute SCI is not certain.

Estrogen

Laboratory evidence supports that female sex hormones may play a role in hormone-dependent neuroprotection. Estrogen-dependent neuroprotection takes place with increased expression of the antiapoptotic factor bcl-2 and by the activation of protein kinase pathways. Non-behavioral results involve reduced overall secondary tissue damage, reduced MPO activity, microglial/macrophage accumulation and reduced apoptosis.

Progesterone

Progesterone receptors are spread widely in the central nervous system. The effect of progesterone is shown by reducing the production of inflammatory cytokines increasing excitotoxicity in secondary neuronal injury. In the SCI model, it has been shown that progesterone can reduce the production of oxidants and free radicals and can provide stability of neurotrophins in the spinal cord[70]. More recently, it has also been shown that progesterone modifies the traditional neurotransmitter systems such as inhibitory GABA and excitatory amino acids in SSS[79]. Progesterone treatment was reported to be able to alter gene and protein expression, cell morphology and receptor and neurotransmitter expression in the injured spinal cord.

Cyclooxygenase inhibitors

These inflammatory prostaglandins have an important role in secondary injury. It has been shown that indomethacin reduces tissue damage and edema in SCI. Meclofenamate and ibuprofen are two non-steroidal anti-inflammatory agents used widely for spinal blood flow after SCI in cats[80]. In this study, the combination of a thromboxane inhibitor with a prostacyclin analogue was found to be similarly effective. It was observed that COX-2 expression increased after the damage of contusions in the SCI of a rat. With SC-236, a COX-2 inhibitor, neuroprotection was provided after SCI in rabbits and improvement was seen in behavioral deficits[81]. Although the application of COX-1

Table 4 Cellular transplantation therapies spinal cord injury

Schwann cells	Secrete growth factors, reestablish microenvironment
Olfactory ensheathing cells	Promoting axonal regeneration
Bone marrow cells	Produce neuroprotective cytokines
Stimulated macrophages	Removal of myelin debris, release of cytokines
Oligodendrocyte progenitor cells	Achieve remyelination

and COX-2 inhibitions in humans in SCI has not been reported, the widespread use of these in people has been disposed of because of many safety and pharmacokinetic issues.

Riluzole

Riluzole is a sodium channel blocker approved by the Food and Drug Administration for amyotrophic lateral sclerosis. It has been shown that riluzole has a neuroprotective effect and reduces the damage in gray and white matter after clip compression injury of spinal cord in a rat model. It also improves locomotor functions. Therefore, many pharmacokinetic and toxicity studies were carried out in humans for riluzole. There are no reports that dose response has an effect on the thoracic contusion SCI models. Kitzman *et al*[82] showed that signs of tail spasticity decreased with both 8 and 10 mg/kg doses but systemic side effects (lethargy, locomotor ataxia) were attributed to the higher dose in the 2009. It was demonstrated that there was a therapeutic neuroprotective efficacy with a postponement in intervention of 15 min[83] and 30 min[84].

Atorvastatin

Atorvastatin treatment provides protection against reactive gliosis, trauma-induced tissue necrosis and demyelination. It also prevents neuronal and oligodendrocytic apoptosis by reducing Inducible nitric oxide synthase, tumor necrosis factor-α and interleukin1-β expression from inflammatory cytokines[85].

Antioxidants

Free radicals increase significantly after spinal cord trauma in animals. Despite their different mechanisms, ascorbic acid and hypothermia with a synergistic effect reduce the production of free radicals and associated damage[21]. Melatonin[18], EPC-K1[86], vitamin E and selenium[6] free radical are scavenger agents and have been shown to be beneficial in SCI. Studies on spinal cord injuries which are related to nitric oxide synthase inhibitors[87], polyethylene glycol[88], lipopolysaccharide[89], anti-CD 11d antibodies[90], inosine[91] and pioglitazone[92] have been performed.

CELLULAR TRANSPLANTATION THERAPIES

As a repair strategy for SCI, the neural transplantation procedure has been studied over the past several decades in many animal models. The rationale for cell transplantation treatments are to provide the injured tissue with growth promoting factors, cell replacements, structural elements and myelinating units[93]. The aim of cell therapies is to provide functional recovery of deficit by an axonal regeneration and restoration (Table 4). Reconstructive and regenerative experimental cellular strategies containing embryonic or adult stem cells or tissue[94,95], genetically modified fibroblasts[96], Schwann cells (SCs)[97,98], olfactory ensheathing cells[93,99], bone marrow stromal cells[100,101], neural stem cells[102] and activated macrophages[103,104] have been reported with varying degrees of recovery in different models of SCI.

SCs

The Schwann cell is one of the most widely used cell types for repair of the spinal cord. In experimental models of SCI, SCs are the myelin-forming cells of the peripheral nervous system and have been shown not only to myelinate (remyelinate) axons after transplantation into the injured spinal cord, but also to form a permissive substrate for regenerating axons, as reported in many studies[98,105,106]. Schwann cell transplantation in a wide variety of SCI models, such as photochemical[93], transection[97] and subacute contusion[107], has resulted in improvements in locomotion as well as neurobiological indices of recovery. Oudega *et al*[97] demonstrated that SCs play a key role in peripheral nerve regeneration and also lead to release of various growth factors, creating a growth permissive feature for axonal regeneration. In addition, SCs can produce axon growth promoting substrates such as fibronectin and laminin[97]. On the other hand, SCs are able to myelinate both intact and regenerating central axons[108]. For this reason, it can be said that SC is one of the best cell types for cell transplant therapy SCI. Pre-clinical experiments regarding the survival and efficacy of human SCs in contusion models of SCI are needed.

Olfactory ensheathing cells

The olfactory mucosa contains multipotent progenitor cells capable of differentiating into both neural and non-neural cells[109]. Olfactory ensheathing cells (OECs) are capable of promoting axonal regeneration and remyelination after injury. As a possible source for autologous cells, the olfactory mucosa is capable of lifelong regeneration and is readily accessible with minimally invasive techniques. Adult neural stem progenitor cells from the subventricular zone of the brain and the spinal cord of rodents contain neuron precursors, oligodendrocytes and astroglia, some stem-like cells. Transplanting OECs into damaged spinal cord promotes axonal remyelination and regeneration, facilitating recovery of the SCI[110-112]. On the other hand, clinical studies showed that OEC transplantation is a safe method[113] with improved sensory-motor function of injured spinal cord[114,115].

Bone marrow cells

In recent years, some studies showed that bone marrow cells (BMCs) can be differentiated into glial cells or mature

Table 5 Timing of surgery and nonsurgical treatment options of spinal cord injury including pharmacological and cellular therapy

Timing of surgery
Early surgical intervention is safe and feasible which can improve clinical and neurological outcomes and reduce health care costs
Early surgical intervention helps minimize the secondary damage caused by compression of the spinal cord after trauma
Pharmacological and cellular therapy
There is still no accepted pharmacological treatment protocol in SCI
Methylprednisolone is the accepted agent used in SCI, however, some criticism has been reported by some authors. It might be used in young patients without accompanying diseases such as diabetes mellitus
Cellular treatment studies are continuing

SCI: Spinal cord injury.

neurons under special experimental procedures[101,116]. BMCs grafting on SCI injury models have been studied and it has been observed that the transplanted BMCs improve neurological deficits by generating myelin producing cells or neural cells[117,118]. Furthermore, BMCs can produce neuroprotective cytokines, rescuing the neurons with impending cell death in case of injury[119,120]. Also, several clinical trials have explored the hypothesis that cell transplantation may enhance the recovery of neurological functions after SCI.

Stimulated macrophages

After an injury, macrophages and their associated cytokines invade the impaired tissue[121,122]. In the nervous system, macrophage-derived cytokines can induce regeneration-associated components such as nerve growth factor[123] and cell adhesion molecules. Stimulated macrophage implantation into transected rat spinal cord showed promoted tissue repair, including recovery of motor function, observed behaviorally and electrophysiologically[103]. On the other hand, in a study on sciatic nerve injury, it has been demonstrated that the blockage of macrophage invasion led to impairment of regeneration[104].

Oligodendrocyte progenitor cells

The oligodendrocyte progenitor cells (OPCs) and oligodendrocytes derived from OPC show great promise in CNS repair. They produce myelin in the CNS and originate from the neuroepithelial cells[124]. Whether OPCs could support the regeneration of injured axons is not yet clear but the promise of using OPCs in cell therapies lies in their ability to produce myelin on demyelinated axons. Demyelination due to oligodendrocyte death occurs in both contusive animal models of SCI[125] and humans[126]. After CNS disorders and traumas, demyelination of axons contributes to functional and physiological deficits. In addition, apoptosis plays a main role in oligodendrocyte death[127,128]. The remyelination of regenerated axons and demyelinated intact axons is a substantial repair strategy to accelerate functional recovery.

The high quality of the trials and the intense scrutiny of their design and interpretation of outcome measures play a critical role in shaping the next generation of trials. We propose the following recommendations for researchers for future trials: (1) statistical power needed for clinical trials; (2) injury severity and timing of experimental therapy administration; (3) appropriate clinical trial outcome measures; and (4) prospective clinical trial design. These recommendations will be helpful for the SCI community in its further clinical evaluation of novel therapies[129].

Measuring the success of the Walking Index for SCI might be used, which was revised recently and is an international attempt to make a complex, valid and reliable device for assessing walking independent of burden of care[130]. Later, a multinational collaboration, led by the Toronto SCI team and several centers in Canada, the United States and Europe, developed a novel outcome measure to quantitatively assess hand and upper extremity function in tetraplegic patients (the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) outcome measure). There are two important parameters in the development of new outcome measures, one which establishes psychometric properties and the other that provides insights into functional and neurological impairment[131].

CONCLUSION

A number of studies suggest early surgical intervention. Recovery of loss of neurological function after acute SCI is one of the most important topics of the neurological sciences (Table 5). For many years, many researchers have tried to find a method to improve neurological function in acute SCI but regeneration of the spinal cord has not yet been demonstrated in humans. Although there are major developments in the pharmacological and surgical approaches, SCI continues to be a very complex medical problem.

ACKNOWLEDGMENTS

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P- Reviewer: Canavese F, Erkan S, Sewell M **S- Editor**: Ma YJ
L- Editor: Roemmele A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.56

World J Orthop 2015 January 18; 6(1): 56-61
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (2): Arthroscopic

Subtalar arthroscopy: When, why and how

Tun Hing Lui, Sheung Chi Tong

Tun Hing Lui, Department of Orthopaedics and Traumatology, North District Hospital, Hong Kong, China
Sheung Chi Tong, Department of Orthopaedics and Traumatology, United Christian Hospital, Hong Kong, China
Author contributions: Lui TH and Tong SC solely contributed to this paper.

Correspondence to: Tun Hing Lui, MBBS (HK), FRCS (Edin), FHKAM, FHKCOS, Consultant, Department of Orthopaedics and Traumatology, North District Hospital, 9 Po Kin Road, Sheung Shui, NT, Hong Kong, China. luithderek@yahoo.co.uk
Telephone: +852-2-6837588
Fax: +852-2-6837576
Received: May 14, 2014
Peer-review started: May 15, 2014
First decision: June 27, 2014
Revised: July 9, 2014
Accepted: July 27, 2014
Article in press: July 29, 2014
Published online: January 18, 2015

Abstract

Technique of subtalar arthroscopy is rapidly evolving. Increasing number of traditional open procedures for the subtalar joint can now be done arthroscopically. It is hoped that less wound complications, faster rehabilitation and better cosmetic outcomes can be achieved with this minimally invasive technique.

Key words: Subtalar arthroscopy; Subtalar stiffness; Arthrodesis; Calcaneofibular impingement; Tarsal canal

Core tip: With the advance of small joint arthroscopy, different zones of the anterior and posterior subtalar joint can be approached arthroscopically. These can widen the list of indications for the subtalar arthroscopy.

Lui TH, Tong SC. Subtalar arthroscopy: When, why and how. *World J Orthop* 2015; 6(1): 56-61 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/56.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.56

INTRODUCTION

Subtalar arthroscopy was first described in 1980s. After its introduction, subtalar arthroscopy has been employed in various diagnostic and therapeutic procedures. The list of its application is ever expanding. With proper use of this powerful tool, many traditional procedures can be done minimally invasively to reduce wound complications and to achieve better outcomes.

HISTORY

In 1985, Parisien *et al*[1] published their experience in experimental subtalar arthroscopy in six lower limb cadaver specimens. They described anterior and posterior portals for approaching the posterior facet of subtalar joint using 2.7-mm arthroscope. They concluded that subtalar arthroscopy would be possibly indicated in assessment of the state of subtalar joint cartilage in cases of degenerative arthritis and infection; visualization of the joint after intraarticular fracture; management of sinus tarsi syndrome as well as loose body removal.

Frey *et al*[2] introduced the middle portals for subtalar arthroscopy in 1994. She discussed the relative safety of the anterior, middle and posterior portals by measuring their distance from neurovascular structures and tendons on lateral side of the foot in 15 specimens.

Since its introduction, subtalar arthroscopy has thrived.

The list of indications for its application is continuously expanding to include different diagnostic and therapeutic purposes.

SURGICAL TECHNIQUE

Posterior subtalar arthroscopy

Patient positioning: Standard posterior subtalar arthroscopy can be performed under spinal or general anaesthesia. It can be performed with the patient in lateral, prone or supine position depending on the concomitant procedures needed. Distraction is not routinely required.

Instruments: The subtalar joint can be approached with 30 degrees 2.7-mm arthroscope. Siddiqui *et al*[3] has also reported the use of 2.4-mm zero-degree arthroscope for subtalar arthroscopy.

Portals: The tip of the lateral malleolus is the landmark for portal placement. Anterolateral portal is made just above the angle of Gissane and is about 2 cm anterior and 1cm distal to fibular tip. Posterolateral portal is made at the lateral side of the Achilles tendon just above the posterosuperior calcaneal tubercle and is about 2 cm posterior and 1cm proximal to fibular tip. Middle portal is placed just anterior to the tip of fibula. All the portals are made with the "nick and spread" technique.

The abovementioned portals can only approach the lateral part of the subtalar joint. To approach the posteromedial part of the posterior subtalar joint, posterolateral and posteromedial portals can be used[4-7]. These portals are made when posterior ankle arthroscopy together with subtalar arthroscopy is performed.

Patient positioning: Patient is prone position with a thigh tourniquet.

Portals: With the foot in neutral position, a straight line is drawn parallel to the sole at the level fibular tip. The posterolateral portal is made just proximal to this line and tangential to the lateral border of the Achilles tendon. It should be just above the superoposterior calcaneal tubercle. The posteromedial portal is made at the same level just medial to the medial border of the Achilles tendon. In case of zone 2 flexor hallucis longus tendoscopy is planned, the posteromedial portal would be at the point of intersection of the medial border of the Achilles tendon and the projection line at the inferior border of 1st metatarsal and substentaculum tali

Anterior subtalar arthroscopy

Apart from posterior talocalcaneal articulation, the subtalar joint also consists of the anterior talocalcaneonavicular articulation. It includes the posterior articular facet of the navicular bone, the plantar spring ligament, the anterior and middle facet of the talus. This articulation is separated from the posterior articulation by the tarsal tunnel and sinus tarsi. The posterior articulation has a separate joint capsule and does not communicate with the anterior articulation.

Traditionally, to expose this anterior articulation, extensive medial approach is required. Anterior subtalar arthroscopy to treat anterior subtalar joint pathologies has been reported in 2008[8].

Patient positioning: The positioning is the same as standard subtalar arthroscopy. Lateral position is the most preferred one and the prone position is the least preferred one.

Portals: Primary visualization portal slightly dorsal to the angle of Gissane (consistent with the anterolateral portal of posterior subtalar arthroscopy). Primary working portal (consistent with the dorsolateral midtarsal portal for arthroscopic triple arthrodesis, see later) at the junction between the talonavicular and calcaneocuboid joints. These portals can be located by a needle and checked under fluoroscopy. The portals are interchangeable.

Surgical technique: Using a 2.7 mm, 30-degree arthroscope and arthroscopic shaver, the soft tissue at the junction between the talonavicular joint and calcaneocuboid joint is removed. The inferior corner of the lateral talar head will then be exposed. The talar head contour is then traced dorsally to the talonavicular joint and proximally to the anterior and middle calcaneal facets. This technique requires only resection of lateral capsule of the talonavicular joint. Most of the important ligamentous structures of the sinus tarsi are preserved.

This anterior arthroscopy technique has been applied in resection of symptomatic talocalcaneal coalition and synovectomy for the middle calcaneal facet synovitis.

With these two portals, an average of 95% of the anterior subtalar articulations can be reached[9]. Sural nerve is located at an average distance of 13 mm plantar to the primary working portal whereas the dorsal intermediate branch of the superficial peroneal nerve is at an average distance of 10 mm medial to the primary working portal.

Medial subtalar arthroscopy

Even with all the portals described, the anteromedial part of posterior subtalar joint and the medial gutter of the anterior subtalar joint are still relatively inaccessible. In order to achieve an all-around subtalar arthroscopy, medial portals are therefore required. Mekhail *et al*[10] described a medial portal for subtalar arthroscopy in his cadaveric study in 1995. Clinical application of the medial subtalar arthroscopy has been reported in 2012[11].

Patient positioning: Patient is in supine position with the hip abducted.

Portals: Medial subtalar portals include the standard posteromedial portal, locating at medial border of Achilles tendon; The medial midtarsal portal, which is just above the tibialis posterior tendon insertion onto the navicular

tubercle; And the medial tarsal canal portal.

Surgical technique: The medial tarsal canal portal is made with inside-out technique. The lateral portion of the tarsal canal is first cleared up with shaver *via* the anterolateral and middle portals for standard subtalar arthroscopy. The lateral opening of the tarsal canal is then identified. Under arthroscopic guidance, a Kirschner wire is inserted into the tarsal canal. The position of the Kirschner wire is confirmed with fluoroscopy. The medial tarsal canal portal can then be made on medial side of the foot. The foot is kept pronated so that the medial end of the tarsal canal opens to allow passage of arthroscopic instruments.

Lui *et al*[12] evaluated the safety of the tarsal canal portal and found that there is risk of injury to the flexor digitorum longus tendon and the posterior tibial neurovascular bundle. It is advised that when making the medial tarsal canal portal, it is better to align the Kirschner wire/Wissenger rod anteromedially to reduce the chance neurovascular injury. The tarsal canal portal should be used with caution.

INDICATIONS

Minimally invasive treatment for calcaneal fractures

Restoring articular congruity of the subtalar joint improves the outcome of calcaneal fractures. Traditionally, this is achieved by open reduction and internal fixation using the standard lateral extensile approach[13-15]. The major drawback of the open approach is wound complications including infection, wound dehiscence, haematoma and wound edge necrosis[16-19]. To minimize these complications, minimally invasive technique was developed to treat calcaneal fractures. Subtalar arthroscopy complements intra-operative fluoroscopy for anatomical reduction of articular surface[20-22].

Surgical technique: After manipulation and temporary fixation of the fracture fragments percutaneously with K-wires or pins, the subtalar cartilage congruity can be checked with subtalar arthroscopy. Fixation can then be accomplished with screws.

Outcome: Rammelt *et al*[22] reported no wound complications in his series of 18 patients with calcaneal fractures treated with arthroscopically assisted percutaneous reduction and fixation. Similarly, Schuberth *et al*[20] reported no soft tissue complications in his 10 patients treated with percutaneous fixation under arthroscopic assistance.

Subtalar arthrodesis

Arthroscopic subtalar arthrodesis was first developed by Tasto[23] in 1992. The arthroscopic technique was intended to yield less morbidity and preserve blood supply, as well as preserve proprioception and neurosensory input of the subtalar joint. Tasto[23] reported that all 25 patients of his series have radiological and clinical union, with the average time of fusion of 8.9 wk.

Surgical technique: The procedure can be done with the patient in lateral or prone position under general or regional anaesthesia. Supine position is less favorable for the screw placement. Standard portals include the anterolateral portal and the middle portal. Accessory portals are sometimes used for better instrumentation or visualization[24]. Posterolateral and posteromedial portals can also be used for subtalar arthrodesis. Bone graft/bone substitute is not usually required. Fixation can be accomplished with one or two cannulated screws inserted in either antegrade or retrograde fashion under X-ray control[23-25].

Outcome: Lee reported 16 cases of post-traumatic subtalar arthritis after calcaneal fracture treated with subtalar arthrodesis using the posterior 2-portal approach in prone position[25]. The union rate was 94% at a mean of 11 wk in his series.

Triple arthrodesis

Subtalar arthroscopy also has a role in triple arthrodesis. Traditionally, triple arthrodesis is done in open fashion with extensive surgical exposure. With the advancement of arthroscopic technique, triple arthrodesis can now be done arthroscopically.

The advantage of having arthrodesis done arthroscopically is that it allows better intra-articular visualization, more complete cartilage debridement, preservation of subchondral bone and better cosmetic results[26]. Arthroscopic triple arthrodesis has been reported in 2006[27].

Surgical technique: The subtalar joint is approached with anterolateral and middle portals. The mid-tarsal joints are approached with lateral, dorsolateral (*i.e.*, working portal for anterior subtalar arthroscopy), dorsomedial and medial portals. Articular cartilage is denuded with a small periosteal elevator, arthroscopic curette and arthroscopic osteotome. The subchondral bone is then microfractured with an arthroscopic awl. Fixation is accomplished with 7.3 mm cannulated screw for the subtalar joint and 4.0 mm cannulated screws for the mid-tarsal joints. The junction space between the talus, navicular, calcaneus and cuboid is packed with autologous cancellous bone graft harvested from the ipsilateral iliac wing.

Outcome: Lui applied this technique to a patient with post-polio equinovarus deformity[27]. Solid fusion was achieved 4 mo after the procedure. In 2009, Lui[28] reported his results of arthroscopic triple arthrodesis for 10 feet with Muller Weiss disease. Solid fusion was achieved in average of 21 wk. There were no wound complications or neurovascular injury. The limit of the degree of deformity correction with this arthroscopic approach is yet to be determined although the degree of deformity correction have been increased by "closing wedge procedure"[29,30].

Extra-articular endoscopy

Apart from treating intra-articular pathologies, endoscopy can be employed in treating extra-articular pathologies, in

particular, complications of calcaneal fractures[29].

Calcaneofibular impingement: Lateral calcaneal cortical bulging frequently occurs in patients whose calcaneal fracture are treated conservatively. This can cause calcaneofibular or peroneal impingement syndrome or shoe wear problems. Typically, patients complain of pain under the tip of lateral malleolus. Physical examination reveals tenderness on palpation under the tip of the fibula. Hindfoot valgus test may provoke the pain. The diagnosis can be confirmed with CT scan[31]. Lateral calcaneal ostectomy should be considered if conservative treatment cannot relieve the symptoms[32-34].

Traditionally, lateral calcaneal ostectomy is performed as an open procedure. It is important to have adequate removal of lateral bone in order to decompress the calcaneofibular recess and the far lateral arthrosis should be excised in order to have good clinical results[35]. Examination of the entire subtalar joint posterior facet can be difficult with open procedure. Excessive or inadequate debridement of cartilage may result. Endoscopic lateral calcaneal ostectomy for calcaneofibular impingement has been reported in 2007[36].

Surgical technique: Subtalar joint is examined with anterolateral and middle subtalar portals using 2.7 mm 30 degrees arthroscope. After dealing with the intra-articular pathology, lateral calcaneal ostectomy is performed using 4.0 mm 30 degrees arthroscopy and acrominizer. Lateral subtalar capsule and lateral subtalar ligamentous structures are stripped from lateral calcaneal cortical surface with arthroscopic shaver or a small periosteal elevator in the middle portal. A plantar portal, locating at plantar border of lateral calcaneal cortex (plantar to the cortical bulge), is used to approach the plantar half of the lateral cortical bulge. Posterolateral portal is sometimes required for complete soft tissue stripping. By switching the portals for visualization and instrumentation, complete lateral bulge ostectomy can be achieved. With this minimal invasive approach, wound complication can be reduced and immediate subtalar mobilization can be started without risking the wound healing.

Bauer *et al*[31] also described his two-portals endoscopic technique for treating calcaneofibular impingement in 2011. Apart from excising the lateral cortical bulge, scar tissue and fibrosis on the lateral cortex of the calcaneus and around lateral malleolus is excised. The peroneal tendons are also debrided along its course from retromalleolar groove and then distally.

Post-traumatic subtalar joint stiffness

Subtalar arthroscopy can also be used to treat post-traumatic subtalar stiffness[29,37].

Surgical technique: Under posterior subtalar arthroscopy, fibrous bands at sinus tarsi and dense fibrous tissue of lateral subtalar gutter can be debrided. The most lateral part of the interosseous talocalcaneal ligament is released. Posterior capsule release and debridement of fibrous tissue at posterior corner of subtalar joint can then be carried out. Finally, lateral subtalar capsule and lateral subtalar ligamentous structures are stripped from lateral calcaneal surface to regain subtalar motion.

Tarsal coalition

Some tarsal coalitions can also been treated arthroscopically. Lui described his arthroscopic technique in resection of calcaneonavicular coalition or the " too long" anterior process of calcaneus with 2 portals (*i.e.*, visualization portal and working portal for anterior subtalar arthroscopy)[38]. Bonasia used posteromedial and posterolateral portals for resection of talocalcaneal coalition arthroscopically[5]. Field has also reported his technique of arthroscopic assisted resection of middle facet coalition in 2009.

DISCUSSION

Lateral approach and posterior approach are the standard approaches for subtalar arthroscopy. With the lateral approach, majority of the posterior subtalar joint can be visualized except the medial part of posterior subtalar joint.

There are two solutions for this problem. Firstly, a combined posterior and lateral approach can be done with the patient put in prone position. Secondly, joint distraction can be applied[5]. However, traction can increase the tension of the neurovascular structures as well. In majority of time, it would distract the ankle joint rather than the subtalar joint.

Anterior subtalar joint cannot be reached with the standard middle, anterolateral portals due to the ligamentous structures at the sinus tarsi and the thick intraosseous ligaments inside the tarsal canal. In order to perform anterior subtalar arthroscopy, two other portals have to be established as described above. The portals tracts are along the lateral border of the anterior subtalar joint and the anterior border of the posterior subtalar joint. This can avoid damage of the important ligaments of the sinus tarsi[8,9]. However, with these extra portals, only the lateral anterior subtalar joint can be reached. The medial part of the anterior subtalar joint can just be seen but cannot be reached.

With the development of medial subtalar arthroscopy, medial part of the anterior and posterior subtalar joint, tarsal canal can now be reached. Medial tarsal canal portal and the medial midtarsal portal are established with the medial tarsal canal portal being the keystone portal for medial subtalar arthroscopy (Figure 1). The main indication of medial subtalar arthroscopy is extensive synovitis in tarsal canal and medial anterior subtalar joint. Structures at risk during medial subtalar arthroscopy include flexor digitorum longus tendon, posterior tibial neurovascular bundles and medial talar branch of the posterior tibial artery.

In order to prevent damage to these structures, portal tract of medial tarsal canal should be made anterior to the flexor digitorum longus tendon, immediately behind the posterior tibial tendon. During insertion of the guide

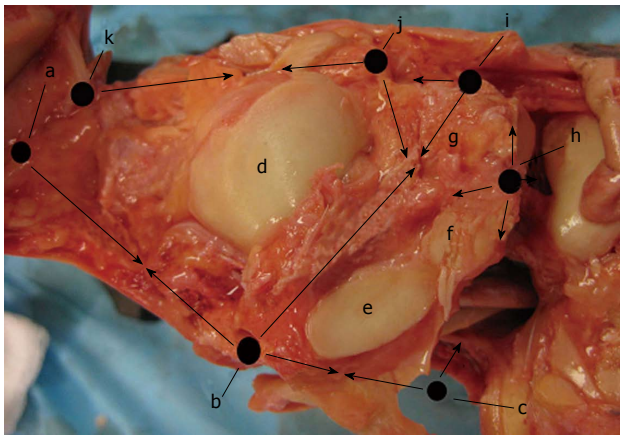

Figure 1 Summary of the locations of the subtalar portals. a: Posteromedial portal; b: Medial tarsal canal portal; c: Medial midtarsal portal; d: Posterior calcaneal facet; e: Middle calcaneal facet; f: Anterior calcaneal facet; g: Sinus tarsi; h: Dorsolateral midtarsal portal (working portal of anterior subtalar arthroscopy); i: anterolateral portal; j: Middle portal; k: Posterolateral portal. The arrows show the possible areas to be reached by individual portal.

rod, it should be directed anteromedially with foot in pronation to open up the medial orifice of the tarsal canal[11]. During medial subtalar arthroscopy, the medical capsule should not be stripped dorsally to prevent injury to the medial talar branch of the posterior tibial artery[11].

CONCLUSION

Technique of subtalar arthroscopy is continuously evolving. With the advancement of the arthroscopic technique, increasing number of traditional open procedures can now be done arthroscopically. This allows less soft tissue dissection, better cosmesis and shorter duration of recovery.

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P- Reviewer: Nikolaou VS **S- Editor**: Song XX
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.62

World J Orthop 2015 January 18; 6(1): 62-76
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (3): Foot

Diabetic foot syndrome: Immune-inflammatory features as possible cardiovascular markers in diabetes

Antonino Tuttolomondo, Carlo Maida, Antonio Pinto

Antonino Tuttolomondo, Carlo Maida, Antonio Pinto, Dipartimento Biomedico di Medicina Interna e Specialistica, U.O.C di Medicina Interna e Cardioangiologia, Università degli Studi di Palermo, 90127 Palermo, Italy
Author contributions: Tuttolomondo A and Pinto A prepared the manuscript; Maida C contributed to the manuscript preparation and literature review.

Correspondence to: Antonino Tuttolomondo, MD, PhD, Professor, Dipartimento Biomedico di Medicina Interna e Specialistica, U.O.C di Medicina Interna e Cardioangiologia, Università degli Studi di Palermo, P.zza delle Cliniche n.2, 90127 Palermo, Italy. bruno.tuttolomondo@unipa.it
Telephone: +39-091-6552128
Fax: +39-091-6552285
Received: March 13, 2014
Peer-review started: March 14, 2014
First decision: May 14, 2014
Revised: June 6, 2014
Accepted: August 27,2014
Article in press: August 31, 2014
Published online: January 18, 2015

Abstract

Diabetic foot ulcerations have been extensively reported as vascular complications of diabetes mellitus associated with a high degree of morbidity and mortality. Diabetic foot syndrome (DFS), as defined by the World Health Organization, is an "ulceration of the foot (distally from the ankle and including the ankle) associated with neuropathy and different grades of ischemia and infection". Pathogenic events able to cause diabetic foot ulcers are multifactorial. Among the commonest causes of this pathogenic pathway it's possible to consider peripheral neuropathy, foot deformity, abnormal foot pressures, abnormal joint mobility, trauma, peripheral artery disease. Several studies reported how diabetic patients show a higher mortality rate compared to patients without diabetes and in particular these studies under filled how cardiovascular mortality and morbidity is 2-4 times higher among patients affected by type 2 diabetes mellitus. This higher degree of cardiovascular morbidity has been explained as due to the observed higher prevalence of major cardiovascular risk factor, of asymptomatic findings of cardiovascular diseases, and of prevalence and incidence of cardiovascular and cerebrovascular events in diabetic patients with foot complications. In diabetes a fundamental pathogenic pathway of most of vascular complications has been reported as linked to a complex interplay of inflammatory, metabolic and procoagulant variables. These pathogenetic aspects have a direct interplay with an insulin resistance, subsequent obesity, diabetes, hypertension, prothrombotic state and blood lipid disorder. Involvement of inflammatory markers such as IL-6 plasma levels and resistin in diabetic subjects as reported by Tuttolomondo *et al* confirmed the pathogenetic issue of the a "adipo-vascular" axis that may contribute to cardiovascular risk in patients with type 2 diabetes. This "adipo-vascular axis" in patients with type 2 diabetes has been reported as characterized by lower plasma levels of adiponectin and higher plasma levels of interleukin-6 thus linking foot ulcers pathogenesis to microvascular and inflammatory events. The purpose of this review is to highlight the immune inflammatory features of DFS and its possible role as a marker of cardiovascular risk in diabetes patients and to focus the management of major complications related to diabetes such as infections and peripheral arteriopathy.

Key words: Diabetic foot syndrome; Inflammation; Cytokines; Cardiovascular risk; Marker

Core tip: An immune activation has been reported as important at several stages in the development of chronic wounds of diabetic foot syndrome (DFS). Immune-inflammatory up regulation may precede the incidence of DFS in the same way that it precedes some major cardiovascular diabetic complication such as coronary heart disease as reported by some studies that showed a significant negative correlation of adiponectin plasma levels with cardiovascular risk factors such as hypertension, dyslipidaemia and with previous cerebrovascular events such as previous transient *ischemic* attack/stroke and new onset events thus underlining the role of hypo-adiponectinaemia as a cardiovascular predictive factor in DFS.

Tuttolomondo A, Maida C, Pinto A. Diabetic foot syndrome: Immune-inflammatory features as possible cardiovascular markers in diabetes. *World J Orthop* 2015; 6(1): 62-76 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/62.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.62

INTRODUCTION

Diabetes is a disease of metabolism clinically expressed by chronic hyperglycemia and blood lipid and protein disorders that have been extensively reported as linked to several complications that significantly impair the quality of life. Among diabetic vascular complications, foot ulcers represents the first cause of hospitalization in diabetics and a significant cause of health care costs (more than 20%-40% of health care resources have been reported as related to diabetes-related foot care)[1,2].

According World Health Organization, its' possible encompass all foot complications in the term diabetic foot syndrome (DFS) that has been defined as "ulceration of the foot (distally from the ankle and including the ankle) associated with neuropathy and different grades of ischemia and infection"[3]. More than 80000 amputations directly related to diabetes have been registrated in the United States annually[4] and the majority (80%) of these have been performed in patients with a previous foot ulceration[5]. These foot vascular complications represent a very common precursor event prior of lower extremity amputation among persons with diabetes[6,7]. Thus it explains that the foot ulcerations are considered as significantly predictive of morbidity, mortality, and disability.

It has been extimated that 15% of patients with diabetes will develop a lower extremity complication in their life[8]. Some authors reported a 0.5% to 3% incidence of diabetic foot ulcers[9], whereas foot ulcer prevalence, as reported by some population surveys, ranges from 2% to 10%[9]. A retrospective cohort study conducted in United States and enrolling more than 8000 patients with type 1 and type 2 diabetes showed that new cases of DFS were 5.8 % over an period of 3 years[10]. More than 15% of patients with DFS experienced a lower limb amputation and some authors reported that survival rate in patients that undertaken a lower limb amputation is significantly shorter and more than $ 2700 is the cost for a 2-year care of a new-diagnosed foot ulcer.

Foot ulcers have a complex and multifactorial pathogenesis with several causes working together to create pathogenetic pathway linked to foot ulceration onset in diabetic patients. Pathogenetic events able to cause diabetic foot ulcers are multifactorial. Among the commonest causes of these pathways it's possible to consider some triggers such as peripheral neuropathy, foot deformity, abnormal foot pressures, abnormal joint mobility, trauma, peripheral artery disease (PAD).

Peripheral neuropathy represents the most important cause in the pathway that causes foot ulceration in diabetic patients. Diabetic peripheral neuropathy (DPN) significantly impairs nerve activity throughout the body and can affect autonomic, motor, and sensory functions[11]. In sensory involvement the impairment of sensation that protects foot skin integrity makes the foot vulnerable to thraumatic damage caused by an excess of pressure, mechanical or thermal injury.

As reported by a recent study, sensory neuropathy represents the most frequent event in the patogenetic axis that causes ulceration in diabetic patients[12]. Other forms of neuropathy may also play a role in foot ulceration. Motor neuropathy impairs the balance of biomechanical forces, alter the integrity of foot anatomy by means foot deformities, impaired joint mobility and compromised loading of the extremities. These pathogenetic events impair mechanical forces balance during walking and induce a reactive thickening of skin (callus) and thus facilitating ischemic necrosis of tissues nearest to callus and leading to loss of skin and subcutaneous tissue integrity (breakdown) and to ulcers that represent the final step of this pathogenetic way.

Also autonomic neuropathy has a role in ulcer pathogenesis causing impairment and texture changes of skin integrity thus predisposing dryness and fissuring and opening potential entry for bacteria.

Another disorder that contributes to the development of foot ulcers is peripheral vascular disease that affects the blood vessels of small and large size. Both macro- and microvascular diseases are believed to contribute to the consequences of peripheral vascular disease, resulting in the inability of the ischemic limb to heal itself properly.

PAD has an increased incidence and prevalence in subjects with diabetes in relation of age and duration of disease. Hypertension, smoke habit, and lipid blood disorders are frequent comorbidities in diabetes with a well demonstred role in PAD pathogenesis. Studies have shown that peripheral vascular disease develops at a younger age among patients with diabetes as compared to the general population[13]. Ankle-brachial index (ABI), that originates by comparation of the systolic blood pressure at posterior tibial or dorsalis pedal level with brachial blood pressure, it's widely used to diagnose and evaluate severity of PAD. In patients with an ABI < 0.90, the relative risk has been

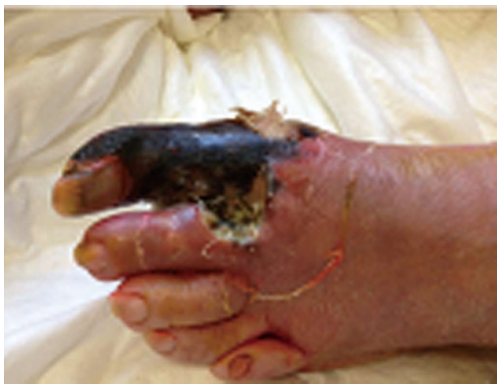

Figure 1 Infected diabetic foot ulcer. Tuttolomondo *et al*[21], personal data.

reported to be 1.25 (95%CI: 1.05, 1.47) for developing an ulcer *vs* diabetic patients with a normal ABI[14]. Lower limb ischaemia due to proximal arterial occlusive atherosclerosis is an important cause able to predispose to ulceration in more than 30% of cases[15]. Nevertheless a recent study reported that diabetic patients with PAD are more likely in comparison to non-diabetic subjects to have a distal occlusive arterial disease and an higher incidence of amputions and death related to cardiovascular causes[13].

An ischaemic diabetic foot appears as red, dry and with clinical findings suggestive of peripheral neuropathy and it also is susceptible to pressure damage by footwear.

Thus diabetic foot with ulceration is a complex problem resulting of the interplay of multiple pathogenetic noxae such as neuropathy, peripheral vascular disease, trauma and infections. Neuropathy and ischaemia may represent the first acting factors, most often together as neuroi-schaemia that is peripheral neuropathy and vascular disease in overlapping, whereas infection is mostly a super-infection.

It's possible to classify a diabetic foot in a pathophysiological and clinical way in: ischemic diabetic foot, neuropathic ischemic foot and infected diabetic foot, but this type of classification in clinical practice may appear too simple owing to the fact that it's possible to distinguish more frequent mixed clinical variants called neuro-ischemic diabetic foot. All these clinical variants of DFS have typical morphologic and clinical findings (Figures 1 and 2).

In this review, we will examine research articles with regard of involvement of immune-inflammatory markers in DFS and the role of DFS as a possible marker of cardiovascular risk in diabetic subjects.

CARDIOVASCULAR MORBIDITY IN PATIENTS WITH DFS

Diabetic patients show a poorer survival rate compared to patients without diabetes. Cardiovascular mortality and morbidity rates in diabetics have been reported by several studies as 2-4 times higher than in non-diabetic subjects. Different studies also indicate that foot ulcers in diabetic patients are linked to a higher mortality[13-17]. Furthermore diabetic foot represents an independent risk factor of morbidity in diabetic patients with a twice mortality rate

Table 1 Prevalence of previous cardiovascular events in patients with and without diabetic foot

	Pts with diabetic foot (n = 102) <	Pts without diabetic foot (n = 123)	P
CAD (%)	33 (32.3)	24 (19.5)	0.0043
TIA (%)	15 (14.7)	9 (7.3)	< 0.0001
Stroke (%)	18 (17.6)	11 (8.9)	< 0.05
Stroke toast subtypes			
LAAS	6 (33.3)	5 (45.4)	
Lacunar	12 (66.6)	6 (54.5)	
CEI	0	0	
Diabetic retinopathy (%)	55 (53.9)	47 (38.2)	< 0.0001
Renal failure (%)	6 (5.8)	7 (5.6)	NS

Modified from Pinto *et al*[19]. CAD: Coronary artery disease; TIA: Transient ischemic attack; LAAS: Large artery atherosclerotic stroke; CEI: Cardioembolic.

due to cardiovascular disease in diabetic subjects with foot ulceration compared to those without foot ulceration[16,17].

In a study conducted by Roper *et al*[18], these authors hypothesized that patients with type 2 diabetes mellitus with diabetic foot could have a poorer cardiovascular prophile with a higher prevalence of sublinical cardiovascular damage and of cardiovascular morbidity. Thus authors evaluated differences between subjects with type 2 diabetes mellitus with and without diabetic foot with regard of: (1) cardiovascular risk profile; (2) previous cardiovascular event prevalence; (3) frequency of markers of asymptomatic cardiovascular damage; and (4) new-onset vascular events incidence. They reported a higher prevalence of major cardiovascular risk factor, of asymptomatic markers of CVD, and a higher prevalence and incidence of previous and new-onset cardiovascular events in diabetic patients with foot complications (Tables 1 and 2).

These findings go along with previous reports of higher degree of cardiovascular morbidity and mortality in diabetic patients with amputations[19,20]. The main cause of death in these patients was coronary artery disease (CAD)[19,20].

Another finding of this study was the higher prevalence of major cardiovascular risk factors such as hypercholesterolemia, LDL plasma levels > 130 mg/dL, hypertriglyceridemia, and microalbuminuria/proteinuria in patients with foot complications compared to diabetic patients without foot complications thus strengthening the issue that DFS in diabetic subjects act as a real and important cardiovascular risk marker.

Authors also reported that patients with diabetic foot were more likely to have a cerebrovascular event [transient ischemic attack (TIA) and ischemic stroke] both on retrospective evaluation (previous TIA and ischemic stroke) and on prospective evaluation (new onset TIA and stroke on a 5 years follow up). The most prevalent subtypes of stroke were lacunar and LAAS subtype (Tables 3 and 4). The higher frequency of lacunar subtype could underline the possible pathogenetic importance of cerebrovascular disease either atherosclerotic and microvessel disease in patients with diabetic foot.

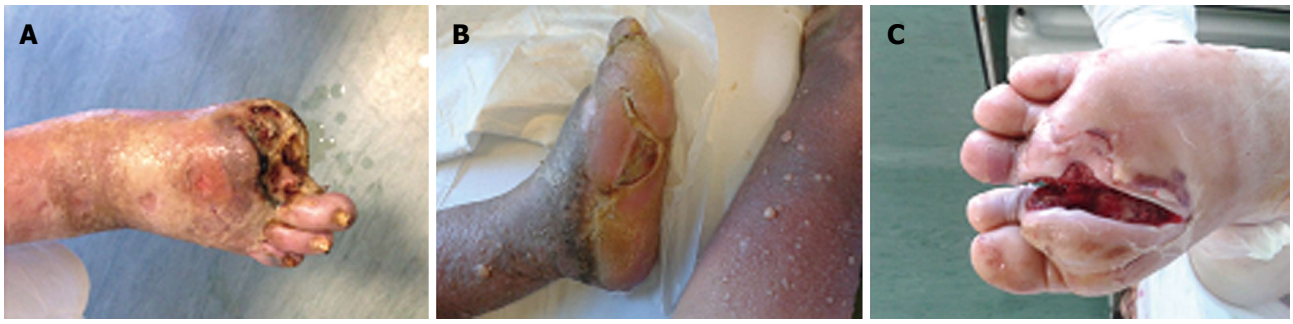

Figure 2 Diabetic foot ulcer. A: Neuroischemic diabetic foot ulcer; B: Neuropathic diabetic foot ulcer; C: Neuroischemic diabetic foot ulcer. Tuttolomondo *et al*[21], personal data.

Table 2 Cox regression analysis of demographic and clinical variables associated with cardiovascular morbidity *n* (%)

	Pts with diabeticfoot (*n* = 102)	Pts without diabetic foot (*n* = 123)	*P*
CAD	12 (11.7)	7 (5.6)	< 0.005
Angina	4 (3.9)	3 (2.4)	< 0.005
Myocardialinfarction	8 (7.8)	4 (3.5)	< 0.001
TIA	6 (5.8)	4 (3.2)	< 0.0001
Stroke	7 (6.8)	5 (4.0)	< 0.005
Renal failure	4 (3.9)	5 (4)	NS
Deaths	14 (13.7)	10 (8.1)	< 0.005
Cardiovascular cause	13 (12.7)	9 (7.3)	
AMI	(3.9)	1 (0.81)	NS
Stroke	3 (2.9)	2 (1.6)	
CHF	3 (2.9)	3 (2.4)	
Other vascular cause	3 (2.9)	3 (2.4)	
Other cause	1 (0.9)	1 (0.81)	

From Pinto *et al*[19]. CAD: Coronary artery disease; TIA: Transient ischemic attack; AMI: Acute myocardial infarction; CHF: Congestive heart failure.

Furthermore cardiovascular risk profile linked to diabetic foot seems to be related to the effects of each cardiovascular risk factor added up a neuropathy and vasculopathy clinical background[21,22], but another further explanation could be in the role of microangiopathy as a pathogenetic background of overall vascular risk.

Another study has been conducted by Pinto *et al*[20] to analyze diabetic foot as a stroke risk marker in type 2 diabetic patients. Authors enrolled 102 type 2 diabetes patients with diabetic foot and 123 diabetic patients without diabetic foot. These authors reported a higher prevalence of previous cerebrovascular events and a higher incidence of new-onset strokes in patients with diabetic foot. They also reported a higher frequency of lacunar and large artery atherosclerosis subtype thus confirming previous findings by the same group of a worse stroke risk profile in diabetic patients with diabetic foot than in diabetic subjects without foot ulceration.

ROLE OF CARDIOVASCULAR RISK FACTORS

Microalbuminuria

Microalbuminuria is defined by the detection of urinary albumin excretion rates of 30 to 300 mg in a 24-h urine collection. It is still the only anomaly of early diabetic kidney that has prognostic value statements. In fact, the appearance of microalbuminuria in diabetic patients is a very important index for progression to overt proteinuria and overt nephropathy. It has been reported as a cardiovascular risk indicator in diabetic populations owing to the fact that microalbuminuria is linked to an increased risk for all-cause and cardiovascular mortality also PAD. In a recent study conducted by Tuttolomondo *et al*[21] authors reported a higher prevalence of microalbuminuria in patients with diabetic foot. These authors also reported a significant positive correlation between microalbuminuria, and interleukin (IL)-6 and resistin serum levels (Tables 5-7).

Table 3 Previous cerebro-vascular events in patients with and without diabetic foot

	Diabetic foot (*n* = 102)	No diabetic foot (*n* = 123)	*P*
TIA	15 (14.7)	9 (7.3)	< 0.0001
Ischemic stroke	18 (17.6)	11.8 (8.9)	< 0.0001
Stroke toast subtype			
LAAS	6 (33.3)	5 (45.4)	< 0005
LAC	12 (66.6)	6 (54.5)	< 0.005
CEI	0	0	

From Pinto *et al*[20]. TIA: Transient ischemic attack; LAAS: Large artery atherosclerotic stroke; LAC: Lacunar stroke; CEI: Cardioembolic.

Table 4 Incidence of stroke at follow-up in subjects with and without diabetic foot

	Diabetic foot (*n* = 102)	No diabetic foot (*n* = 123)	*P*
TIA	6 (5.8)	4 (3.2)	< 0.0001
Ischemicstroke	7 (6.8)	5 (4.0)	< 0.005
LAAS	4	3	< 0.005
LAC	3	2	< 0.005
CEI	0	0	NS

From Pinto *et al*[20]. TIA: Transient ischemic attack; LAAS: Large artery atherosclerotic stroke; LAC: Lacunar stroke; CEI: Cardioembolic.

HYPERTENSION

Diabetes mellitus and hypertension are frequent comorbidity and they represent two important independent risk factors for atherosclerosis and its complications. Diabetic

Table 5 General and demographic variables in cases and controls *n* (%)

	Pts with diabeticfoot	Pts without diabetic foot	*P*
n	34	37	0.75
Age	66.7 ± 8.5	66.9 ± 7.9	0.027
Sex male	16 (47.1)	15 (41.7)	0.41
Diabetes duration			
< 10 yr	7 (20.6)	21 (58.3)	0.027
= 10 yr	8 (23.5)	11 (30.6)	0.045
= 20 yr	19 (55.9)	4 (11.1)	< 0.001
Treatment			
Diet	4 (11.8)	3 (8.3)	0.65
Oral antidiabetics	3 (8.8)	10 (27.8)	< 0.001
Mixed	6 (17.5)	13 (36.1)	< 0.001
Insulin	21 (61.8)	10 (27.8)	< 0.001
Smoking	7 (20.6)	9 (25)	0.71
Hypertension	20 (58.8)	25 (69.4)	0.041
Dyslipidaemia	14 (41.2)	16 (44.4)	0.35
Obesity	19 (55.9)	13 (36.1)	0.021
Chronic renal failure	15 (44.1)	13 (36.1)	0.064
Mycroalbuminuria	22 (64.7)	6 (14.7)	< 0.001
Retinopathty	19 (55.9)	36 (100)	< 0.001
PAD	10 (29.41)	9 (25)	0.54
CAD	17 (50)	7 (19.4)	< 0.001
TIA/Stroke	14 (41.17)	6 (16.66)	0.021
Other district atherosclerosis	28 (82.35	21 (58.33)	< 0.001
Artropathy	11 (32.4%)	2 (5.6)	< 0.001
Neuropathy	25 (73.52)	14 (38.88)	< 0.001
Diabeticfootgrade			
Grade 0	1 (2.9)		
Grade 1	6 (17.6)		
Grade 2	8 (23.5)		
Grade 3	10 (29.4)		
Grade4	4 (11.8)		
Grade 5	1 (2.9)		
Grade 6	4 (11.8)		

Data are expressed as median and interquartile (lower and upper quartile). Modified from Tuttolomondo *et al*[21]. PAD: Peripheral artery disease; CAD: Coronary artery disease.

nephropathy has been reported as the main factor that contributes to the development of hypertension in patients with type 1 diabetes mellitus, whereas in patients with type 2 diabetes mellitus, hypertension is an expression of insulin resistance and a clinical finding of metabolic syndrome. Nevertheless, in both type 1 and type 2 diabetes, hypertension heavily influences prognosis and increase the risk of macrovascular and microvascular complications.

Hypertension increases the incidence rate of diabetic retinopathy, nephropathy, and peripheral vascular disease. A study by Pinto *et al*[20] showed a similar prevalence of hypertension in both in patients with diabetic foot and those without it. In addition these authors showed a significant positive correlation between some clinical and laboratory variables such as serum levels of IL-6 and resistin, adipocytokines involved in insulin resistance in the pathogenesis of vascular inflammatory responses (Tables 5-7).

DYSLIPIDEMIA

There are numerous cardiovascular diseases that occur in patients with diabetes, both type 1 or 2. Dyslipidemia in diabetics is strictly linked to cardiovascular disease pathogenesis. The defects in the synthesis and clereance of plasma lipoproteins are among the most commonly metabolic abnormalities that accompany diabetes. The diabetic dyslipidemia, a characteristic pattern characterized by the presence of low levels of high density lipoprotein (HDL) cholesterol, hyper-tigliceridemia, and postprandial lipemia and that is observed more frequently in type 2 diabetes, is one of several factors that contribute to accelerating macrovascular disease in diabetic patients. Among the different factors involved in developing of diabetic dyslipidemia the following should be considered: insulin influences on apoprotein synthesis, regulation of lipoprotein lipase, effect of cholesteryl ester transfer protein, and adipose and muscle and peripheral insulin effects. The acknowledgment and treatment of dyslipidemia are therefore two important elements in the framework of a multidisciplinary approach aimed at the prevention of CAD. However, considering the complexity of the profiles of dyslipidemia in diabetic patients, multiple drugs are often required to achieve therapeutic targets. In addition, the other risk factors usually associated with diabetes mellitus, such as hypertension, hyperglycemia and obesity, should be effectively managed, to reinforce the effects of lipid-lowering therapy. Tuttolomondo *et al*[21] in a recent study reported a high frequency of dyslipidemia in patients with diabetic foot ulcers than in those without diabetic foot also reporting a correlation between dyslipidemia and serum levels of IL-6 and resistin indicating a possible role of inflammation pathogenetic markers on insulin resistance and its linked vascular damage (Tables 5-7).

INFLAMMATION MARKERS IN PATIENTS WITH DFS

In diabetes, there is a complex interplay of several inflammatory and metabolic aspects thus affecting cardiovascular system. Inflammation enhances insulin resistance, that is strictly linked to obesity, diabetes, hyper-tension, prothrombotic conditions and blood lipid disorders[23]. Some studies[22,24-26] suggested a possible interplay between some hormones, inflammatory cytokines and adipose markers such as resistin. Moreover, circulating levels of adiponectin, an important adipocytokine, have been reported as reduced in obesity, type 2 diabetes and CAD[27-29]. This finding could explain how low serum level of adiponectin were linked to low HDL-cholesterol (HDL-C) concentrations[30], low LDL particle size[28], and high serum levels of markers of inflammation[31]. Jeffcoate *et al*[32], reported that it's possible to delineate a inflammatory cascade in diabetic foot pathogenesis as expressed by high serum levels of some inflammatory cytokines such as TNF-α and IL-1β.

Although subclinical inflammation may represent a possible risk determinant of type 2 diabetes and of its vascular complications, available data on diabetic neuropathies are poor. Thus some authors[33] analyzed the possible role of serum levels of some acute-phase

Table 6 Laboratory variables in cases and controls

	Diabetic foot patients	Diabetics without foot complications	*P*
HbA1c	8 (7.28-9.40)	6.85 (6.10-8.00)	0.018
CRP	4 (2.25-5.15)	2.25 (1.90-3.08)	0.041
Total cholesterol (mg/dL)	215.50 (166.50-243.00)	204.00 (185.50-210.00)	0.054
LDL cholesterol (mg/dL)	121.70 (98.75-148.75)	104.50 (78.00-123.00)	0.032
Tryglicerids (mg/dL)	160.50 (119.50-209.25)	180.50 (144.50-199.00)	0.012
Globuli bianchi	12.675 (10775.00-14140.00)	10.700 (8850.00-12027.50)	0.032
Adiponectin (μg/mL)	7.1450 (4.47-12.17)	8.480 (5.15-12.87)	0.022
Resistin (ng/mL)	5.160 (2.96-6.29)	3.290 (2.37-6.5)	0.021
IL-6 (pg/mL)	3.21 (1.23-5.34)	2.13 (1.24-3.97)	0.033

Demographic and anamnestic data are expressed as n° (percentage). Modified from Tuttolomondo *et al*[21]. HbA1c: Hemoglobin A1c; CRP: C-reactive protein; IL-6: Interleukin-6.

Table 7 Correlations of interleukin-1β, adiponectinresistin with clinical and laboratory variables in subjects with diabetic foot

Variable	Adipenectin		Resistin		IL-6
	R	*P* values	*R*	*P* values	
Diabetes duration	0.36 (s)	< 0.001 (s)	0.09	0.37	
Smoking	0.35 (s)	< 0.001 (s)	0.10	0.22	
Hypertension	0.27 (s)	< 0.05 (s)	0.12	0.35	
Dyslipidaemia	0.42 (s)	< 0.001 (s)	0.14	0.15	
Obesity	0.13	0.42	0.12	0.22	
Chronicrenalfailure	0.11	0.56	0.12	0.35	
Mycroalbuminuria	0.08	0.37	0.08	0.37	
Retinopathty	0.10	0. 7	0.10	0. 7	
AOPC	0.11	0.81	0.10	0.77	
CHD	0.46	< 0.001 (s)	0.38 (s)	< 0.0001 (s)	
TIA/stroke	0.12	0.42	0.13	0.32	
Other district atherosclerosis	0.15 (s)	0.42 (s)	0.14 (s)	0.36 (s)	

Coefficients (*R*) and *P* values are calculated by the Pearson correlation mode. Modified from Tuttolomondo *et al*[21]. s: Significative; CRP: C-reactive protein; TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β; IL-6: Interleukin-6; IL-10: Interleukin-10; ICAM-1: Intercellular adhesion molecule-1; V-CAM-1: Vascular cell adhesion molecule-1; vWF: Von willebrand factor; TPA: Tissue plasminogen activator; PAI-1: Plasminogen activator inhibitor-1.

proteins, cytokines, and chemokines. These authors evaluated 10 markers of subclinical inflammation in more than 220 subjects with type 2 diabetic patients and diabetic neuropathy diagnosed by means the Michigan Neuropathy Screening Instrument (MNSI), showing that high levels of C-reactive protein (CRP) and IL-6 were most likely to be linked with diabetic polyneuropathy, high MNSI score, and specific neuropathic deficits, whereas an inverse relationship has been reported with regard of IL-18. This study clearly reported that subclinical inflammation is associated with peripheral nervous system involvement in diabetics.

Nevertheless, few data exist regarding the importance of inflammation markers in patients with DFS. It has well demonstred how low-grade immune activation may represent an risk factor of type 2 diabetes and for its vascular complications such as macrovascular (myocardial infarction and stroke) and microvascular ones (neuropathy and nephropathy).

An immune activation has been reported as important at several stages in the development of chronic wounds. Immune-inflammatory up regulation may precede the incidence of a diabetic foot ulcer in the same way that it precedes some major cardiovascular diabetic complication such as CAD. Owing to the fact that pro- and anti-inflammatory abnormalities could be important in different phase of wound healing, it is suggestive that an immune-inflammatory impairment may damage tissue homeostasis and wound healing leading to the chronic wounds and realizing a complex clinical condition such as DFS.

Weigelt *et al*[34] analyzed the possible relationship between foot ulcers and immune status in diabetic subjects with and without foot ulcers by evaluating some immune mediators. Authors reported how circulating levels of some inflammatory markers such as acute-phase proteins, cytokines, and chemokines were higher in patients with diabetic foot. Authors showed an higher degree of serum levels of CRP, fibrinogen, IL-6, macrophage migration inhibitory factor, macrophage inflammatory protein-1β, and interferon-γ-inducible protein-10.

However, since the existence of a strict relationship between inflammatory and adypocite dysfunction marker, a possible interesting issue should be to evaluate the role of adiponectin, resistin and inflammatory cytokines in patients with diabetic foot compared with those without foot complications.

A recent study by Tuttolomondo *et al*[21] has been conducted with this aim and and authors analyzed serum levels of adiponectin, resistin and IL-6 in subjects with diabetic foot in 34 patients with type 2 diabetes mellitus and foot ulceration and in control subjects with type 2 diabetes mellitus without foot ulceration (Table 5). This study reported how diabetics with diabetic foot showed compared to diabetics without diabetic foot showed higher IL-6 and resistin plasma levels and lower adiponectin plasma levels (Table 6). Resistin, strictly involved in pathogenesis of insulin resistance, may also have inflammatory interactions. A study[35] reported that lipopolysaccharide increased resistin expression in rat WAT, 3T3-L1 adipocytes and human monocytes. Studies conducted in animal models (murine) showed not univocal findings with regard a possible role of pro-inflammatory cytokines as regulation factors of resistin, nevertheless recent human studies reported and underlined a role

of inflammatory cytokine on resistin induction[36,37]. Osawa *et al*[38] reported how high serum resistin levels play as independent risk factor for ischemic stroke in a Japanese population also showing that high resistin serum levels associated with diabetes or hypertension furtherly increased cerebrovascular risk. Findings by Tuttolomondo *et al*[21] with regard of higher plasma levels IL-6 plasma levels and resistin in diabetic subjects with foot ulceration in comparison with diabetics without foot complications seem to confirm this issue.

Reilly *et al*[39] reported the role of resistin as a metabolic mediator of an interplay between inflammation and atherosclerosis. In contrast with resistin, adiponectin may inhibit resistin-mediated increase in vascular cell adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule 1 (ICAM-1) serum levels[40,41].

Thus hypo-adiponectinemia can represent an early indicator of a complex cardiovascular risk factor pattern predisposing to atherosclerosis and its organ-end damage complications as well as a contributing factor increasing progression of the atherosclerotic plaque.

Adiponectin has anti-inflammatory and athero-protective actions in various tissues by an inhibition action of the expression of vascular adhesion molecules and scavenger receptors, a reduction of expression of the inflammatory cytokine TNF-α, increasing of NO production and lowering the proliferation and migration of smooth muscle cells[42]. To date, two receptors mediate adiponectin's actions in lipid and glucose metabolism such as ADIPOR1 and ADIPOR2[43]. Halvatsiotis *et al*[44] reported how a sequence variant in the intron 5 of the ADIPOR2, rs767870 is more significantly associated with cardiovascular disease in a Greek population.

Findings by Tuttolomondo *et al*[23] of lower median plasma levels of adiponectin in subjects with diabetic foot seem to confirm this issue. Furthermore the same authors reported a significant negative correlation of adiponectin plasma levels with cardiovascular risk factors such as hypertension, dyslipidaemia and with previous cardiovascular events such as morbidity such as previous TIA/Stroke and new onset events such as neuropathy, micro- albuminuria thus further underlining the role of hypo-adiponectinaemia as a predictive factor of cardiovascular events.

Adipose tissue has also inflammatory properties as expressed by cytokine production[45], thus it's possible to hypothesize the existence of an "adipo-vascular" axis[46], strictly involved in the pathogenesis of increased cardiovascular risk in patients with type 2 diabetes. Findings such as lower degree of serum adiponectin levels and and higher degree of IL-6 serum levels may represent the pathogenetic and biological phenotype of this "adipo-vascular axis" in subjects with DFS involving both microvascular and inflammatory mechanisms.

Some authors[47] analyzed adipocyte volume and its association with tumor necrosis factor alpha (TNF-α), IL-6, adiponectin and high sensitivity CRP (hs-CRP) levels showing how mean adipocyte volumes were higher in obese diabetic patients than in other groups. Authors also reported a significant positive correlation between adipocyte size and inflammatory markers, whereas a negative correlation has been reported between adipocyte size and adiponectin levels. These findings furtherly confirm the existence of an adipose-inflammatory vascular axis strictly involved in diabetic complications such as DFS owing to the fact that adiposity and its related conditions, such as diabetes, are at the same time pro-inflammatory and inflamed conditions.

The evaluation of association of adipokines with the macrovascular complications of type 1 diabetes mellitus (DM) was the aim of a study[48] that analyzed serum adiponectin, leptin, and resistin levels in type 1 DM patients evaluating their association with carotid intima media thickness (CIMT). Authors showed how adiponectin is negatively correlated with CIMT, age, BMI, waist-to-hip ratio, and that exist a correlation between resistin and CIMT and systolic blood pressure.

Indeed recent studies suggest that adiponectin may influence inflammatory vascular interactions by means a down-regulation of adhesion molecules expression on endothelial cells[47], inhibition of endothelial cell NF-kB signaling[48], and lowering macrophage function[49,50]. Other studies showed how adiponectin can inhibit TNF-α mediated expression of E-selectin, VCAM-1 and ICAM-1 in human endothelial cells[47-49,51,52]. These findings furtherly confirm the vasoprotective action of adiponectin45[53-60] and how this molecule may negatively modulate atherogenesis also by means its influence on inflammatory variables such as TNF-α.

The pathophysiology of insulin resistance and atherosclerosis share a common inflammatory basis. Thus some authors[59] to test this hypothesis, evaluated 40 patients with a myocardial infarction [M]. Endothelium-dependent flow-mediated dilation (FMD) and -independent nitroglycerine vasodilatation (determined by ultrasound), S(I) (insulin sensitivity index; determined by isoglycaemic-hyperinsulinaemic clamp) and serum levels of CRP, TNF-α, IL-6, resistin and adiponectin (determined by ELISA) were measured. FMD, S(I) and adiponectin levels resulted significantly lower in patients with T2DM, whereas TNF-α and IL-6 levels have been observed as significantly higher in patients with T2DM. Authors also reported that TNF-α concentrations and brachial artery diameter were negatively, whereas S(I) was positively, correlated with FMD. These results indicate how endothelium is negatively impacted in multiple ways by the diabetic state after an MI also suggesting endothelium as the main organ-target of adipose-inflammatory dysfunction of diabetes.

Furthermore, in a recent paper Zietz *et al*[49] reported an association between low levels of adiponectin and low levels of HDL-cholesterol and how this relationship seems to act as independent cardiovascular risk factor. The same authors also reported that high levels of adiponectin are associated with high levels of HDL-cholesterol thus suggesting how adyponectin can be involved in a so called "cardioprotective" pathway together with HDL levels. This findings could find a confirmation in results reported by Tuttolomondo *et al*[21] showing respectively a positive

Table 8 Diabetic foot infection classification schemes: Infectious Diseases Society of America Infectious Diseases

Clinical description	Infectious Diseases Society of America
Wound without purulence or any manifestations of inflammation	Uninfected
⩾ 2 Manifestations of inflammation (purulence or erythema, pain, tenderness, warmth, or induration); anyc ellulitis or erythemaextends 52 cm around ulcer, and infection is limited to skin or superficial subcutaneous stissues; no localcomplications or systemic illness	Mild
Infection in a patientwho is systemicallywell and metabolicall ystable buthas 2 cm; lymphangitis; spread beneath fascia; deeptissue abscess; gangrene; muscle, tendon, joint, or bone involvement	Moderate
Infection in a patient with systemic toxicity or metabolic instability (*e.g.*, fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, hyperglycemia, or azotemia)	Severe

Adapted from Lavery *et al*[67].

(for IL-6 and resistin) and negative [for adiponectin] correlation in subjects with diabetic foot with regard of some metabolic markers and some clinical and laboratory variables. Recently DFS has been reported by Pinto *et al*[19] as a predictive factor of cardiovascular morbidity in diabetic patients.

Other research underlined the positive correlation between inflammatory cytokines and cardiovascular morbidity in diabetic patients. Tuttle *et al*[52] reported higher degree of serum levels of IL-6 and TNF-α in diabetic women with and without CVD compared to nondiabetic women thus suggesting a common inflammatory state in both diabetes and cardiovascular diseases.

In diabetic foot have been described some abnormalities such as an inflammatory state, low collagen levels due to low synthesis and higher degradation and these changes have an important role in impairment of wound healing. Cathepsin D, an aspartic endopeptidase is able to reverse the inhibition of collagen biosynthesis in wounded rat skin with diabetes. Some authors[54] reported how patients with diabetic foot ulcer have higher median plasma level of Cathepsin D and lower median plasma levels of adiponectin, also showing a positive correlation between variables such as ulcer severity, BMI, A1c and retinopathy and Cathepsin D and a negative correlation with adiponectin. Thus most of research experiences seem to suggest that atherosclerosis in diabetes could be a real inflammatory disorder. A study[60] evaluated the prevalence of inflammatory markers such as high-sensitivity CRP, adiponectin, and nuclear factor-κB (NF-κB) expression, in peripheral blood mononuclear cells in patients with type 2 diabetes mellitus (T2DM) with and without macrovascular disease. Authors reported how diabetic subjects with T2DM showed a higher hsCRP and NF-κB expression and a lower degree of adiponectin serum levels compared to healthy controls.

INFECTIONS IN PATIENTS WITH DFS

Definition of diabetic foot infections (Table 8) indicate infectious diabetic foot as a "clinical syndrome characterized by the presence of local signs of inflammation such as redness, warmth, induration, pain or tenderness and purulence, sometimes in the context of a framework of sepsis, that occurs in a site below the malleoli in a person with diabetes"[61]. Infections on diabetic foot can represent a common and dangerous complication of diabetes owing to the fact that they can involve deeper soft and bone tissuse (cellulitis and osteomyelitis) thus significantly increasing the risk of amputation.

Diabetes is the main cause of non-traumatic amputation of the lower limbs in the world. In a recent study[62,63] enrolling patients with DFS, infections increased the risk of a minor amputation by 50% compared to patients without infection. Among factors able to predispose to infections on diabetic foot it's possible to include: foot ulcer duration of longer than 30 d, a history of recurrent foot ulcers, traumatic causes, peripheral vascular disease and neuropathy.

Wound infections are polymicrobial including gram-positive cocci (Staphylococcus aureus, β-streptococci, usually group B, or coagulase-negative staphylococci), Gram-negative rods (*e.g.*, *Escherichia coli*, Proteus, Klebsiella), sometimes including non-fermentative Gram-negatives (*P. aeruginosa*), and anaerobes (*e.g.*, *Finegoldia, Bacteroides*).

Infectious Disease Society of America (IDSA) guidelines indicate that infection on diabetic foot is present when there is purulent drainage and/or the presence of two or more signs of inflammation[63]. Possible infection signs are: fever, chills, hypotension, anorexia, nausea, vomiting, change in mental status and hyperglycaemic state and blood abnormalities such as leukocytosis, elevated sedimentation rate, CRP or procalcitonin levels or positive blood cultures are further signs of a severe infection. Nevertheless in more than 50% of patients with diabetes and infectious DFS these signs were absent[64].

Different classification systems developed in the last years for the stadiation of diabetic foot infections, but a widely accepted method is the IDSA classification scheme, with four progressive levels of infection and with a good correlation with clinical findings[65,66].

The diabetic foot ulcers require an appropriate antimicrobial treatment preferably targeted on the basis of microbiological culture and that includes agent active against gram positive cocci which are the most common pathogens. Surgical management is sometimes necessary.

PERIPHERAL ARTERIAL DISEASE AND DFS

Diabetic foot ulceration (DFU) with its high morbidity and mortality represents an important cause of hospitalization in

diabetics and it is an independent risk factor for peripheral arterial disease. PAD, presents in half of patients with DFU, is a condition characterized by steno-obstructive lesions downstream of the renal arteries that lead to a reduction in the perfusion of the lower limbs and it represents a common cause of impaired ambulation and is a leading cause of lower extremity wounds and amputations[53,54]. In fact, diabetes mellitus which can be considered as a whole as an inflammatory disease is burdened with microvascular complications such as nephropathy, retinopathy and neuropathy and macrovascular complications including stroke, myocardial infarction (MI), and PAD that occur earlier than in nondiabetic patients and the underlying pathologies are often more diffuse and severe.

Microvascular and macrovascular complications of diabetes although they affect small vessels, and large vessels, have a similar pathogenetic background. Chronic hyperglycemia has a leading role in this pathogenetic pathway that leads to vascular complications by means either metabolic and structural abnormalities such as advanced glycation end products (AGE) production, activation of protein kinase C (PKC), high degree of reactive oxygen species (ROS, oxygen-), and impairment hemodynamic regulation and activation of the renin-angiotensin system (RAS).

Other pathogenetic factors are inflammation, coagulation disorders, smooth muscle cell involvement, endothelial dysfunction, impairment of blood supply and impairment of platelet action.

Diabetic arteriopathy is characterized by changes in the arterial wall that include arterial narrowing with increased intima-media thickness. The first site of injury is the vascular endothelium that is the central candidate barrier against atherogenesis process. Endothelium produces important substances such as nitric oxide (NO) that induces vasodilatation and also regulates platelet-vessel wall interaction, thereby functioning as an antiplatelet agent.

The alterations that occur in diabetes such as chronic hyperglycemia and insulin resistance alter the endothelial production of NO and impaired arterial vasodilation in diabetes. In addition to the reduction in the vasodilatory response in diabetes occurs overproduction of vasoconstrictor substances such as endothelin 1. This endothelial dysregulation causes structural and functional alterations that characterize the later diabetic arterial disease[67-69]. Another atherosclerotic pathogenetic background is an inflammatory activation. In fact, an increased expression of adhesion molecules induces inflammatory cells cross endothelial barrier and reach into intima media of the vessel wall and subsequent ingesting oxidized LDL and forming foam cells, an important component of atherosclerotic fatty streaks that represent an early marker of macrovascular disease.

Impairment in coagulation, fibrinolysis, and platelet action, represents the basis of the thrombophilic state leading to increased risks for thrombogenesis, atherosclerosis progression, and plaque events which are involved in the development of cardiovascular complications in diabetes. Age and duration of diabetes are strictly related with frequency of PAD in both diabetic and nondiabetic patients. Other risk factors such as hypertension, smoking, and blood lipid disorders have a high prevalence in diabetic subjects thus enhancing vascular risk. However, if the supply of blood fails to satisfy ongoing metabolic requirements as a consequence of arterial narrowing, symptoms will occur, the severity of which depends on the degree of arterial narrowing, number of arteries affected, and the activity level of the patients. PAD can present with pain of one or more lower extremity muscle groups related to activity (intermittent claudication), atypical pain, pain at rest, or with nonhealing wounds, ulceration, or gangrene.

Clinical history and physical examination are essential to diagnose a condition of PAD in a diabetic subject. Suggestive of PAD diagnosis are a history of intermittent claudication, coronary artery disease, cerebrovascular events, foot ulcers, angioplasty, or surgical bypass.

Objective exam can help to determine the extent and distribution of peripheral vascular disease[70,71] in diabetics, but measurement of the ankle-brachial index (ABI) calculated as systolic blood pressure at posterior tibial or dorsalis pedal level compared with brachial blood pressure, is a useful method to evaluated an occlusive PAD. An ABI of $\leqslant$ 0.90, is higly sensitive and specifical for a diagnosis of PAD. To assess the severity of the perfusion, the evaluation of below-knee vessels is particularly important in patients with diabetes and duplex ultrasound is a first line investigation[72].

Multiple factors impair wound healing in diabetes in addition to PAD. Patients with mild PAD and ABI > 0.6, should be initially managed with local wound care (debridement and treatment of infection) and a period of observation. Extended ulcers and infected ulcers with a poor extended outcome a early vascular intervention may be required[73]. Revascularization is indicated for critical limb ischemia and for some patients with claudication. Surgical risks and the degree of severity of foot ulcers may influence the surgical therapeutic option *vs* endovascular intervention. Thus depending upon the characterization of a given arterial lesion, a diabetic patient with PAD may benefit from a surgery-first or an angioplasty-first approach. Most diabetics with critical ischemia have popliteal/tibial site of occlusion thus therapeutic option requires a surgical approach below-the-knee or bypass grafting[74].

A study conducted by Ciccone *et al*[75] evaluated the outcome of patients with diabetic foot who underwent angioplasty (PTA) revascularization. Authors reported at 1 year follow-up, a "major"/"minor" events incidence of 15%. Authors also reported that obesity, high LDL levels and an arterial lesion at a distal site were statistically significantly associated with major events and how high levels of inflammatory markers such as PCR had a significant relationship with the ulcer recurrence.

The results of this study highlighted the fact that diabetic foot disease is an important social problem because of the hight incidence in the population and the risk of major and minor complications and therefore a rapid diagnosis and prompt revascularization treatment, if needed, are essential to improve the quality of live

and prolong survival. Nevertheless, other experimental therapeutic options could be useful in clinical setting of diabetic foot ulcerations. Clinical care of patients with foot ulcers and infection is not easy and often it is required a revascularization treatment by surgical or endovascular approach. However, it is appropriate to consider novel therapeutic approaches such as extracorporeal shockwave (SW). Extracorporeal SW therapy could improve the natural course of such a disease due to its action on the endothelium of blood vessels to improve angiogenesis and ameliorate symptoms in patients with limb ischemia. A recent study conducted by Ciccone *et al*[76] analyzed the effects of SW therapy in patients with PAD. In this study twenty-two patients were enrolled and were randomly assigned into two groups: SW treatment (12 patients, 67 ± 9 years) and control (10 patients, 68 ± 12 years). Stenosis greater than 75% causing a hemodynamic impairment was treated with SW therapy. All patients underwent a Doppler ultrasound of the lower limb arteries in their entirety and a clinical-functional evaluation of their condition (*e.g.*, ABI) before and after the treatment. Findings of this study showed a significant improvement of stenosis degree after treatment in patients treated with SW.

In addition, a significantly higher number of treated patients than controls showed a reduction in the Fontaine stage. On the basis of these data, although studies in larger samples are needed to confirm the results of this study, the authors hypothesized that SW therapy could represent a useful tool in PAD therapy, and may prepare patients for more aggressive therapy.

FOCUS ON NON ALCHOLIC FATTY LIVER DISEASE AND DIABETES

Non-alcoholic fatty liver disease (NAFLD) is a frequent comorbidity in diabetic subjects (type 2 diabetes mellitus) and in those with metabolic syndrome (MS), with a frequence of more than 30%. NAFLD represents the hepatic organ damage related to MS that encompasses multiple cardiovascular risk factors and that recognize as central pathogenetic basis insulin resistance and as clinical expression several diseases such as visceral obesity, hypertension, blood lipid disorders and type 2 diabetes. The term NAFLD encompasses some hepatic disorders with the primary pathologic findings of microvesicular hepatic steatosis that occurs without a clinical history of significant alcohol consumption. In this clinical setting context it has been distinguished a disease with histologic essential fat accumulation (steatosis) and a disease in which steatosis coexists with a state of liver-cell injury and inflammation called non-alcoholic steatohepatitis (NASH). These two conditions show an increased prevalence and incidence thus becoming a real public health problem due to their strict relationship with diabetes and obesity pandemias. The pathogenesis of NAFLD is not fully clear, but insulin resistance appears to be as the main pathogenetic metabolic event, even if many other predisposing conditions such as obesity, oxidative stress, cytokine/adipokine axis have been reported as plausible coexisting pathogenetic[77].

Insulin resistance represents the clinical expression of the inability of endogenous insulin to enhance glucose uptake and its utilization and it is the physiopathological main factor able to induce the metabolic syndrome. Insulin acts by means of binding to its plasma membrane receptor and its effects are mediated by a series of cellular messengers acting by mechanisms of protein-protein interactions that have been reported as impaired by several factors such as increased levels of fatty free acids (FFAs), oxidative damage, inflammation and abnormalities of cytokines/adipokines interplay able to induce a peripheral (muscle and adipose tissue) and hepatic insulin resistance. Insulin resistance enhances hepatic lipid accumulation thus increasing liver FFA influx and stimulating some enzymes involved in lipogenesis in liver and thus may be indicated as the typical physiopathological finding of NAFLD[78]. Furthermore, visceral fat plays a central role in the pathogenesis of insulin resistance and NAFLD owing to the fact that adipose tissue is not an inert tissue but it acts as a real active endocrine organ, thus furtherly impairing insulin resistance and influencing cytokine/adipokine pathways in terms of increased levels of FFA, adiponectin, leptin, TNF-α, IL-6. In particular adiponectin acts as a leading mediator in this pathogenetic events and its decreased levels are directly related to steatosis grade owing to the fact that adiponectin has a protective role decreasing lipid accumulation and fibrosis processes in liver[79].

Fatty free acids represent a well demonstred pathogenetic markers of insulin resistance and of its complications such as NAFLD owing to the fact that FFA cause liver cellular apoptosis and impair interplay between hepatic cells and immune system, cytokines, ROS and finally also impairing insulin production and signaling mechanisms[80-86].

FFA and their derivatives induce insulin resistance, increase liver inflammation and promote instability in atherosclerotic plaque by a common pathogenetic pathway involving Jun N-terminal kinases (JNKs) that are one of the mitogen-activated protein kinase (MAPK) superfamily as pointed out by some authors in a recent work[87]. High degree of oxidative stress and its related JNK activation, as well as an impaired activation of pro- and anti-apoptotic proteins of the Bcl-2 family has been reported as factors able to contribute to hepatocyte apoptosis in a murine model of non-alcoholic steatohepatitis[88]. Therefore, a direct role is attributed to FFAs that seem able to directly cause the apoptotic events by activating the proapoptotic protein Bax, by menas c-jun N-terminal kinase-dependent mechanisms as reported by a recent study conducted by Tarantino *et al*[89]. In this study authors analyzed the relationship between anti-apoptotic serum Bcl-2 concentrations and grade of steatosis and inflammation in subjects with NAFLD and steatohepatitis (NASH) reporting a significant predictive value of Bcl-2 serum levels towards a higher frequency of metabolically unhealthy overweight/obese patients (MUOs) (obese subjects without hepatic steatosis) suggesting that the anti-apoptotic process could have a significant role to block FFA hepatotoxic actions. Although the development of NAFLD has some common mechanisms with the

development of metabolic syndrome, as they share the pathophysiologic basis of insulin resistance, NAFLD is currently not a component of the diagnostic criteria for metabolic syndrome. Nevertheless a recent study showed that ultrasonographically detected NAFLD could act as a possible predictive factor of insulin resistance[90,91]. On this basis US-NAFLD could be used as a new criterion to define metabolic syndrome also in consideration of the high sensitivity and specificity of abdominal US in the diagnosis of NAFLD. These data have been underlined by Tarantino *et al*[91] in a recent article. In the light of the various pathways thought to be central in the pathogenesis of NAFLD, the main therapeutic approach consists in the modification of risk factors, in particular lifestyle through diet and physical activity and the more promising pharmacological approach seems to be the use of drugs able to improve insulin sensitivity such as metformin and PPAR (Peroxisome Proliferator Activated nuclear Receptor agonist). However, further studies on the pathogenesis of NAFLD would be needed to identify new potential therapeutic targets in these patients and to define the most appropriate pharmacological and non-pharmacological therapeutic approach. Therefore, NAFLD is commonly associated with the metabolic syndrome which is considered as the hepatic expression and results from a complex interaction between genetic and environmental factors with insulin resistance as a fundamental pathogenic mechanism and in consideration of the progressive increase in the prevalence of insulin resistance, NAFLD/NASH should be considered as emerging diseases, involving a high percentage of the Western population.

CONCLUSION

Diabetic foot and its related clinical conditions such as foot ulcers and infective complications represent the most common cause of hospitalization in subjects with diabetes. Management of DFS and its related treatment of infectious diabetic foot and amputations also represent a health problem in terms of cost (several millions of euro every year).

"The majority of foot ulcers appear to result from minor trauma in the presence of sensory neuropathy." This sentence[92] underlines the critical pathogenetic triad of DFS in diabetics: peripheral sensory neuropathy, deformity, and trauma. These risk factors have been reported as present in more than 60% of diabetic foot complications.

Our review aimed to underline the complex metabolic and inflammatory interplay that could explain high cardiovascular event rate of patients with diabetic foot. Diabetic vascular complications recognize a well described inflammatory pathogenesis, but only few studies evaluated immune-inflammatory background of DFS.

Only a few previous studies[18-21] evaluated inflammatory markers such as cytokine and adypokines in patients with diabetic foot. Nevertheless several reports clearly underlined the role of low serum level of adiponectin that has been reported as complex metabolic and inflammatory axis able to predispose to atherogenesis. Adiponectin with its anti-inflammatory and vascular effects in is able to inhibit inflammatory effects of vascular adhesion molecules and scavenger receptors and to lower the expression of the inflammatory cytokine TNF-α, furthermore adiponectin enhances NO production and inhibit the proliferation and migration of smooth muscle cells[93].

Findings reported by Tuttolomondo *et al*[21] of low serum levels of adiponectin and the significant negative correlation between adiponectin and several traditional cardiovascular risk factors in subjects with diabetic foot could represent a well confirmation of this issue. Thus owing to the fact that several cytokines are also produced by adipose tissue[46] it has been hypothesized that the high rate of cardiovascular events in diabetes could be due to a pathogenetic axis called as an "adipo-vascular" axis[44]. This "adipo-vascular axis" represented by low serum levels of adiponectin and high serum levels of IL-6 and resistin could be related to foot ulcers pathogenesis by microvascular and inflammatory mechanisms.

Adiponectin has been also reported by recent studies as involved in the regulation of inflammatory vascular response by reducing the expression of adhesion molecules on endothelial cells[62], impairing endothelial cell NF-κB-related mechanisms[45] and altering macrophage actions[64]. A recent research also reported how adiponectin inhibits the TNF-α related expression of E-selectin, VCAM-1and ICAM-1 in human endothelial cells[46] thus indicating how adiponectin has been evaluated as real vasoprotective and anti-atherogenic factor .

Recently, Ouchi *et al*[48] showed how low degree of serum adiponectin is linked to low levels of HDL-cholesterol, thus representing a real independent cardiova-scular risk factor, whereas high levels of adiponectin are associated to a protective cardiovascular risk profile associated to high levels of HDL-cholesterol. Findings by Tuttolomondo *et al*[21] of a positive (for IL-6 and resistin) and negative (for adiponectin) correlation in subjects with diabetic foot between these immuno-inflammatory and metabolic markers and some clinical and laboratory variables could represent a further confirmation of the crucial role of inflammatory and metabolic "milieu" such as cytokines and adipose hormones in foot complications in diabetics, as already reported for other vascular complications of diabetes.

Thus inflammation marker evaluation has in DFS multiple points of potential importance concerning a better evaluation and analysis of these crucial key points: (1) pathogenetic role in ulcers and their micro and macro-vascular background; (2)possible link between inflammation state and adipo-metabolic axis; (3) predictive role towards foot complications such as ulcers incidence; (4) putative role as markers of gravity of wounds and ulcers in a diabetic foot; (5) association with cardiovascular co-morbidity (prevalent and incident) in subjects with DFS; (6) prognostic role towards ulcer healing; (7) strict association with peripheral artery comorbidity (PAD); and (8) pathogentic links with metabolic syndrome and NASH[93-99].

It explains that a strict and prospective inflammation

marker evaluation could be useful in practical management of foot complications in diabetic subjects in every medical setting (Internal Medicine, Diabetology, Surgery, Orthopedics) to better evaluate a complex disease such as DFS in a multispecialistic management contest.

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P- Reviewer: Chang ST, Ciccone MM **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.77

World J Orthop 2015 January 18; 6(1): 77-94
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (4): Hip

Biotribology of artificial hip joints

Francesca Di Puccio, Lorenza Mattei

Francesca Di Puccio, Lorenza Mattei, Department of Civil and Industrial Engineering, University of Pisa, 56126 Pisa, Italy
Author contributions: The two authors co-worked in the preparation of the paper, revision of the literature and collecting the data; Mattei L also performed numerical simulations.

Correspondence to: Lorenza Mattei, MD, PhD, Department of Civil and Industrial Engineering, University of Pisa, Largo Lazzarino, 56126 Pisa, Italy. l.mattei@ing.unipi.it
Telephone: +39-050-2218019
Fax: +39-050-2218069
Received: December 28, 2013
Peer-review started: December 29, 2013
First decision: February 13, 2014
Revised: March 25, 2014
Accepted: May 14, 2014
Article in press: May 14, 2014
Published online: January 18, 2015

Abstract

Hip arthroplasty can be considered one of the major successes of orthopedic surgery, with more than 350000 replacements performed every year in the United States with a constantly increasing rate. The main limitations to the lifespan of these devices are due to tribological aspects, in particular the wear of mating surfaces, which implies a loss of matter and modification of surface geometry. However, wear is a complex phenomenon, also involving lubrication and friction. The present paper deals with the tribological performance of hip implants and is organized in to three main sections. Firstly, the basic elements of tribology are presented, from contact mechanics of ball-in-socket joints to ultra high molecular weight polyethylene wear laws. Some fundamental equations are also reported, with the aim of providing the reader with some simple tools for tribological investigations. In the second section, the focus moves to artificial hip joints, defining materials and geometrical properties and discussing their friction, lubrication and wear characteristics. In particular, the features of different couplings, from metal-on-plastic to metal-on-metal and ceramic-on-ceramic, are discussed as well as the role of the head radius and clearance. How friction, lubrication and wear are interconnected and most of all how they are specific for each loading and kinematic condition is highlighted. Thus, the significant differences in patients and their lifestyles account for the high dispersion of clinical data. Furthermore, such consideration has raised a new discussion on the most suitable *in vitro* tests for hip implants as simplified gait cycles can be too far from effective implant working conditions. In the third section, the trends of hip implants in the years from 2003 to 2012 provided by the National Joint Registry of England, Wales and Northern Ireland are summarized and commented on in a discussion.

Key words: Arthroplasty; Replacement; Hip; Biotribology; Wear; Lubrication; Friction

Core tip: In this paper, the biotribology of hip implants is described at different levels, from the more general definitions of friction, lubrication and wear and from some basic equations, to clinical data of different implants. The topic is presented both qualitatively and quantitatively, which we believe is an original approach for a review of this kind. Some simple mathematical tools are provided, which can also be useful for non-specialists to better understand the matter and to deal with simple tribological problems. Finally, the trends of artificial hip joints over the last ten years are discussed on the basis of tribological concepts.

Di Puccio F, Mattei L. Biotribology of artificial hip joints. *World*

J Orthop 2015; 6(1): 77-94 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/77.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.77

INTRODUCTION

Although tribological phenomena are widespread in everyday life, the word tribology sounds new and strange to most people. Thus, it is usual, before speaking of tribology to non-tribologists, to introduce its literal meaning. The term tribology comes from the Greek words *tribos* = rubbing/friction and *logos* = science, so it is defined as the science of rubbing surfaces. In other words, it is known as the science of interacting surfaces in relative motion and encompasses many concepts, such as friction, wear and lubrication[1]. Therefore, tribology is in the tyre rolling over the road, in the head-disk interface of a hard disk driver, in the blinking of the eye, and so on.

When interacting surfaces belong to the human body or animals, including artificial joints, the term biotribology is usually preferred. The importance of the tribological performance of an artificial hip joint is well known in clinical practice. In fact, although hip arthroplasty is considered one of the major successes of orthopedic surgery, wear still remains a critical issue that limits the implant lifespan to 10-15 years. The incidence of hip arthroplasties is proved by the increasing rate of procedures per year, about 332000 in 2010 in the United States[2] and 76500 in 2012 in the United Kingdom (+ 7% compared to 2011)[3]. Additionally, according to the United Kingdom National Report 2013[3], 10000 revision surgeries were performed, with a 12% increment that can be attributed to the younger and more active patients who were treated with this procedure.

This paper describes the tribological features of hip implants with the aim of providing some key concepts for analyzing and improving current designs and maybe suggesting new solutions. A background on the main concepts of tribology is premised. Finally, the trend of hip arthroplasty over the last ten years is discussed.

HIP REPLACEMENT OVERVIEW

Nowadays, the world market has several hundred different brands of hip replacements, among which the surgeon will select one on the basis of patient symptoms and characteristics (*e.g.*, gender, age) and her/his own clinical experience. This huge number of hip replacements can be classified according to their geometry (structure and dimensions) and materials. The structure of a total hip replacement (THR) and resurfacing hip replacement (RHR) can be compared (Figure 1).

The former is made up of a stem, a femoral head, an acetabular cup combined with, if cementless, a metallic shell which helps bone grow into it. RHR covers the articulating surfaces with a traditional cup and a head liner, thus preserving more bone. Both types of implants are available in several sizes but, in general, RHRs are characterized by bigger heads which should improve the implant stability.

The most commonly used materials for implant components are plastic (P), metal (M) and ceramic (C). The plastic is used only for the socket, whilst the others are used for both head and cup. The most common material combinations for the bearing surfaces are: metal-on-plastic (MoP), ceramic-on-plastic (CoP), ceramic-on-ceramic (CoC) and metal-on-metal (MoM) (Figure 2). In these acronyms, the first letter refers to the cup material and the third to the head. It is worth noting that RHRs are available only in MoM (MoMRHR) or CoM combinations. As the materials strongly influence the device tribological behavior, some further details on their properties will be discussed in Sec. 4.2.

BASIC BACKGROUND ON TRIBOLOGY

In this section, the basic aspects of tribological phenomena are summarized in order to provide the main concepts for understanding the behavior and design of implants. More detailed explanations can be found in tribology textbooks as in[4,5].

Let us consider two interacting surfaces in relative motion. Phenomena that occur between them can be considered at macro or micro scale and are mainly dependent on the loading and kinematic (motion) conditions, as well as the presence of a lubricant.

Surface mechanics

Geometrical characteristics: When dealing with the geometrical characteristics of interacting bodies, a first distinction is made between conformal and non-conformal surfaces; in the first case, surfaces fit together geometrically so that the contact involves a wide area, while the opposite happens in the second case.

From a mechanical point of view, the natural/artificial hip is considered a conformal spherical or ball-in-socket joint, where the head and the cup have the same nominal radius. For practical manufacturing but also tribological reasons, a small clearance between the elements, usually in the order of tenth of microns, is properly defined. The higher the clearance, the less conformal the surfaces.

The nominal contact surfaces of the cup and head are portions of spheres. However, real surfaces (even in the initial unworn conditions) can have some deviations from the nominal shape, which are usually described in terms of roundness, waviness and roughness (Figure 3). The roundness (Figure 3A) defines the maximum radial distance between two concentric spheres that limits the real surface of the cup/head; it is associated with the manufacturing process and is usually in the order of a few microns.

In Figure 3B, a scheme of the nominal and real surfaces is reported, showing the meaning of waviness and roughness as deviations from the nominal profile, the former on a wider wavelength than the latter. It can be

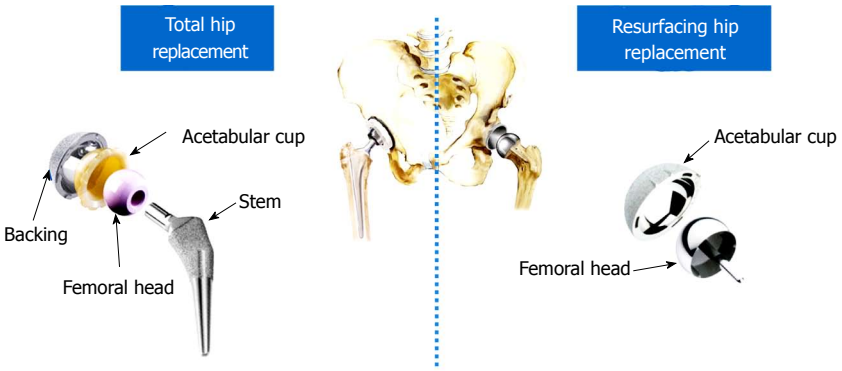

Figure 1 Total and resurfacing hip replacements.

Figure 2 Material couplings in hip implants.

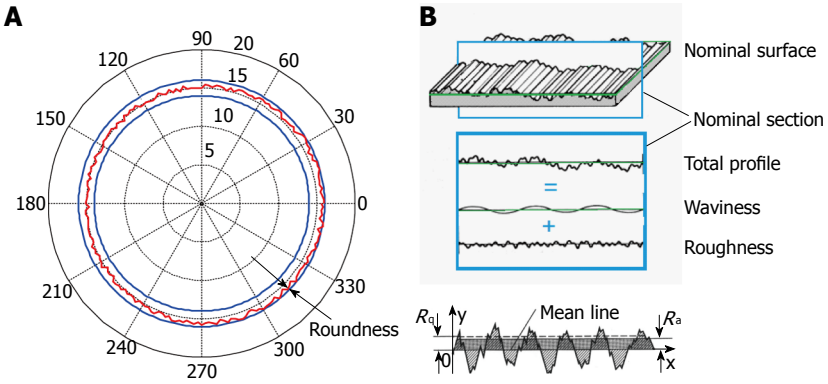

Figure 3 Nominal *vs* real surfaces. A: Roundness; B: Roughness and waviness. Adapted from ASME B46.1-1995.

observed that roughness refers to the micro scale (finely spaced) irregularities of the real/measured surface, which can be described by means of several parameters, such as the average roughness R_a and the root mean squared roughness R_q, defined as

$$R_a = \sqrt{\frac{1}{n}\sum_{i=1}^{n}|y_i|} \quad \text{and} \quad R_q = \sqrt{\frac{1}{n}\sum_{i=1}^{n}y_i^2} \qquad (1)$$

where $i = 1..n$ is the number of points where heights y_i were measured (Figure 3B).

The surface characteristics can vary during the lifetime of an implant, mainly as a consequence of wear phenomena, with a reciprocal adaptation of mating surfaces.

Contact forces: Tribological investigations usually move from the analysis of the contact problem of mating surfaces that means the estimation of the contact pressure at the interface at a macro scale level. For this purpose, two approaches are usually adopted in the literature, based on analytical formulas or numerical methods. However, both approaches are founded on the fundamental concept that real bodies are not rigid but (under given conditions) behave elastically, meaning that they can deform when loaded and go back to the initial shape as soon as the load is removed. The elasticity of the bodies depends on the material elastic properties that, in simple cases, are characterized by two quantities: the elastic or Young's modulus E and the Poisson's ratio ν.

The most widely used analytical solution for the contact actions between non-conformal bodies is due to Heinrich Hertz[6] (1882) and quantifies the contact pressure and the contact area (Figure 4). Such a solution assumes that, when two spheres 1 and 2 are in contact, the interacting surface

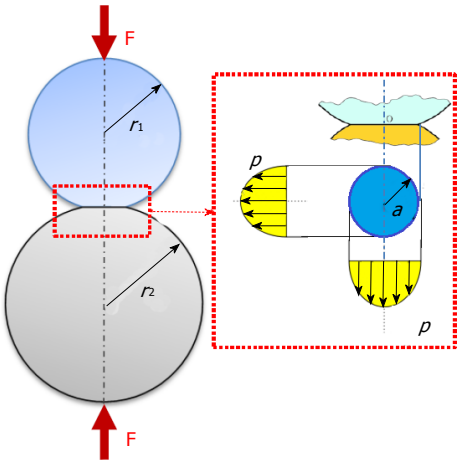

Figure 4 Hertz problem of spheres in contact.

can be approximated by a plane circle of radius *a*, which depends on the load F (of magnitude $|F| = F$) on the sphere radii (r_1 and r_2) and the material properties (E_1, ν_1 and E_2, ν_2) according to the following equations:

$$a = \sqrt[3]{\frac{3F\,r_{eq}}{4E_{eq}}} \tag{2}$$

where

$$\frac{1}{r_{eq}} = \frac{1}{r_1} \pm \frac{1}{r_2} \quad r_2 > r_1 \tag{3}$$

$$\frac{1}{E_{eq}} = \frac{1-\nu_1^2}{E_1} + \frac{1-\nu_2^2}{E_2} \tag{4}$$

The sign in equation (3) should be plus for external spheres (as in Figure 4) and minus for a sphere in a cup. Accordingly, pressure distribution can be calculated as

$$p(x) = p_m\sqrt{1-(x/a)^2} \quad \text{, with } p_m = 3F/2\pi a^2 \tag{5}$$

where p_m is the maximum pressure, at the center of the contact area.

Although Hertz theory is based on the hypothesis of non-conformal surfaces (so that $a << r_1, r_2$), it is also frequently applied to the hip joints, particularly for hard-on-hard couplings (defined in Figure 2).

For soft-on-hard implants, several approximated analytical solutions were proposed, as in[7,8], usually assuming that the metal ball is much more rigid than the plastic cup, so that only the latter deforms. One of the most satisfactory solutions for a rigid sphere against a soft cup was proposed by Bartel *et al*[7] in 1985 based on geometrical considerations. However, the most widespread approach for solving contact problems is the finite element method (FEM)[9], actually implemented in a huge number of commercial codes. It can also deal with complex geometries and complex material behaviors (Figure 5).

In Figure 6, the contact radius and maximum pressure for a MoP implant, estimated according to different approaches, are compared. It can be observed that Hertz theory estimates a wider contact even larger than the cup radius and consequently a lower pressure peak. On the other side, an approximated solution by Bartel *et al*[7] appears to be in good agreement with FEM analyses obtained with the model shown in Figure 5[10].

It must be added that the above mentioned approaches hold at a macro scale level. In fact, at a microscopic scale, contact occurs among surface asperities (Figure 7), inducing higher stresses and strains, which can be the onset of microdamage as cracks, debris detachment and so on. Statistical theories of multiple asperities contact have been proposed in the literature, starting from the studies of Greenwood *et al*[11]. Their application to hip implants is still limited to a few studies[12].

Friction

Friction is commonly defined as the resistance restraining the relative motion of two surfaces. It is usually classified as rolling or sliding friction, although they can be observed simultaneously. Sliding or kinetic friction is quantified through a coefficient, the coefficient of friction (COF) *f*, defined as the ratio between the magnitudes of the tangential/friction force T and the normal force N at the interface (Figure 8):

$$f = \frac{|T|}{|N|} = \frac{T}{N} \tag{6}$$

Note that vector quantities are indicated with a normal font while their magnitude is in italics. The COF value, usually in the range 0.05-1, depends on the materials in contact, surface roughness, presence of a lubricant etc.

Equation (6) describes the first law of friction: friction force is proportional to the normal load. The second and third laws state that friction is independent of the apparent (nominal) contact area and of the sliding velocity, respectively. Such laws were derived from experimental observations but are not as general as usually expected; for example, polymers do not strictly obey them.

It is known that the major contribution to friction actions is due to the interaction between asperities, usually a combination of adhesion and deformation forces at the asperity junctions. The adhesion actions become detectable when the contact happens between clean surfaces, free from oxide or other surface films, which is not the case in implants, however. The deformation forces depend on the surface geometry and the material properties since asperities can deform elastically or plastically (permanently).

For metallic surfaces in air, contact is mainly through a thin film of oxide (apart from gold), whose thickness can be reduced by the normal load, and asperities tends to deform plastically. Also, temperature can play a role, both for oxide formation and phase transformation. Friction between ceramic materials is mainly affected by the elastic deformation of asperities. However, a wide variability of COF values can be found in the literature due to the role of environmental factors. Polymers have a peculiar viscoelastic behavior, thus deformation also induces dissipation (evident in rolling friction). Polymers usually obey the first law of friction, equation (6), only at low normal loads when the real contact area

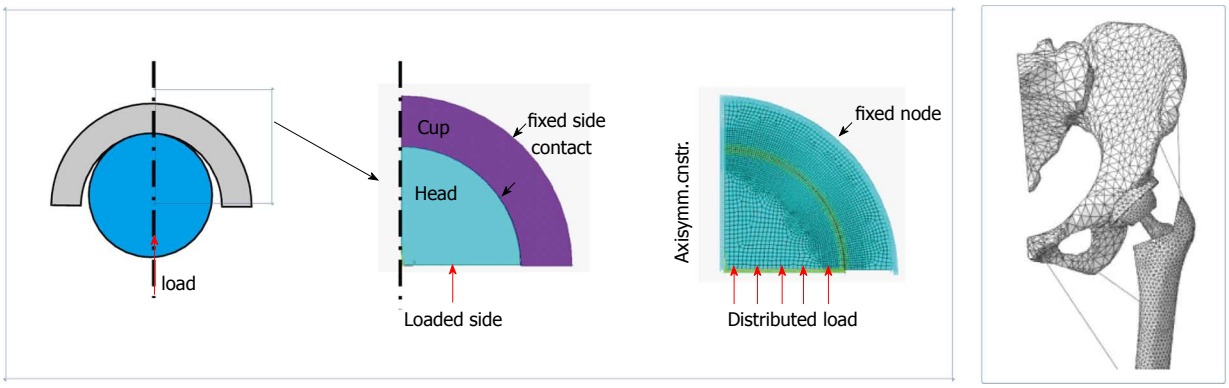

Figure 5 Examples of finite element models of hip implants.

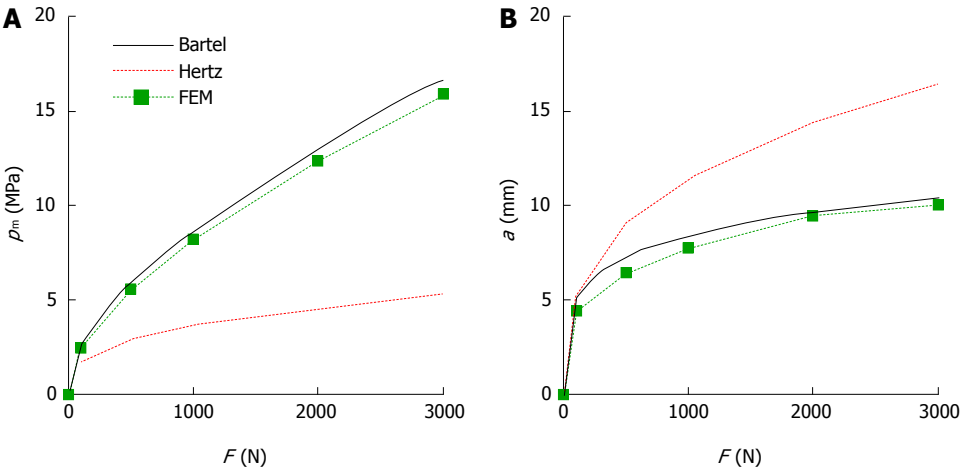

Figure 6 Maximum pressure (A) and contact radius (B) *vs* load for a MoP implant (head radius 14 mm, diametrical clearance 0.2 mm, cup thickness 6 mm).

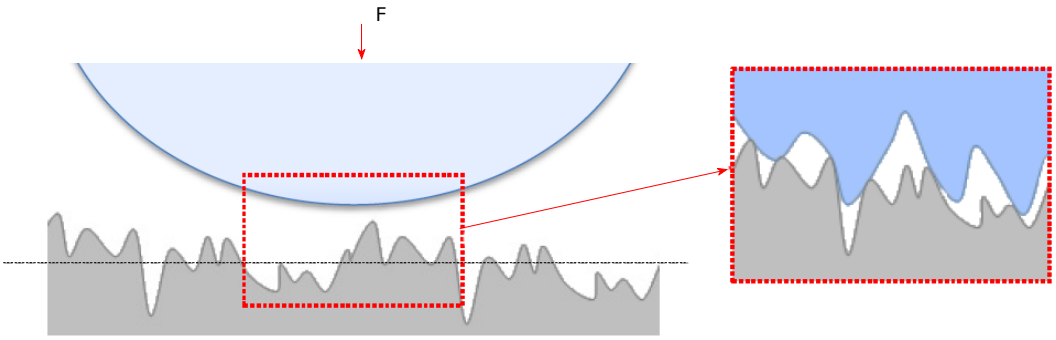

Figure 7 Microscopic detail of a rough contact.

is proportional to *N*. At high loads or for very smooth surfaces, asperities are almost flattened due to the high compliance of the material and COF decreases while *N* increases.

Finally, it is worth noting the peculiar behavior of a revolute/spherical joint with frictional contact, shown in Figure 9. Let us consider a pin rotating within a collar with constant angular velocity ω, under a load W through the center of the pin itself. In a smooth (frictionless) contact, the equilibrium of the pin is guaranteed by a normal (radial) force N = - W applied at the contact point *K* on the line of action of W. If friction cannot be neglected, the total contact force at the interface R, still with the same magnitude of W, is the sum of two components N and T, respectively normal and tangent to the surface at the contact point. Thus, in this case, *K* is shifted backwards in an angle $\phi = arctan(f)$, so that R restrains the motion and a torque Mr must be introduced to maintain the pin rotation.

Lubrication

As friction causes energy dissipation, resulting in heating or permanent surface deformation/damage, lubrication is

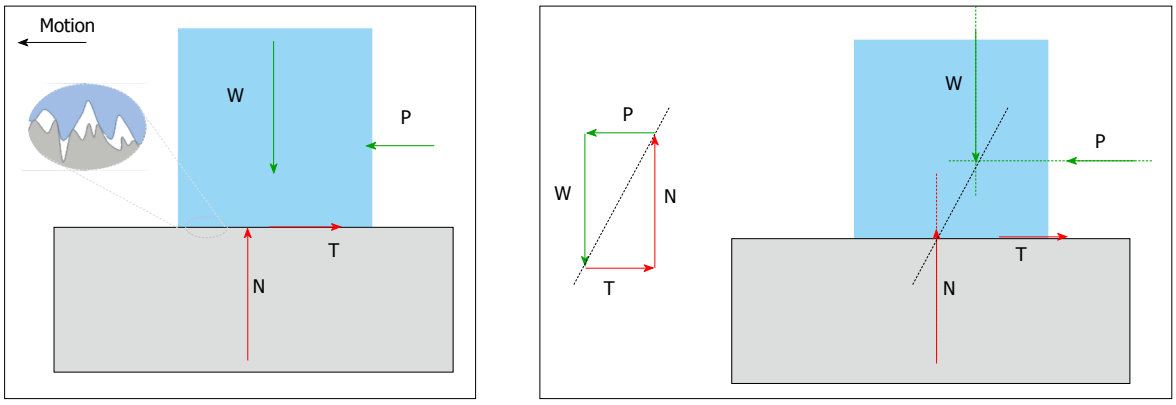

Figure 8 Forces and equilibrium in sliding contact. N and T are the normal and frictional forces acting on the upper body at the interface. Note that T is opposite to the motion direction. W and P are external forces. At the equilibrium force magnitudes must satisfy $W = N$ and $T = P$; moreover the line of action of N + T must be the same of W + P.

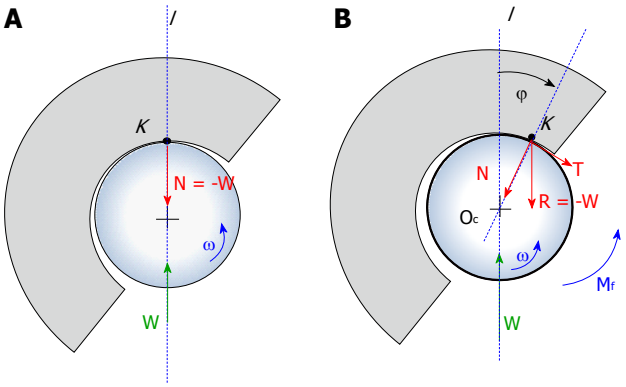

Figure 9 Forces in a revolute/spherical joint: Frictionless (A) and frictional contact (B).

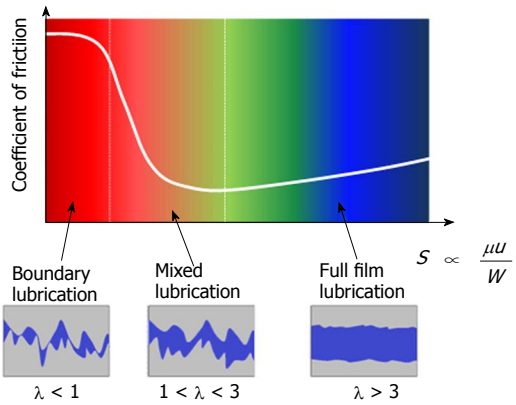

Figure 10 Stribeck diagram: Coefficient of friction *vs* Sommerfeld number and identification of lubrication regimes.

usually introduced to assist motion. The same also happens in nature, for example in synovial joints or in the eyes.

A lubricant, which can be a fluid or a solid, is interposed between the contact surfaces so that their asperities are completely separated or, at least, their interactions reduced, decreasing the frictional force. An estimate of the "distance" between the asperities of the mating surfaces is usually expressed by means of the parameter λ, which is the ratio between the minimum film thickness h_{min} and the composite roughness of the two surfaces:

$$\lambda = \frac{h_{min}}{\sqrt{R_{q1}^2 + R_{q2}^2}} \quad (7)$$

where R_q is the root mean squared roughness introduced in equation (1), subscripts 1 and 2 distinguish the two bodies in contact. It is worth noting that λ can also be estimated replacing $R_{a1,2}$ to $R_{q1,2}$ in equation (7), as they typically differ less than 10%.

The Stribeck curve, shown in Figure 10, describes the relationship between the COF and λ in three lubrication regimes: (1) Regime I ($\lambda > 3$): fluid film lubrication or hydrodynamic lubrication, where surfaces are completely separated; the pressure of the lubricant equilibrates the loading; (2) Regime II ($1 < \lambda < 3$): mixed-film lubrication, where only some asperities get in contact; the lubricant is pressurized and the loading is partly balanced by the direct contact between asperities and partly by the fluid hydrodynamic pressure; and (3) Regime III ($1 > \lambda$): boundary lubrication, where the lubricant thickness is of the order of the magnitude of molecules. The loading is carried by asperities which are protected by adsorbed molecules.

The abscissa in Figure 10 is denoted as a bearing characteristic number, or Sommerfeld number S, and for a given geometry is proportional to the dynamic viscosity of the lubricant μ, to the speed u and to the inverse of the load magnitude W, *i.e.*:

$$S \propto \frac{\mu u}{W} \quad (8)$$

Such factors determine the thickness of the lubricant meatus h, which can be estimated by means of analytical, numerical or empirical relationships.

Hydrodynamic lubrication (HDL) is based on Reynolds equations, derived from the more general Navier-Stokes equations for fluid flow, whose solution usually implies simplifications and/or numerical methods. To understand what happens in HDL, let us consider a simple two-

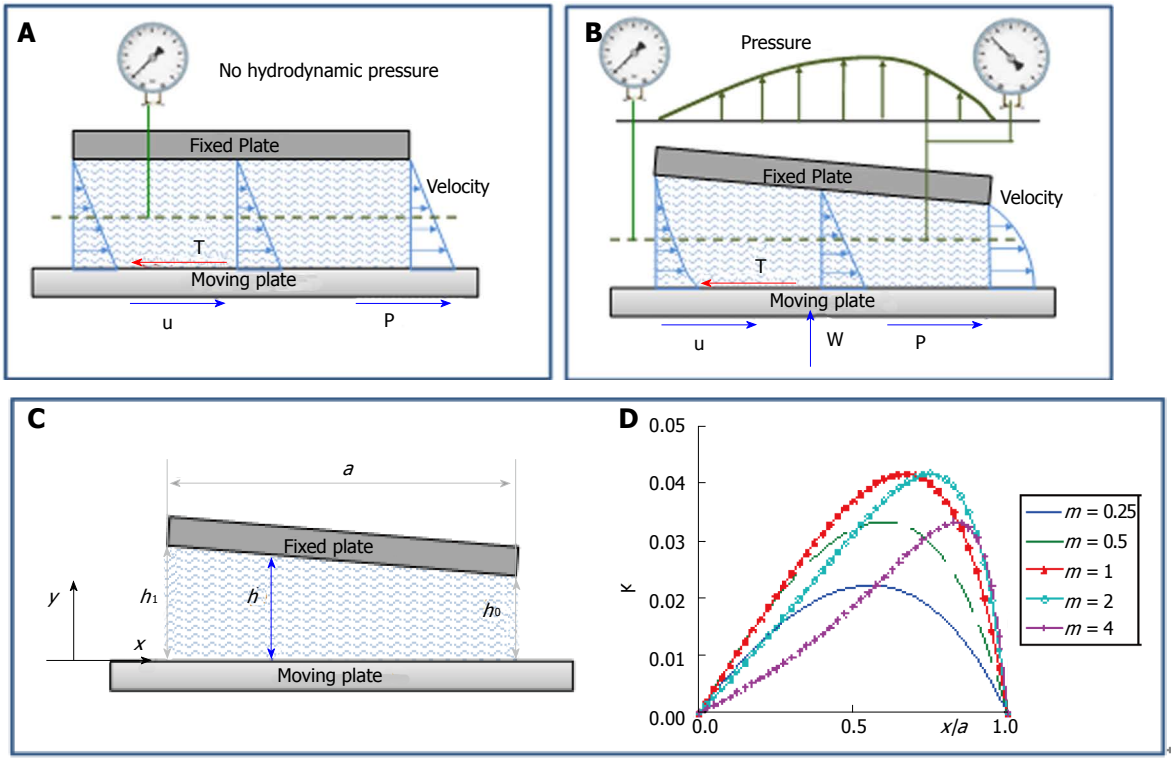

Figure 11 Hydrodynamic lubrication. A: Parallel plates; B, C: Fixed inclined slider bearing; D: k plot from equation (12).

dimensional problem with two plates, separated by a fluid meatus, moving one over the other with a relative velocity u, as in Figure 11. It can be observed that the fluid particles adhering to the fixed plate have null velocity, while those adhering to the moving plate gain its velocity u. Thus, a gradient of velocity is achieved across each cross section of the meatus, approximately given by u/h. As arguably observed by Isaac Newton, such a gradient is related to the shear actions of the fluid (on other fluid particles as well as on the delimiting surfaces) through its viscosity:

$$\tau = \mu \frac{\partial u}{\partial y} \approx \mu \frac{u}{h} \tag{9}$$

Thus, a resistance action T develops at the interface between the plates and the fluid (with an area A), having magnitude

$$T = A\tau \tag{10}$$

and a force P is required to move the plate. However, until surfaces are parallel (Figure 11A), no hydrodynamic pressure generates within the interposed lubricant as it requires a variation of τ (or of the velocity gradient) along the interface. As suggested by experience, a lift or bearing action of the fluid develops when: (1) an angle of convergence of the surfaces is introduced; (2) the plate moves orthogonally to the surfaces (squeeze); or (3) there are different pressures at the endpoints.

For a fixed plane inclined bearing, as the meatus thickness h varies along the interface, velocity profiles in the cross sections change, as shown in Figure 11B, and according to Reynolds equation:

$$\frac{d}{dx}\left(h^3 \frac{dp}{dx}\right) = 6\mu u \frac{dh}{dx}, \tag{11}$$

pressure develops within the fluid. By solving the above equation, the following relationships can be obtained:

$$p = \frac{6\mu ua}{h_0^2} k \quad \text{with} \quad k = \frac{m(1 - x/a)x/a}{(2 + m)[1 + m(1 - x/a)]^2} \quad \text{and}$$

$$m = \frac{h_1 - h_0}{h_0} \tag{12}$$

with the parameters a, h_0 and h_1 defined in Figure 11C and the pressure profiles in the meatus plotted in Figure 11D. Moreover, the normal load carrying capacity of the slider, balancing the total pressure on the moving plate, is:

$$W = b\int_0^a p\,dx = \mu ub \left(\frac{a}{h_0}\right)^2 \psi \quad , \quad \psi = 6\frac{(2+m)\ln(1+m) - 2m}{(2 + m)m^2} \tag{13}$$

that is maximum for m ≈ 1.2 and the frictional load:

$$T = b\int_0^a \tau\,dx = \mu ub \frac{a}{h_0} \theta(m), \quad \theta = 4\frac{(2+m)\ln(1+m) - 3m}{(2 + m)m} \tag{14}$$

The COF is therefore given by the ratio $f = T/W$ for this lubricated contact.

Squeeze lubrication (Figure 12) occurs when the two surfaces approach, pressurizing the lubricant, which balances the normal load:

$$W = \frac{\mu v a^3}{h^3} \tag{15}$$

where v is the squeezing speed.

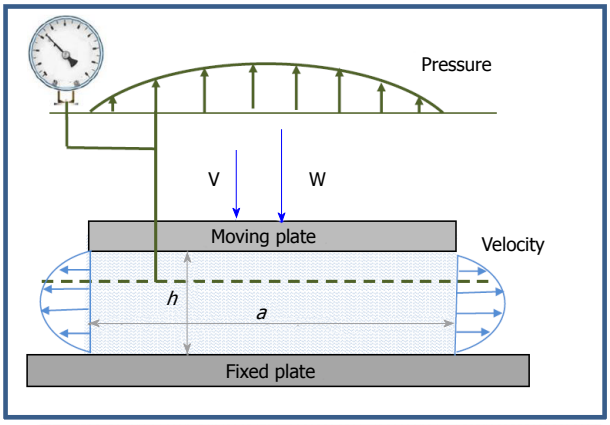

Figure 12 Squeeze film lubrication.

Things become much more complex for non-steady state or three-dimensional cases and numerical approaches are necessary to solve equations. The same happens when the description of the lubricant rheology needs to be improved, considering a non-Newtonian behavior (not obeying equation (9) even characterized by a temperature and pressure dependent viscosity (*i.e.*, piezoviscosity), *e.g.*,

$$\mu(p) = \mu_0 \exp(\alpha p) \quad (16)$$

where μ_0 and α are material constants.

Moreover, when pressure increases, surface deformations cannot be neglected, thus contributing to what becomes elastohydrodynamic lubrication (EHL), which is typical of non-conformal contacts such as cams, gears, *etc*. In such cases, contact pressure resembles a Hertzian solution, as shown in Figure 13, differing in a tail at the inlet region and a peak at the outlet, where a reduction of the meatus thickness occurs.

The solution of EHL problems usually requires numerical methods. However, several empirical formulas were proposed in the literature for estimating the minimum film thickness. As an example, for a ball on plane case, the following relationships are usually applied[4]:

$$h_{min} = 2.79 r_{eq}^{0.77} \mu^{0.65} u^{0.65} E_{eq}^{-0.44} W^{*-0.21} \quad (17)$$

$$h_{min} = 1.79 r_{eq}^{0.47} \alpha^{0.49} \mu_0^{0.68} u^{0.68} E_{eq}^{-0.12} W^{*-0.07} \quad (18)$$

which hold for isoviscous and piezoviscous lubricants, respectively.

For spherical joints, such as the hip joint, two models are usually used for describing lubrication: a ball-in-socket and an equivalent ball-on-plane model[13,14]. The former employs Reynolds equations in spherical coordinates, where the elastic deformation can be estimated by means of the spherical fast Fourier transform or the multi-level multi-integration methods, both typically requiring a FE analysis for evaluating the deformation coefficients. On the other hand, ball-on-plane equivalent models, where the ball radius is r_{eq} defined in equation (3), are much simpler but have been proved to provide satisfactory approximations, at least for hard-on-hard implants[13].

Wear

Wear is a surface damage combined with material loss or transfer between the articulating surfaces. Several wear mechanisms have been identified in the literature, here reduced to four types for simplicity: adhesion, abrasion, surface fatigue and tribochemical reactions (Figure 14).

Adhesive wear is used when local welding between asperities occurs, subsequently broken in the movement. Abrasion is due to the action of hard particles or asperities that plough the softer counterpart. Surface fatigue is due to repeated stress cycles in the subsurface material, which can be the onset of microcracks and debris detachment. Finally, tribochemical reactions, as corrosion, can be produced by a chemical reaction between surface materials and the interposed fluid.

Wear depends on many factors so it can be rather hard to predict which mechanism will affect the sliding bodies. This is done usually a posteriori and in many cases several types of wear are detected, as reported in[15] for knee replacements.

In this part, we will deal with sliding wear, meaning a combination of adhesive and abrasive wear, and in particular with the mathematical relationships that can be used to predict it, in terms of loss/worn volume V. Moving on experimental observations on metallic surfaces, in 1956 Archard proposed a rather simple wear law[16], known as Archard law, stating that:

$$V = K N s / H \quad (19)$$

where N the normal load, H the material hardness, s the sliding distance and K the (adimensional) wear coefficient. Most frequently, a modified version with a dimensional wear coefficient k is employed

$$V = k N s \quad (20)$$

also expressed as wear rate, by time-deriving and introducing the sliding speed v

$$dV/dt = kNv \quad (21)$$

More detailed information is achieved by means of wear maps, describing the wear depth (linear wear h) at every single point of the surface.

The wear coefficient is fundamental for estimating the wear strength of a coupling; for example, in dry contacts K can range from $1.3\ 10^{-7}$ to $7\ 10^{-3}$ for steel-mild steel and polyethylene-steel couples, respectively[16]. Such values refer to the steady state phase of the wear process, approximately above 1 million cycles. Higher wear coefficients are typically observed for the initial running-in phase, according to Figure 15.

Usually such coefficients are determined experimentally by means of pin-on-disc test rigs. However, as wear and both k-K are affected by many variables, from the lubrication regime, to temperature, to loading condition etc., it is important that wear tests reproduce the real operating conditions of the coupling. This is the reason why specific hip/knee simulators were developed, for replicating the loading and kinematic conditions of a gait cycle. However, it is still under discussion whether a simplified gait cycle, *e.g.*, the one suggested by standard (ISO), is really representative of the joint operative conditions since remarkable differences are observed in worn volumes/surfaces of *in vitro* tested and retrieved implants.

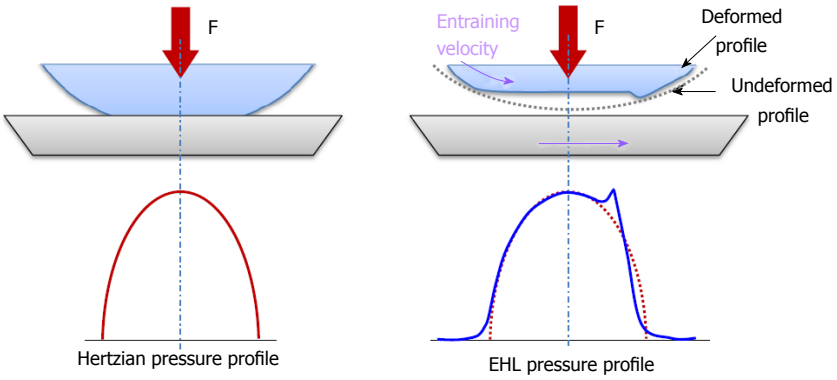

Figure 13 Dry and lubricated contact: From Hertzian to elastohydrodynamic lubrication pressure profiles. EHL: Elastohydrodynamic lubrication.

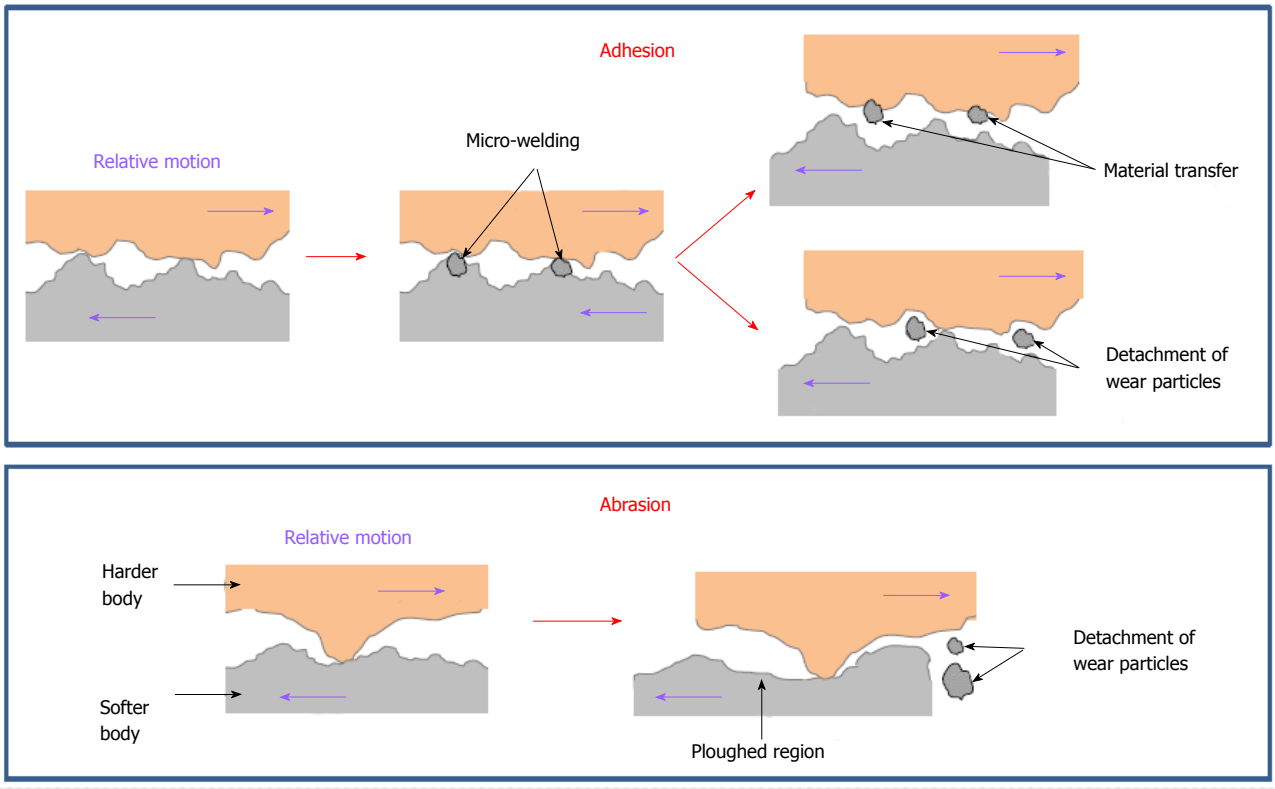

Figure 14 Adhesion and abrasion wear mechanisms.

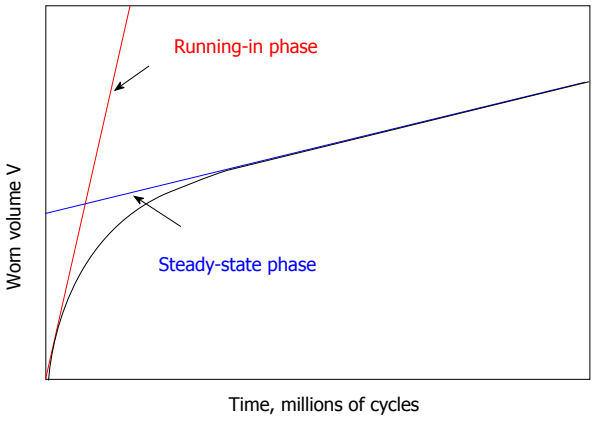

Figure 15 Wear trends *vs* time for metallic surfaces.

Despite being developed for metallic contacts, the Archard wear law is also widely applied to other materials. For ultra high molecular weight polyethylene (UHMWPE), a modified wear coefficient was proposed to take into account the peculiar anisotropic wear behavior of the polymer. In fact, it was observed that when UHMWPE is subjected to multidirectional sliding against a metallic counterface, the polymeric chains tend to align along a principal molecular orientation (PMO), thus increasing their wear strength in such a direction while reducing it in the orthogonal one (Figure 16)[17-20]. This phenomenon is usually denoted as "cross-shear" and has been extensively investigated in the last ten years as reviewed in[10]. Nevertheless, there is still a lack of understanding and many ongoing studies on the topic[10,21,22].

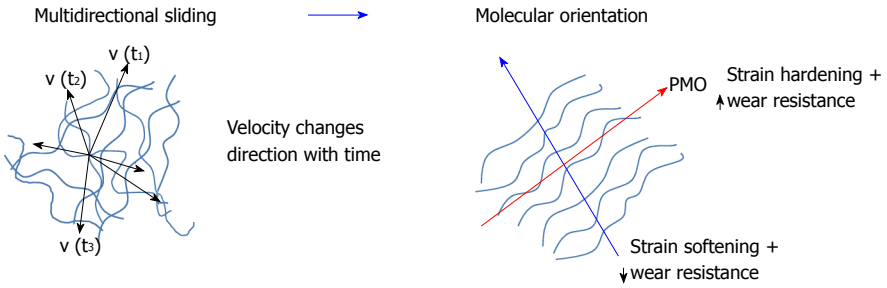

Figure 16 Anisotropic wear in UHMWPE: Cross shear phenomenon.

Table 1 Geometrical characteristics of hip implants: head diameter D_h and diametrical clearance *Cl*

Head/cup	D_h (mm)	*Cl* (μm)
MoP	22.2-44	160-400
CoP	22.2-36	160-400
MoM	22.2-54	50-150
MoM_{RHR}	42-62	50-300
CoC	22.2-44	20-100

MoP: Metal on plastic; CoP: Ceramic on plastic; MoM_{RHR}: Metal on metal resurfacing; CoC: Ceramic on ceramic.

As wear tests are expensive and require long experimental procedures, predictive models are gaining interest, particularly for comparing different design solutions, geometrical characteristics and so on.

IMPLANT TRIBOLOGY

In this section, the general concepts described above are applied to hip implants in order to discuss their tribological behavior.

Geometry

Firstly, some data on the most commonly used sizes of head diameter D_h and diametrical clearance *Cl* are summarized in Table 1. No distinction is made between normal and large head implants, the latter having $D_h \geqslant$ 36 mm. In MoP and CoP implants, the cup thickness is also important and can vary in the range 5-18 mm.

Materials

As already mentioned in Sec. 2, hip implants are made up of different types of materials, roughly distinguished between plastics, metals and ceramics, whose main mechanical properties are summarized in Table 2. The UHMWPE is the traditional plastic material for hip replacements, also adopted in the first THRs. In the last few decades, the mechanical properties of UHMWPE have been improved, leading to the highly cross-linked polyethylene (HXLPE)[23,24]. Indeed, the cross-linking of polymeric chains, accomplished by gamma or electron beam irradiation, significantly increases the wear resistance. However, an increase in the irradiation dose improves the wear resistance but only up to a threshold value. Moreover, the irradiation generates a certain amount of free radicals whose oxidation causes a

Table 2 Implant material properties: Young's modulus *E*, Poisson's ratio *ν* and surface roughness R_a

Material		*E* (GPa)	*n*	R_a (μm)
P	UHMWPE	0.5-1	0.4	0.1-2
M	CoCrMo	230	0.3	0.01-0.05
C	Biolox delta	350	0.26	0.001-0.005

degradation of the mechanical properties[24]. Consequently, the irradiation dose is typically kept low, below 10 MRad, and further treatments are used to control these drawbacks. In the first generation of HXLPE (1998), either melting or annealing was adopted[24]. The former allows elimination of free radicals, whilst the latter maintains mechanical properties. In order to achieve both results, a second generation of HXLPE has been recently introduced (2005)[23]. This material can be obtained by two different manufacturing processes: a sequential repetition of irradiation and annealing cycles; and the annealing of the material in presence of antioxidants such as vitamin E. The clinical follow up of both first and second generation of HXLPE cup has shown good outcomes with a reduction of wear rates up to 80% compared to the conventional UHMWPE[25,26].

The metal alloys used for hip implants encompass CoCrMo, CoCr and stainless steel. CoCrMo is the most widely used. This alloy can be obtained indifferently from wrought and cast materials, with or without heat treatment. Indeed, the manufacturing process has been revealed not to affect the mechanical properties of the alloy[27,28]. On the other hand, the carbon content covers a critical role in the wear resistance: high carbon content (> 0.15%) alloys actually in use exhibit a 64%-94% wear reduction compared to the low carbon content (< 0.08%) one[27-29].

Nowadays, the gold standard for ceramic materials is the Biolox delta, an alumina matrix composite recently introduced to the market (2007). The ceramic materials originally used for CoC implants, such as alumina (Al_2O_3) and zirconia (ZrO_2), have been largely abandoned mainly because of their brittleness. Important advances in ceramic engineering technology have entailed the new material class of mixed oxide ceramics which combine the excellent tribological behavior of alumina with the good mechanical properties of yttrium-stabilized zirconia[30]. Biolox delta belongs to this class, made up

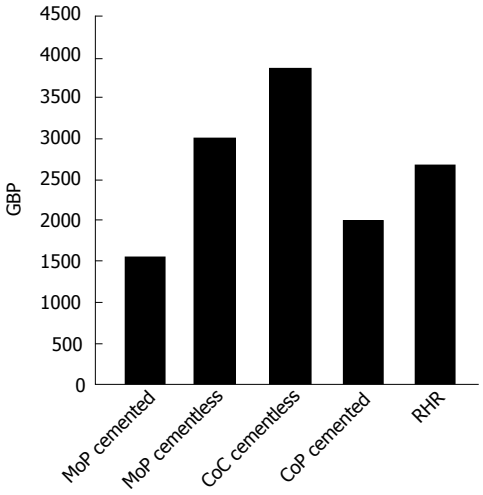

Figure 17 Averages implant prices. MoP: Metal on plastic; CoC: Ceramic on ceramic; CoP: Ceramic on plastic; RHR: Resurfacing hip replacement.

of 82% alumina, 17% zirconia, 0.6% strontium oxide and 0.3% chromium oxide. Nanosized particles of yttrium-stabilized zirconia increase the strength and toughness of the alumina matrix by obstructing crack propagation. Also, strontium oxide contributes to improving the mechanical characteristics by generating platelet-like crystals able to deflect the cracks. On the other hand, chromium oxide improves the hardness and wear properties. The main limitations to a wide use of CoC implants are their high cost and the squeaking phenomenon.

Indications of average list prices across manufacturers, taken from[31], are reported in Figure 17.

Surface mechanics

In order to provide some indications on the contact pressures and contact half-width in a hip implant, equations presented in Sec. 3.1.2 were applied to compare MoM and MoP couplings, assuming a normal load of 2500 N. Results are reported in Figure 18, as contour plots, for different values of the D_b and Cl. It can be observed that the pressure is a maximum for lower diameter and higher clearance, *i.e.*, less conformal surfaces. Moreover, on equal implant size, the contact pressure is tenfold higher in MoM bearings compared to MoP, whilst the contact width is about four times lower. It is important to note that wear occurs only where contact pressure is not null, thus in MoP the worn areas are larger.

Friction

As already discussed in Sec. 3.2, for a hip implant the COF can vary largely with the system conditions, *i.e.*, geometrical and material properties, lubricant type and kinematic/loading conditions. This has been demonstrated by several experimental studies on hip simulators devoted to friction measurements in simplified gait conditions (*e.g.*, vertical load and flexion-extension motion)[32-36]. Table 3 provides typical values of COF for different bearing types, tested under the same conditions (flexion-extension of ± 25° at a frequency 1 Hz; sinusoidal load through

Table 3 Experimental estimations of coefficient of friction for different bearing types, obtained using 25% and 100% bovine serum as lubricants (test conditions: load range 0.1-2 kN, rotation ± 25°, frequency 1 Hz)[32,33]

Head/cup	COF 25% Bovine serum	COF 100% Bovine serum
MoP	0.062 (+ 0.008)	0.064 (± 0.01)
CoP	0.056 (+ 0.01)	0.06 (± 0.012)
MoM	0.12 (± 0.02)	0.096 (± 0.012)
MoM$_{RHR}$	0.098 (± 0.02)	0.079 (± 0.011)
CoC	0.04 (+ 0.007)	0.056 (± 0.01)

COF: Coefficient of friction; CoP: Ceramic on plastic; MoM$_{RHR}$: Metal on metal resurfacing; CoC: Ceramic on ceramic.

60% of the cycle, with a peak of 2 kN and a constant swing phase load of 100 N) and using two lubricant types (25% and 100% bovine serum)[32,33]. All the THRs were characterized by D_b = 28 mm and an averaged Cl = 126 μm, whilst MoM$_{RHR}$ implants had a D_b = 55 mm and a Cl = 92 μm. The highest COFs are observed for MoM implants with average values in the range 0.096-0.12. The MoM resurfacing implants are affected by lower friction compared to the MoM total ones, with average COFs approximately 0.079-0.098. On the other hand, similar COFs of about 0.04-0.064 are reported for MoP, CoP and CoC implants, with the lowest values observed in CoC.

The experimental studies reported in[32-35] describe how the COF is affected by the system conditions: the higher the head and clearance, the lower the COF, since more conformal bearings promote lubrication. Moreover, the higher the load (*i.e.*, swing phase load), the higher the COF[32,33]. Also, the lubricant type strongly affects the COF, as highlighted in Table 3. In particular, a higher concentration of proteins in the lubricant (*i.e.*, in 100% bovine serum) increases the COF for all implant types, with the exception of MoM ones which probably take advantage of a protein protective layer deposited over the bearing surfaces. Consequently, reliable friction measurements require the use of lubricants with a rheological behavior as much as possible similar to the synovial fluid. It is worth noting that 25% bovine serum is more widely used than 100% in simulator studies.

Lubrication

As previously discussed, lubrication, like friction, is a complex phenomenon which depends on the tribological, chemical and mechanical conditions of the system. Thus, the lubrication performance of a hip replacement assessed from a specific test condition cannot be generalized. Usually, the reference task for hip and knee implants is a gait cycle, sometimes with simplified loading/kinematic condition.

While friction and wear phenomena are mainly investigated by means of an experimental approach, the literature has a large number of theoretical studies focused on the lubrication of hip replacements, as reviewed in[37], and only a few experimental investigations (*e.g.*,[38-40]). Lubrication studies, both theoretical and experimental, aim to estimate the minimum film thickness, comparing it

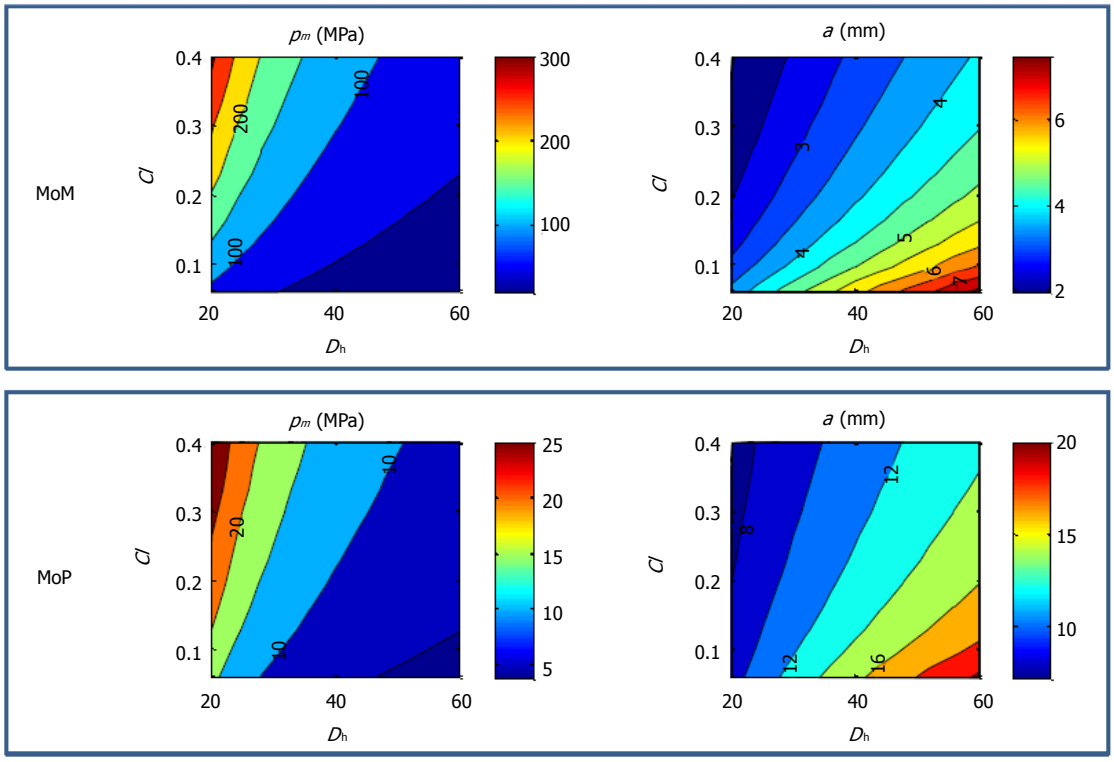

Figure 18 Maximum pressure pm and contact half-width a, for different D_h (mm) and *Cl* (μm), in metal-on-metal (E = 230 GPa, v = 0.3) and metal on plastic (E = 1 GPa, v = 0.4) implants under 2500 N load. MoP: Metal on plastic; MoM: Metal-on-metal.

Table 4 Theoretical estimation of the lubrication regime according to equation (17)

Head/cup	h_{min} (μm)	R_a (μm)	λ	Lubrication regime
MoP	0.065-0.144 (0.105)	0.1-2	0.1-1	Boundary to Mixed
CoP	0.076-0.107 (0.092)	0.1-2	0.05-0.9	Boundary to Mixed
MoM	0.020-0.061 (0.041)	0.014-0.071	0.6-2.9	Boundary to Mixed
MoM$_{RHR}$	0.082-0.049 (0.066)	0.014-0.071	0.9-4.6	Boundary to Fluid-film
CoC	0.035-0.045 (0.04)	0.0014-0.0071	5.7-28.3	Fluid-film

The range of h_{min} is obtained considering two geometrical cases extracted from Table 1: minimum D_h combined with lowest *Cl*; maximum D_h combined with higher *Cl*. The averaged h_{min} reported in the bracket is used for calculating λ. Test case: W = 2 kN, ω = 2 rad/s, μ = 2.5 mPas.

to the composite roughness of the bearing surfaces and assessing the lubrication regime. It is worth mentioning that the experimental approach exploits a resistivity technique to measure the thickness of the meatus, usually performing in *in vitro* measurements on hip simulators.

Typical values of minimum film thickness (equation (17)), λ ratio and indications of the lubrication regime are summarized in Table 4 for the hip implants described in Table 1, adopting the material/surface properties of Table 2 (for plastic E = 1GPa).It can be observed that implants with the plastic cup (MoP and CoP) are subjected to a boundary/mixed lubrication regime, almost independently from the size: h_{min} results comparable to R_a and hence λ values remain low, inferior to 1. MoM hip implants exhibit only a slightly improved lubrication, with λ values in the range 0.6-2.9. Indeed, although metallic surfaces have a R_a lower than the plastic ones, they have a thinner lubricant film because of their lower elasticity. As confirmed by experimental evidence[39], even although the prevailing lubrication mode of MoM implants is mixed, they can span all lubrication regimes, from the boundary to fluid film. Both theoretical and experimental studies demonstrate the high sensitivity of the MoM lubrication regime to implant geometry[38,40-42], bearing design/manufacturing[42] and loading/kinematic conditions[43,44]. In particular, increased head size coupled with decreased clearance has been proved to improve lubrication, as happens both for MoM large head and RHR, which can operate under a fluid-film regime (Table 4)[38,40-42]. The best lubrication behavior is estimated for CoC implants[38]; their high surface finishing (*i.e.*, very low roughness) balances the low film thickness, guaranteeing a fluid-film regime (λ in the range 5.3-28.3). It is worth noting that the clearance must be dimensioned properly, avoiding both large values which would lead to the boundary regime and low values, which might cause edge contact and thus lubricant starvation.

In order to clarify the key role of geometry and materials on the lubrication regime of hard-on-hard implants, some meaningful results from numerical simulations are portrayed in Figure 19[45]. The minimum film thickness and the lubrication regime of three bearing types (MoM, MoM$_{RHR}$

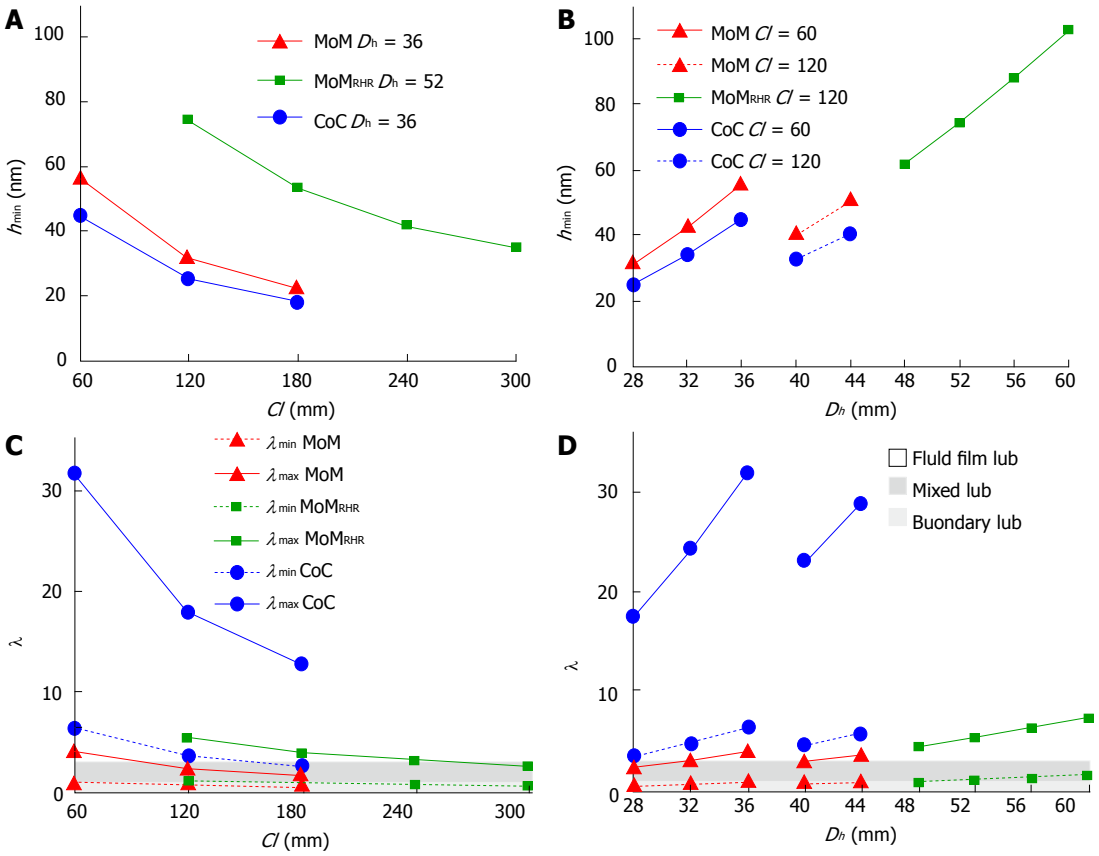

Figure 19 Effect of the clearance *Cl* and the head diameter D_h of hip implants on the lubrication, in terms of minimum film thickness (A, B) and dimensionless film thickness λ (C, D)[46]. Test case: W = 2 kN, ω = 2 rad/s, μ = 2.5 mPas. MoM: Metal-on-metal; CoC: Ceramic on ceramic; MoM$_{RHR}$: Metal on metal resurfacing.

and CoC) are estimated by means of a simplified 3D ball-on-plane EHL model, assuming the synovial fluid as lubricant (μ = 2.5 mPa s) and typical gait conditions (vertical load W = 2 kN, angular velocity in flexion-extension ω = 2 rad/s). The effect of diametrical clearance Cl (Figure 19A, C) and head diameter D_h (Figure 19) was investigated, confirming that lower Cl and higher D_h, which means more conformal bearings, promote the lubrication regime causing thicker film thickness (Figure 19A, B) and higher λ values (Figure 19C, D). On equal Cl or D_h, the minimum film thickness is highest in MoM$_{RHR}$ implants and lowest in CoC ones, the ceramic being harder than the metals. On the other hand, for their very smooth surfaces, CoC implants turn out to be the only ones that undergo fluid film lubrication in the simulated gait conditions, almost independently from their dimensions. It is worth noting that these results are in good agreement with those obtained from empirical formula (Table 4).

As far as the relevant effect of the geometry on the lubrication is concerned, recently a novel MoM implant design characterized by a non-spherical bearing surface was proposed in[46,47]. Numerical EHL simulations demonstrate the superiority of the non-spherical couple which significantly improves the lubrication by increasing the couple conformity in the loaded area.

It is worth mentioning that, although EHL predictions are very useful for carrying out comparative analysis on implant performances and hence for implant design optimization, some of the recent literature studies suggest that protein-containing fluids, such as synovial fluid, do not obey classical Newtonian EHL models[48,49]. This aspect is particularly relevant for MoM implants, as mentioned in Sec. 4.4. According to experimental observations[48,49], two main effects should be considered when a metallic surface is lubricated by a protein-containing solution: the adsorption of a protective protein layer on the surface; and the formation of a high-viscosity film in the inlet region due to protein molecule aggregation, which allows a thick film particularly at low speed. As this complex phenomenon is highly dependent both on time and shear rate, the classical Newtonian model [equation (9)] is no longer valid.

Wear

Wear can be considered the most relevant tribological phenomenon from a clinical point of view. Indeed, wear is recognized as the main reason of hip implant failure, causing inflammatory reactions and osteolysis, which can lead to implant loosening. Compared to friction and lubrication, experimentally investigated mainly *in vitro*, wear can also be studied *in vivo* (*e.g.*, radiographically) and *ex vivo* (from retrieved implants), providing a clinical insight of the tribological life of the implant. Typical values of the linear (h_{clin}) and volumetric (V_{clin}) wear rates observed clinically are summarized in Table 5. It soon becomes apparent that the wear rates are very scattered,

Table 5 Typical wear rates reported in clinical studies (when available, the average value is indicated in the brackets)

Head/cup	h_{clin} (μm/Mc)	V_{clin} (mm^3/Mc)
MoP	50-500 (50)	10-500 (80)
CoP	30-150	15-50
MoM (RI)	1-50	0.1-25
MoM (SS)	0.1-1	0.05-4
MoMRHR (RI + SS)	0.2-10	0.2-2.9
MoMRHR (ADT)	1.5-46	0.2-95
CoC	0.01-1	0.005-2

RI: Running-In; SS: Steady state; ADT: Adverse tissue reaction; 1 Mc: 10^6 cycles.

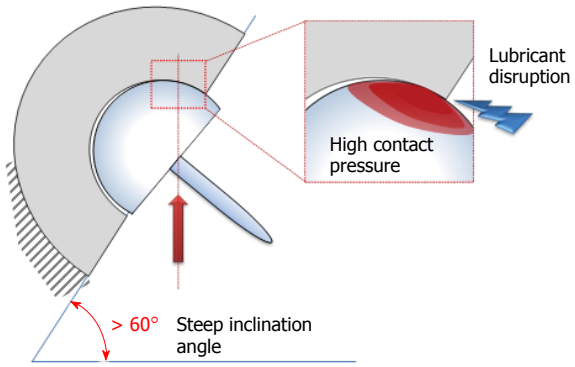

Figure 20 Edge loading phenomenon caused by steep cup inclination angles[52].

probably because of the variability of the clinical scenarios involving both patient characteristics (age, gender, body weight index, daily activities) and their physiological/pathological conditions.

Soft-on-hard couples are affected by the highest wear rates, in agreement with the estimated boundary/mixed lubrication regime (see Sec. 4.4-5). In particular, MoP implants are characterized by average h_{clin} and V_{clin} of about 50 μm/y and 80 mm^3/y, respectively. Wear rates of MoM implants are definitely lower, even up to 2 orders of magnitude. Indeed, although a prevalent mixed/boundary lubrication regime is predicted for MoM and MoP implants, the former exhibit a higher wear resistance due to hard surfaces and protein boundary layers which protect the bearing surfaces. The biphasic wear behavior of MoM is highlighted: passing from the running-in to the steady-state phase, h_{clin} decreases from 1-50 to 0.1-1 μm/y, while V_{clin} decreases from 0.1-25 to 0.05-4 mm^3/y. The wear rate of resurfacing implants is a debated issue. Some successful MoMRHR devices have showed lower wear rates in agreement with the fluid-film lubrication, predicted under favorable conditions, with h_{clin} and V_{clin} in the ranges 0.2-10 μm/y and 0.2-2.9 mm^3/y, respectively[50]. On the other hand, an important percentage of these implants, showing adverse tissue reaction (ADT) at the moment of the explantation, were subjected to high wear rates, in the ranges of 1.5-46 μm/y and 0.2-95 mm^3/y[51]. Such values are very concerning as the wear of metallic surfaces causes the release of dangerous toxic metallic ions[51,52]. One of the main causes of MoMRHR excessive wear rates is a too steep cup inclination which leads to the edge loading, *i.e.*, the collision between the femoral head and the rim of the acetabular cup (Figure 20). Indeed, the edge loading causes concentrated high contact pressures and, furthermore, can cause the disruption of the lubricant.

CoC implants are recognized as the most wear resistant thanks to their very hard surfaces and effective lubrication. Under normal conditions, extremely low wear rates have been found for the ceramic bearings of about 0.01-1 μm/y and 0.005-2 mm^3/y. Furthermore, ceramic debris are bioinert and not clinically relevant. On the other side, one of the current main drawbacks of CoC is not the wear but the squeaking, *i.e.*, the audible sound generated by these implants during the motion. The lubricant starvation, caused by edge loading, seems to be one of the main cause of this phenomenon[30].

Beyond clinical studies, experimental *in vitro* wear analyses remain fundamental for characterizing the wear of an implant, comparing different bearing types, as well as for the screening of innovative materials and implant design optimization. Such studies are carried out both in traditional pin-on-plate/pin-on-disk test machines and in hip joint simulators, generally simulating physiological simplified gait conditions. Recently, multidirectional pin-on-plate devices have also been developed for investigating the cross-shear of UHMWPE. In the attempt to quantify the cross-shear, many wear tests have been carried out, leading to new expressions of the wear coefficient as a function of the multidirectional sliding and to new wear laws[10]. A few studies have been recently carried out on MoMRHR implants, confirming the influence of the cup orientation on wear as it can cause edge loading[53].

Analytical and numerical studies support experimental analyses, allowing long term wear predictions at low cost[37]. Most of them have been applied to MoP implants and only few to MoM and MoMRHR implants. However, one critical aspect of such wear models is the selection of suitable values of the wear coefficient since, as mentioned in Sec. 3.4, it depends on many factors and can vary both spatially and in time. As a confirmation, the wear coefficient values are very scattered in the literature. Typical k ranges are the following: 10^{-7}-10^{-6} mm^3/(N m) for MoP; 10^{-9}-10^{-7} mm^3/(N m) for MoM; and 10^{-10}-10^{-8} mm^3/(N m) for CoC implants. However, numerical predictions are in good agreement with the experimental ones obtained from a hip simulator, whilst underestimating the clinical ones, probably because they do not simulate all the *in vivo* implant conditions, *i.e.*, different daily activities in addition to walking.

The effect of the geometry and the loading/kinematic conditions on wear has been widely investigated, providing findings in agreement with the friction and lubrication studies.

TRENDS

Some major trends are recognized in the implant of a hip prosthesis which reflects the clinical outcomes of hip arthroplasty and thus the revision risk associated

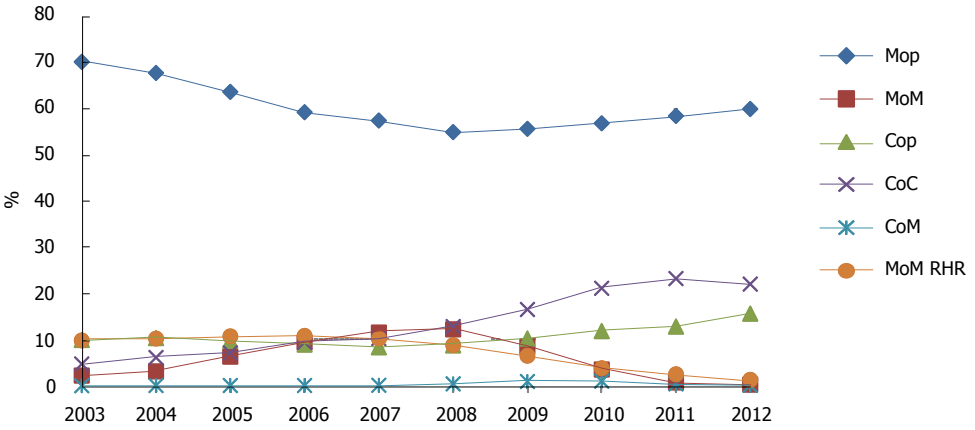

Figure 21 Trends in hip replacement implantation from 2003 to 2012. Data from[3]. MoM: Metal-on-metal; CoC: Ceramic on ceramic; MoM$_{RHR}$: Metal on metal resurfacing.

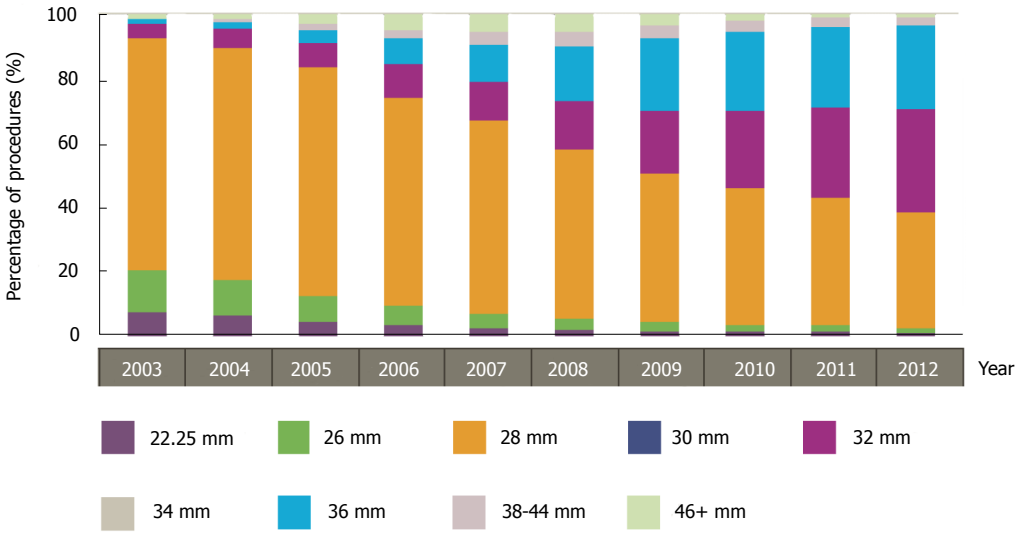

Figure 22 Trend of femoral head size from 2003 to 2012. Data from[3].

with each implant type. A meaningful statistical analysis on this topic is provided by the National Joint Registry of England, Wales and Northern Ireland[3] which has collected data on clinical procedures and outcomes since 2003. This source has been adopted as the main reference of this section as it is one of the more extended and complete registries to the best of our knowledge.

The trends of bearing couplings from 2003 to 2012, expressed as percentages of implant type per year, are depicted in Figure 21. MoP implants, the traditional ones, are still the most widely used, covering about the 60% of all procedures in 2012. This is partly due to the introduction of the high wear resistant HXLPE (see Sec. 4.2). The use of the ceramic components is increasing, with an increase of 22% of CoC and 16% of CoP implants in 2012. Also in this case, the improvements in material properties leading to Biolox delta characterized by a high mechanical strength and high wear resistance have been a determinant. As mentioned above, the wear of ceramic implants is irrelevant and one of the main concerns in their employment is still the squeaking. It is worth noting that the incidence of squeaking reported in the literature varies in the range < 1%-21%, depending on how the sound is defined[50,54]. On the contrary, the use of metal bearings, both total and resurfacing, has decreased in the last few years. After reaching a peak between 2006 and 2008, these implants have been largely abandoned, their use now reduced to 1.5%. This trend is due to the ongoing concerns on pseudotumors caused by toxic metallic ions and the high failure rates of large head and RHRs related to the edge loading, as discussed in Sec. 4.6. Certainly, the decreased implantation of these implants has been further enhanced by the voluntary recall of the RHR system ASR by DePuy (2010). An additional reason behind such percentages can be found in implant costs (Figure 17).

In terms of femoral head size, the trend is characterized by a gradual increase in the use of larger heads, which is in agreement with both theoretical and experimental findings, as bigger implants, *i.e.*, more conformal couples, promote the lubrication and prevent dislocation (Figure 22). The 28 mm heads, mostly used in 2003, have been declining

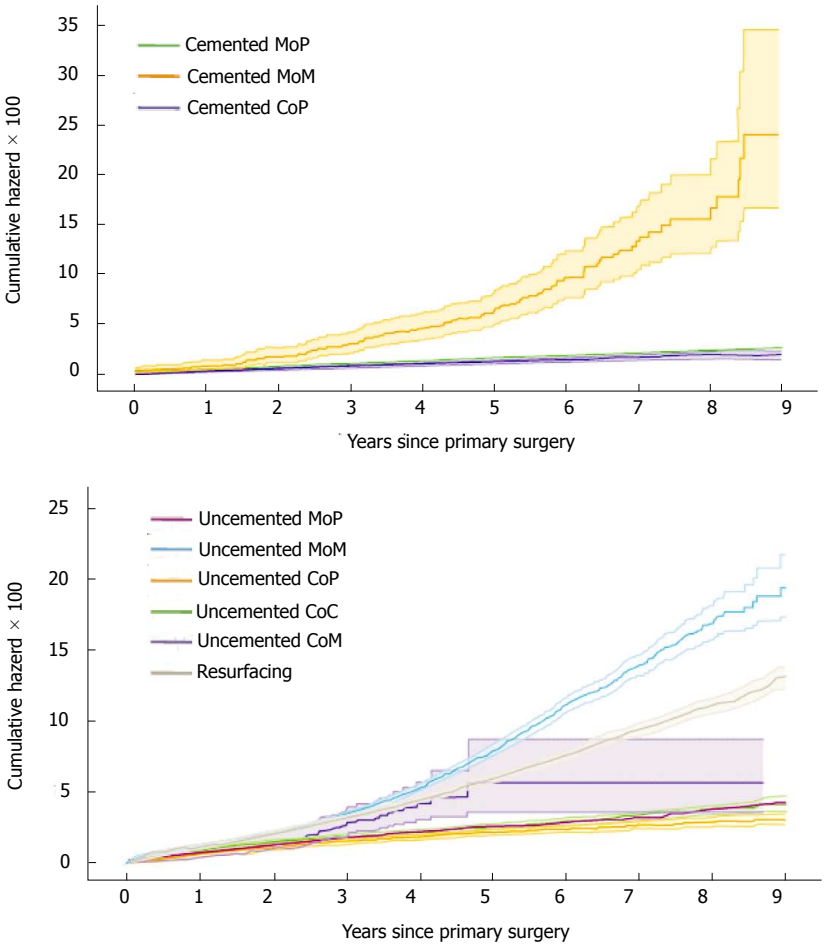

Figure 23 Revision risk (Cumulative hazard with 95%CI) for hip articulation. Data from[3]. MoM: Metal-on-metal; CoC: Ceramic on ceramic.

in favor of 32 and 36 mm heads. Whilst the increase of 32 mm heads is continuing, the 36 mm heads trend has been slightly reversing since 2010, which reflects the actual concerns on large head MoM THRs and MoMRHR.

In order to complete this overview on hip implant procedures, the revision risk for hip articulation type is provided in Figure 23. The trends are in full agreement with the above discussion. The highest revision risk (up to 15%) is reported for MoM bearings, with revision rates of 17.7% and 12.3% for cementless total and resurfacing implants, respectively, and up to 33% for the cemented ASR RHRs. The lowest revision rates, less than 2%, were observed for MoP and CoP implants and similar performances were also reported for CoC.

CONCLUSION

The present review aims to describe the biotribology of hip replacements both qualitatively and quantitatively. The fundamental concepts of tribology, provided in the first part particularly for non-specialists, are applied to artificial hip joints, thus allowing interpretation of the actual trends in hip arthroplasty. The interest in larger head sizes, the increasing use of CoC implants, the squeaking of hard-on-hard couples and even the high failure rates of RHR implants are considered and explained from a tribological point of view.

The wide discussion on the tribological features of each implant type highlights how friction, lubrication and wear are strongly interconnected and cannot be discerned one from the other: the study of biotribology of hip implants should thus be treated as a whole, where each aspect helps, completes and confirms the understanding of the others. Moreover, such tribological features depend on the characteristics of the system taken into consideration, the materials (*e.g.*, Young's modulus, hardness), geometry (*e.g.*, head diameter, clearance, surface finishing), kinematic and loading conditions and lubricant type. Consequently, for each bearing type, friction, lubrication and wear vary during a single activity as well as in the implant lifetime as the patient characteristics, lifestyle and wear itself modify the tribological scenario continuously. These considerations raise some concerns of the suitability of *in vitro* tests for hip implants since simplified gait cycles can be too far from the effective implant working conditions.

This paper points out the complexity of biotribology science and its fundamental role in analyzing and improving hip implant design, as well as the need for further investigations in order to improve hip arthroplasty outcomes.

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P- Reviewer: Azzoni R, Meng QE **S- Editor**: Song XX
L- Editor: Roemmele A **E- Editor**: Lu YJ

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.95

World J Orthop 2015 January 18; 6(1): 95-105
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (5): Knee

Cytokines as biochemical markers for knee osteoarthritis

Thomas Mabey, Sittisak Honsawek

Thomas Mabey, Sittisak Honsawek, Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok 10330, Thailand

Author contributions: Mabey T and Honsawek S solely contributed to this paper.

Supported by Ratchadapiseksompotch Fund (RA55/22), Faculty of Medicine, Chulalongkorn University and Office of the Higher Education Commission (CU-NRU, Aging Society Cluster).

Correspondence to: Sittisak Honsawek, MD, PhD, Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Pathumwan, Bangkok 10330, Thailand. sittisak.h@chula.ac.th
Telephone: +662-256-4482
Fax: +662-256-4482

Received: December 5, 2013
Peer-review started: December 8, 2013
First decision: March 12, 2014
Revised: March 24, 2014
Accepted: July 17, 2014
Article in press: July 17, 2014
Published online: January 18, 2015

Abstract

Osteoarthritis (OA) is a debilitating degenerative joint disease particularly affecting weightbearing joints within the body, principally the hips and knees. Current radiographic techniques are insufficient to show biochemical changes within joint tissue which can occur many years before symptoms become apparent. The need for better diagnostic and prognostic tools is heightened with the prevalence of OA set to increase in aging and obese populations. As inflammation is increasingly being considered an important part of OAs pathophysiology, cytokines are being assessed as possible candidates for biochemical markers. Cytokines, both pro- and anti-inflammatory, as well as angiogenic and chemotactic, have in recent years been studied for relevant characteristics. Biochemical markers show promise in determination of the severity of disease in addition to monitoring of the efficacy and safety of disease-modifying OA drugs, with the potential to act as diagnostic and prognostic tools. Currently, the diagnostic power of interleukin (IL)-6 and the relationship to disease burden of IL-1β, IL-15, tumor necrosis factor-α, and vascular endothelial growth factor make these the best candidates for assessment. Grouping appropriate cytokine markers together and assessing them collectively alongside other bone and cartilage degradation products will yield a more statistically powerful tool in research and clinical applications, and additionally aid in distinguishing between OA and a number of other diseases in which cytokines are known to have an involvement. Further large scale studies are needed to assess the validity and efficacy of current biomarkers, and to discover other potential biomarker candidates.

Key words: Biomarker; Cytokines; Interleukin; Knee osteoarthritis

Core tip: This review discusses the role and significance of cytokines implicated in the pathophysiology and development of knee osteoarthritis. We aim to describe and summarize the current knowledge and advancement of the use of cytokines as biochemical markers in diagnosis and management of knee osteoarthritis (OA). Cytokines play an important role in the pathogenesis of OA. A better understanding of the biological mechanisms involved in this process may result in better treatment for OA patients. Biomarker investigation for OA diagnosis is still in the forefront of the research repertoire in OA. This review highlights some biomarker studies published in the PubMed database.

Mabey T, Honsawek S. Cytokines as biochemical markers for knee osteoarthritis. *World J Orthop* 2015; 6(1): 95-105 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/95.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.95

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease characterized by articular cartilage degradation which can affect many joints in the body, but is particularly common in weight-bearing joints such as the knee and hip. The loss of cartilage can lead to joint space narrowing (JSN), pain, and loss of function and ultimately leads to the need for total joint replacement. There are a number of risk factors associated with OA, including genetic predisposition, obesity, age, and previous joint trauma. With obesity set to rise in future years[1], combined with OA being a frequent condition among the elderly and an ageing population[2], the prevalence of OA is expected to increase. An effective and reliable method for diagnosis and prognosis is needed, with increased demands on health services around the world.

Radiography is routinely used to aid in the diagnosis of OA. The Kellgren-Lawrence (KL) grading system of radiographic OA is one method commonly used to assess the severity of cases[3]. However, radiographic imaging is ineffective at detecting and monitoring the biochemical changes within joint tissue which can occur long before symptoms present. Because OA can take years and even decades to develop, finding biochemical markers associated with OA is an attractive idea. As they can be used to diagnose and predict prognosis in patients in ways that radiography cannot, they can therefore be early indicators of patients at risk of developing the disease. This would prove beneficial as preventative or mitigating measures could be taken.

In recent years, there has been a considerable effort to find biochemical markers which could aid in the monitoring of OA. Research has predominantly looked at two main candidates. The first are products of bone and cartilage degradation such as C-terminal telopeptide of type Ⅱ collagen, cartilage oligomeric matrix protein, a collagen type Ⅱ specific neoepitope, an aggrecan neoepitope, a number of matrix metalloproteinases, and procollagen type I amino-terminal propeptide[4-9].

The second group of possible candidates has come to light with the increased understanding that inflammation plays a key role in OA, which is a shift from the historic opinion that it was solely a "wear and tear" disease. Pro- and anti-inflammatory agents, particularly cytokines, have been studied for their associations with the development and progression of OA in both human and animal models. As well as pro- and anti-inflammatory roles (for example, interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, IL-10, IL-13 and IL-4)[10-15], cytokines also contribute to the pathophysiology of OA through angiogenesis and chemotaxis[16-21].

Different compounds may show different biochemical marker properties at different stages of the disease, reflecting the pathophysiological changes occurring within the joint tissue. Therefore, characterization of potential biomarkers is important to ensure their appropriate and optimal use. The characterization method used to assess biochemical markers in OA is BIPEDS; which stands for: Burden of disease, Investigative, Prognostic, Efficacy of intervention, Diagnostic, and Safety[22,23]. Diagnostic markers, as their name suggests, would aid in the diagnosis of OA. Early and reliable detection of the disease in a patient is obviously beneficial. Potential prognostic markers aid in the prediction of disease progression within OA patients, but also identify individuals who are at a higher risk of developing OA in the future. Due to the slow progression of the disease, which can take a number of decades to develop, preventative or mitigating measures could be taken before any symptoms became apparent to the patient or clinician. Additionally, identifying groups of patients in which the disease will progress at different rates can help physicians assign patients to a more appropriate and tailored treatment program. A burden of disease marker would reflect the severity of the disease in a patient and help in the administration of the appropriate treatment. Efficacy of intervention and safety biochemical markers assist in the ongoing hunt for disease modifying osteoarthritis drugs. Cytokines have also become targets themselves for therapeutic agents and as therapeutic agents[24-27]. Investigative markers are those for which there is insufficient data to assign them to another category.

The ideal scenario, in terms of biochemical markers of OA, would be to have a non-invasive, reliable and valid biochemical marker or cluster of markers that could be measured to aid in the diagnosis and predict the development of OA in patients at an early stage before the disease becomes symptomatic. The ability to reduce the long-term effects of the disease could considerably reduce the substantial socioeconomic costs of OA[28-30].

This review aims to examine and summarize current knowledge of the use of cytokines as biochemical markers in the diagnosis and management of knee OA. Table 1 shows a summary of a number of articles in which possible biochemical markers for OA have been studied.

PROINFLAMMATORY CYTOKINES

Inflammation is increasingly being regarded as an important part of OA. Inflammation can occur locally, within the synovium, and systemically, with inflammatory agents circulating in the blood. In the pathophysiology of OA, proinflammatory cytokines have been shown to play important roles in the destruction of cartilage, synovitis, and pain[31-34]. The severity and form of inflammation appears to change with disease progression, with different cytokine signatures being present in early and advanced stages of the disease.

A number of proinflammatory cytokines have been, and continue to be, studied as potential biochemical markers with possible candidates being found for burden

Table 1 Summary of studies in which cytokines have shown biochemical marker characteristics

Ref.	Year	Cytokines	Joint	Tissue	Condition of samples	Samples	Controls	Assay	Follow-up	Results
Sun *et al*[65]	2013	IL-15	Knee	Serum	Primary Knee OA	226	106	ELISA	N/A	IL-15 Serum OA ↑ Control IL-15 positively correlated with WOMAC (Pain) IL-15 not correlated with KL
Shimura *et al*[45]	2013	IL-6	Knee	Serum	Postmenopausal females with medial knee OA	160	N/A	CLIA	N/A	Serum IL-6 = association with pain severity (VAS) in early stage Serum IL-6 = association with pain severity (JKOM) in early stage
Wang *et al*[66]	2013	IL-18	Knee	Plasma, SF and Articular Cartilage	Primary Knee OA	33	15	ELISA + Immunofluorescence Staining	N/A	IL-18 Plasma +SF OA ↑ Controls IL-18 positive cells AC OA ↑ Controls ↑ KL = ↑ IL-18 Plasma, SF + AC + ↑ IL-18 positive cells IL-18 Plasma, SF + AC = Positive correlation
Vincent *et al*[59]	2013	IL-1β, IL-6, IL-8, IL-12, TNF-α, IL-4, IL-10 + IL-13	Knee	SF	Chronic OA	Adult (50-64 yr): 14 Elderly (≥ 65 yr): 14	N/A	Multiplex	6 mo	↓Pain severity (NRSpain) = ↓IL-1β ↓ IL-1β, IL-6, IL-8 + IL-12 (Baseline – 6 mo) Adults *vs* Elderly (not significant) ↓ TNF-α (Baseline – 6 mo) in Adults *vs* Elderly
Rubenhagen *et al*[42]	2012	IL-1Ra, IL-6, IL-8, IL-10, IL-17, VEGF, MCP-1, IL-7, IL-13, IL-18 + HGF	Knee	SF	Total knee replacements or cruciate ligament, cartilage, or meniscal reconstruction surgery	82	N/A	Multiplex + ELISA	N/A	↑ SF IL-7 = ↑KL SF VEGF 2 × ↑ KL=3/4 *vs* KL=0 IL-7 = positive correlation with age IL-7 2 × ↑ > 60 years old *vs* < 60 years old IL-1Ra, IL-6, IL-8, IL-10, IL-17, MCP-1, IL-13, IL-18 + HGF ≠ association with KL
Chadjichristos *et al*[32]	2012	IL-1β + TNF-α	Knee	SF	OA Established (Medial menlsectomy)	25	5	ELISA	N/A	↑ IL-1β + TNF-α = ↑ Degree of Inflammation IL-1β + TNF-α ↑ in weeks 2 + 4 IL-1β ↓ in week 12 TNF-α ↓ in weeks 8 + 12
Saetan *et al*[83]	2011	IP-10	Knee	Plasma + SF	Knee OA	40	15	ELISA	N/A	OA SF IP10 2.5 × ↓ than plasma OA SF IP10 3 ×↓ than control plasma ↑KL = ↓Plasma + SF IP-10 Plasma + SF IP10 inversely correlated with KL (SF less so)
Vangsness *et al*[84]	2011	IL-1β, IL-6, IL-8, IL-12p70, IFN-γ, IL-2 + IL-5	Knee	SF	Patients underwent an arthroscopy of the knee for a meniscal tear	12	N/A	Immunoassay high-throughput flow cytometry	N/A	↑ IL-2 + IL-5 = ↑ Disease severity (ICRS) ↑ IL-1β, IL-6, IL-8, IL-12p70 + IFN-γ = ↑ Disease Severity (ICRS) (Borderline significance; $P < 0.10$) IL-1β, IL-6, IL-8, IL-12p70, IFN-γ, IL-2 + IL-5 ≠ association with KL
Orita *et al*[85]	2011	IL-6, TNF-α + NGF	Knee	SF	Adult patients with knee pain - No previous OA treatment	47	N/A	ELISA	N/A	TNF-α ≠ correlation with KL TNF-α ↓ KL (2-4) *vs* KL (1) TNF-α = Positive correlation with WOMAC + WOMAC (Pain, stiffness + physical function) IL-6 = Negative correlation with KL IL-6 ↓ KL (3 + 4) *vs* KL (1 + 2) IL-6 = Negative correlation with WOMAC (Stiffness) IL-6 ≠ correlation with WOMAC or WOMAC (Pain or physical function)

Kokebie *et al*[86]	2011	IL-1, IL-6, IL-8, IL-11, LIF, COMP + osteocalcin	Knee	SF	Fulfilled ACR criteria	45	RA: 22 Donor: 20	ELISA	N/A	IL-8 RA ↑ OA + Donors IL-11 RA = OA IL-11 OA ↑ Donors LIF Donors ↑ OA + RA LIF OA = RA SF WBC positive correlation with IL-6 + IL-1 IL-11, IL-8 + LIF no correlation with SF WBC No biomarkers correlated with KL or disease activity (WOMAC)
Santos *et al*[87]	2011	IL-6	Knee	Plasma	Knee OA (ACR)	80	N/A	ELISA	N/A	IL-6 = inverse correlation with muscle resistance + muscle balance (hamstring) IL-6 ≠ correlation with functionality
Stannus *et al*[48]	2010	IL-1 β, IL-6, TNF-α + hs-CRP	Knee	Serum	Selected randomly from the roll of electors	172	N/A	CLIA	3 yr	IL-6 + TNF-α Serum = association with JSN (medial tibiofemoral) IL-6 + TNF-α Serum ≠ association with cartilage volume (tibial) IL-6 Serum predicted ↓ cartilage volume (medial + tibial) IL-6 + TNF-α associated with ↓ cartilage volume (medial + lateral) TNF-α associated with JSN IL-6 serum associated with knee JSN + Knee cartilage loss (older patients)
Stannus *et al*[44]	2010	IL-6	Hip	Serum	Selected randomly from the roll of electors	193	N/A	ELISA	N/A	IL-6 Male = Female ↑ IL-6 = ↑ JSN (Female) IL-6 ≠ association with JSN (Male) Trunk-fat + Total Fat ratios associated with IL-6 IL-6 ≠ association with presence or severity of osteophytes
Scanzello *et al*[88]	2009	IL-15, IL-1β, IL-6, TNF-α, IL-2 + IL-21	Knee	SF	Early: degenerative meniscal tears Adv: Knee replacement surgery	Early: 19 Adv: 15	N/A	ELISA + Quantitative PCR	N/A	SF IL-15 ↑ early *vs* advanced Expression of IL-15 early = advanced Synovial membrane IL-1β, IL-6 + TNF-α early = advanced SF IL-1β, IL-6 + TNF-α early = advanced Synovial membrane IL-21 + IL-2 ↓ early *vs* advanced SF IL-21 + IL-2 early = advanced
Ling *et al*[64]	2009	169 proteins including: cytokines, chemokines + GFs	Hand and Knee	Serum	Radiographic OA in one or both knees and one or both hands	Initial: 21 Classifying: 19	Initial: 61 Classifying: 66	RCA enhanced antibody-based protein microarray	OA: 10.03 ± 0.31 Controls: 9.88 ± 0.22 (Years)	IL-15 predicted OA at Initial X-ray IL-1α, IL-2, IL-15 + 6Ckine OA ≠ Control IL-15 OA ↑ Control (at Initial + Classifying X-rays)
Livshits *et al*[47]	2009	CRP, TNF-α + IL-6	Knee	Serum	White females	Year 5: 430 (IL-6: 429) Year 8: 473 Year 15: 322	N/A	TNF-α: High-sensitivity ELISA IL-6: Ultra-Sensitivity ELISA	Year 5, 8 + 15	TNF-α ≠ association with RKOA IL-6 = association with RKOA IL-6 = association with the development of RKOA
Botha-Scheepers *et al*[57]	2007	TNF-α, IL-1β, IL-1Ra + IL-10	Knee	Whole Blood	Symptomatic knee OA in at least one knee at baseline	86	N/A	ELISA	2 yr	↑ TNF-α (Highest quartile) 6 × ↑ Risk of JSN progression ↑ IL-10 (Highest quartile) 4 × ↑ Risk of JSN progression IL-1β + IL-1Ra ≠ Association with risk of JSN progression ↑ IL-10 (*ex vivo* production with LPS stimulation) = ↑ Knee OA progression

Doss *et al*[49]	2007	IL-6	Knee + Hip	Serum + SF	End-stage OA (Hip or Knee)	49 (Knee: 32, Hip: 17)	N/A	ELISA		16% OA ↑ IL-6 *vs* 84% OA (Possible sub-groups) IL-6 SF = in Knee *vs* Hip OA, age, sex, stage of disease or course
Riyazi *et al*[56]	2005	TNF-α, IL-1β, IL-1Ra, + IL-10	Hand, Spine, Hip or Knee	Whole Blood	OA at multiple sites	305	137	ELISA	N/A	↑ IL-1β + IL-1Ra + ↓ IL-10 (*ex vivo* production with LPS stimulation) = ↑ Multiple site OA familial risk ↑ TNF-α (*ex vivo* production with LPS stimulation) ≠ ↑ OA risk
Phenninx *et al*[61]	2004	IL-6, CRP, TNF-α, IL-6sR, IL-2sR, TNF-sR1, + TNF-sR	Knee	Serum	Over-weight, older (≥ 60 yr) + knee OA	274	N/A	ELISA	N/A	↑TNF-sR1 and TNF-sR2 = ↑ WOMAC (Physical Function) ↑IL-6 = ↓Walking speed ↑ TNF-sR = ↑ Pain, Stiffness + KL IL-1 ≠ association with KL or WOMAC (Physical Function)

ACR: American College of Rheumatology; Adv: Advanced; CLIA: Chemiluminescent enzyme immunoassay; COMP: Cartilage oligomeric matrix protein; CRP: C Reactive protein; ELISA: Enzyme link immunosorbent assay; GF: Growth factor; HGF: Hepatocyte growth factor; hsCRP: High-sensitivity C reactive protein; ICRS: International cartilage repair society; IFN: Interferon; IL: Interleukin; IL-1Ra: IL-1 Receptor antagonist; IP-10: Interferon-γ inducible protein-10; JKOM: Japanese knee osteoarthritis measure; JSN: Joint space narrowing; KL: Kellgren-lawrence grading; LIF: Leukemia inhibitory factor; LPS: Lipopolysaccharides; MCP: Monocyte chemoattractant protein; MIP: Macrophage inflammation protein; NGF: Nerve growth factor; NRSpain: Numerical pain rating scale; OA: Osteoarthritis; PCR: Polymerase chain reaction; RA: Rheumatoid arthritis; RCA: Rolling circle amplification; RKOA: Radiographic knee osteoarthritis; SF: Synovial fluid; sR: Soluble receptor; TNF: Tumor necrosis factor; VAS: Visual analog scale; VEGF: Vascular endothelia growth factor; WBC: White blood cell; WOMAC: Western ontario mcMaster university osteoarthritis index.

of disease assessment, prognostics and diagnostics. IL-1β and TNF-α are among the key players in terms of proinflammatory cytokines involved in OA[35]. IL-6 also plays a major pro-inflammatory role in OA. Alongside these, more minor players, for example IL-15 and IL-18, have also been investigated as potential candidates for biochemical markers in OA.

IL-6

IL-6 is a 184 amino acid residue protein[34] which has been shown in a number of studies to play a pro-inflammatory role in the pathophysiology of OA. Healthy chondrocytes produce low amounts of IL-6 without the presence of a stimulating agent[36] but when exposed to certain cytokines, including IL-1β, a key player in the inflammation of arthritic joints, chondrocytes increase production[10,37]. Likewise TNF-α and interferon-γ have also been shown to induce IL-6 production[36]. IL-6 has been shown to inhibit the production of type Ⅱ collagen in animal models[38].

In animal models, higher levels of IL-6 have been found in osteoarthritic groups compared with controls[39-41]. This is mirrored in human patients with OA in a number of studies. However, synovial fluid (SF) levels of IL-6 have been shown not to correlate with body mass index (BMI), age, or OA severity (KL) in a study of 82 knee OA patients[42]. Conversely, a study of 47 knee OA patients with no previous OA treatment found that SF samples of IL-6 negatively correlated with KL grades and were not associated with WOMAC (Western Ontario McMaster University Osteoarthritis Index[43]) pain and function scores with the exception of the subset of stiffness with which IL-6 correlated slightly. In a cross-sectional study of hip OA patients, serum IL-6 levels in women were positively associated with hip JSN, but not with the presence of osteophytes[44]. Instead, in a recent study of 160 postmenopausal females by Shimura *et al*[45], serum IL-6 levels were associated with pain severity in early stage knee OA but not advanced stages of the disease. Higher serum levels also tended to be associated with decreased walking speeds[46].

A prospective population-based study of females by Livshits *et al*[47] revealed higher serum IL-6 levels associated with an increased chance of diagnosis of OA throughout a 15 year follow-up. This supports the potential of IL-6 to be a biomarker for early diagnosis of OA. This idea that IL-6 plays a role in early stage OA is supported by Stannus *et al*[48], who conducted a study of 172 OA patients in which they found that circulating IL-6 was associated with JSN and knee cartilage loss and that, longitudinally, the baseline levels of IL-6 predicted both medial and lateral tibial cartilage volume. Higher IL-6 levels were also associated with an increased prevalence of osteophytes compared with lower IL-6 levels. The study suggested that IL-6 may play a role in cartilage loss in early stage OA. Because of this early stage role, IL-6 could be classed as a diagnostic and prognostic biomarker; however, further studies are required before a conclusive view can be formed.

Doss *et al*[49] suggested possible subgroups of OA patients with varying levels of IL-6. Patients found to produce relatively high levels of IL-6 showed a possible increase in the frequency of the $^{-174}$C-allele of the IL-6 gene. Whilst the authors note the study size was insufficient to draw a significant result, it does raise an important point that the presence of subgroups could pose an obstacle in the hunt for a universal and specific biochemical marker for OA due to the varying levels of expression between groups. Another consideration to take into account with the use of IL-6 as a biochemical marker is that it appears to have a circadian rhythm[50]. In addition, plasma IL-6 levels have been seen to increase significantly during periods of modest sleep deprivation in healthy adults[51]. These could potentially interfere with measurements of biochemical markers. Another noteworthy point that should be taken into consideration when assessing IL-6 is that levels have been shown to increase with repeated catheter use when drawing blood samples. This is thought to be local production rather than a physiological process[20,52].

IL-1β

One of the most important proinflammatory cytokines to play a role in the pathophysiology of OA is IL-1β. This 17.5 kDa protein[53] is a suppressor of type Ⅱ collagen and aggrecan synthesis which are key constituents of cartilage[31,32]. With a decreased production of these components, cartilage degradation is worsened. Furthermore, IL-1β induces the production of a number of cytokines and chemokines which contribute to the state of inflammation; these include IL-6 and IL-8[36,54] (reviewed by Kapoor *et al*[10]). Due to its large involvement, IL-1β has been investigated in a number of studies as a potential candidate as a biochemical marker.

Ning *et al*[55] examined the expression of IL-1β in 23 patients with medial knee OA. They found, through immunohistochemical analysis, that expression of IL-1β in both the lining and sublining of the medial perimeniscal synovial tissue samples collected had a significant positive correlation with joint space width. The levels were also negatively correlated with joint alignment (femoro-tibial angle). As well as joint alignment, the authors reported a significant negative correlation with physical disability. This study suggested that local expression levels of IL-1β are associated with the severity of disease and thus have potential as burden of disease markers.

Using lipopolysaccharides (LPS) to stimulate whole blood samples, Riyazi *et al*[56] investigated the production of IL-1β, as well as IL-1 receptor antagonist (IL-1Ra), IL-10, and TNF-α in OA patients. The patients had OA in various joints including hips, the spine, hands, and knees. High innate *ex vivo* production of IL-1β and IL-1Ra was associated with an increased risk of familial OA at multiple sites. However, in a separate study, both IL-1β and IL-1Ra failed to show a significant association between innate *ex vivo* production and the progression of knee OA (JSN) over a 2-year period[57].

Very recently, mouse models have shown that IL-1β plays important roles in pain sensitivity[58]. However, interestingly, IL-1β levels in guinea pig serum were statistically similar between OA-prone and OA-resistant strains[39]. In rabbits, the expression levels of IL-1β and TNF-α were suggested to reflect the severity of inflammation in experimental OA. Levels were increased in early stages of the disease but reduced with regression of synovitis[33].

IL-1β has been used as a marker of efficacy of intervention in a study assessing the effects of intraarticular hyaluronic acid treatment in patients with knee OA. A moderate negative correlation between changes in synovial fluid IL-1β and a reduction in pain severity over a 6-mo period was observed[59].

Tumor necrosis factor-α

TNF-α is a 17 kDa protein produced predominately by activated macrophages which effects the production of cytokines including IL-6 and IL-8 among others[36,54,60].

In the same study as previously mentioned in which hyaluronic acid injections in OA patients were assessed through measuring IL-1β, TNF-α also showed a significant reduction from baseline to 6 mo in adults compared with elderly adults[59].

Soluble TNF receptors in serum samples from OA patients showed a positive correlation with pain, joint stiffness and higher radiographic severity of disease[61]. However, in canine models, TNF-α and its receptors did not show an association with mild osteoarthritic changes when increased in articular cartilage[62]. In addition, no association was found between plasma TNF-α levels and OA characteristics in patients with hand OA[63]. Following LPS stimulation, high *ex vivo* production of TNF-α did not increase the risk of OA[56].

TNF-α has shown characteristics as a marker of treatment efficacy, and mixed results as a burden of disease marker. Further study is needed to clarify its position and efficacy as a biochemical marker of OA.

IL-15

IL-15 contributes to inflammation in OA as a proinflammatory cytokine. There have been relatively few studies examining its potential use as a biochemical marker. However, a few articles have suggested it could be a prognostic and burden of disease marker.

In a study of knee and hand OA patients and controls, IL-15 was found to predict the development of OA in patients who were asymptomatic for OA at baseline then assessed at a 10-year follow-up. At baseline and at follow-up, the levels of IL-15 in OA patients' serum were elevated compared with healthy controls. These two findings suggest IL-15 has potential as both a diagnostic and prognostic biochemical marker[64].

IL-15 was found to be slightly, but significantly, elevated in serum samples of OA patients compared with those of controls. In the same study, IL-15 levels were found to have an independent positive correlation with WOMAC pain scores but showed no significant relationship with the severity of OA (KL)[65].

It can be suggested from this that IL-15 is a possible burden of disease biomarker for assessing the pain associated with OA but not, however, for the assessment of the progression of cartilage destruction and severity. IL-15 also has potential as a diagnostic biochemical marker.

IL-18

Whilst SF IL-18 levels have been shown to have no correlation with OA grade (KL), BMI or age[43], IL-18 levels in plasma, SF and articular cartilage samples from knee OA patients have been shown to be significantly higher than in healthy controls. Patients with higher disease severity had significantly higher IL-18 in all three sample media[66]. This would suggest IL-18 has the potential to distinguish between healthy and OA sufferers and to assess the severity of the disease in OA patients.

ANTI-INFLAMMATORY CYTOKINES

Countering the proinflammatory cytokines, antiinflammatory cytokines also play a role in the pathophysiology of OA. In particular, IL-10 and IL-4 contribute to the suppression of inflammation of the synovial membrane[67,68]. By reducing inflammation, these mediators can support cartilage production, acting as anabolic effectors which can slow the progression of OA. In disease-free conditions, the balance between anabolic and catabolic cytokines enables stable levels of cartilage. In OA, an imbalance in this equilibrium contributes to the pathophysiology of the disease. Generally, however, anti-inflammatory cytokines have been less well studied in the search for biochemical markers of OA.

IL-10 and IL-2

Low *ex vivo* production of IL-10 upon LPS stimulation was associated with an increased risk of familial OA at multiple sites[56]. In a similar study using LPS stimulation of knee OA samples, patients in the highest quartile of *ex vivo* IL-10 production had a 4-fold increased risk of radiological progression of JSN. This association was independent of age, sex or BMI[57].

IL-2 was found by Ling *et al*[64] to be higher in knee OA patients at the end of a 10-year follow-up period compared with healthy controls.

CHEMOKINES AND ANGIOGENIC GROWTH FACTORS

Chemotactic cytokines, or chemokines, have been shown to influence inflammation in OA through their ability to influence the number of immune cells in the vicinity of the joint. They also stimulate IL-6 production and proteoglycan depletion[69,70]. Angiogenic growth factors contribute to synovitis and pain as well as cartilage destruction[16,18,71].

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a 46-48 kDa glycosylated polypeptide[72] and a potent angiogenic cytokine that has been shown to play a role in OA[17,73]. It is produced by hypotrophic chondrocytes, macrophages and synovial fibroblasts[73-75].

VEGF in SF has been shown to correlate with OA severity, and no correlation with BMI, with a 2-fold increase between grade 0 and grade 3-4 patients[42]. We recently found similar results in our laboratory. SF and plasma levels were both positively correlated with the severity of OA (KL), though SF samples presented a stronger correlation[76].

IL-7

IL-7 is a hemopoietic growth factor involved in the development of B and T cells. It has been found to increase with age in samples of SF from OA patients, with the median concentration in patients over 60 years old double that of those under 60 years old. However, in the same study, there was no reported association between OA severity and IL-7 levels, and levels were depressed in patients with severe 3-compartment OA. IL-7 levels were found to have a weak correlation with BMI[42].

IL-8

IL-8 (also known as CXXL8) is a potent chemokine in the immune system. Few studies have examined this chemokine in detail with respect to levels in both SF or circulating media, and its relationship with OA. Nevertheless, it has been shown not to correlate with OA grade, BMI or age[42] in SF samples from OA patients. Pierzchala *et al*[77] found no correlation between IL-8 levels and OA severity (WOMAC) nor was there an association with bone remodeling[78]. Hitherto, there is insufficient evidence to suggest IL-8 possesses traditional characteristics of a biochemical marker. However, there have been few studies examining its potential. In contrast, it might be applicable as a housekeeping marker with levels not expected to change throughout the course of the disease or between healthy controls and OA patients.

CONCLUSION

A number of cytokines have shown potential as different types of biochemical markers (Table 2). Currently, IL-6 shows potential as a diagnostic and prognostic biomarker of OA. Other cytokines, including IL-1β, TNF-α, IL-15 and VEGF, show promise as burden of disease markers.

Differences between circulating (systemic) and SF (local) sampling should be taken into consideration when designing future studies and clinical applications to assess cytokine levels.

Due to their increased statistical power, using clusters of markers will have more impact than individual biomarkers. Unfortunately, in the hunt for biochemical markers specific to OA, most cytokines can be associated with a number of diseases. IL-15, for example, plays roles in rheumatoid arthritis, diabetes mellitus type 1 and type 2, and cancers[79-82]. This is a hindrance shared with many cytokines being investigated and supports the need to assess multiple candidates together.

Table 2 Classification of cytokines as biochemical markers in osteoarthritis

Cytokine	BIPEDS classification
IL-6	D, P
IL-1β	B, E
TNF-α	B, E
IL-15	B, D
IL-18	D
IL-10	P
IL-2	D
VEGF	B
IL-7	D

B: Burden of Disease; D: Diagnostic; E: Efficacy of Intervention; I: Investigative; P: Prognostic; S: Safety; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.

Owing to the invasive nature of collecting SF samples, it is usually only collected from patients undergoing knee surgery. In future clinical applications of the use of biochemical markers, this may not be feasible. Less invasive sample mediums, for example serum, plasma, and urine should continue to be investigated and validated.

More large-scale studies are required to assess the use of groups of biochemical markers and their effectiveness. Different groups designed for different purposes, for example diagnostic or prognostic, may prove valuable. In addition to customization of groups for intended purposes, adjusting for the stage of disease to be assessed, particularly for burden of disease assessment, would yield a more finely tuned clinical tool.

ACKNOWLEDGMENTS

The authors commemorate the 100th Anniversary of the King Chulalongkorn Memorial Hospital, Thai Red Cross Society.

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P- Reviewer: Fenichel I, Fisher DA **S- Editor**: Wen LL
L- Editor: Cant MR **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.106

World J Orthop 2015 January 18; 6(1): 106-116
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Hand bone mass in rheumatoid arthritis: A review of the literature

Gamze Kilic, Salih Ozgocmen

Gamze Kilic, Salih Ozgocmen, Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Erciyes University, School of Medicine, Gevher Nesibe Hospital, 38039 Kayseri, Turkey
Author contributions: Kilic G and Ozgocmen S contributed to the collection and analysis of the data, and drafted the manuscript.

Correspondence to: Salih Ozgocmen, MD, Professor, Head, Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Erciyes University, School of Medicine, Gevher Nesibe Hospital, Talas Yolu üzeri, 38039 Kayseri, Turkey. sozgocmen@hotmail.com
Telephone: +90-352-2076666
Received: December 29, 2013
Peer-review started: December 30, 2013
First decision: March 12, 2014
Revised: July 11, 2014
Accepted: July 29, 2014
Article in press: July 29, 2014
Published online: January 18, 2015

Abstract

Rheumatoid arthritis (RA) is a common chronic inflammatory disease and periarticular osteoporosis or osteopenia of the inflamed hand joints is an early feature of RA. Quantitative measurement of hand bone loss may be an outcome measure for the detection of joint destruction and disease progression in early RA. This systematic review examines the published literature reporting hand bone mass in patients with RA, particularly those using the dual X-ray absorptiometry (DXA) methods. The majority of the studies reported that hand bone loss is associated with disease activity, functional status and radiological progression in early RA. Quantitative measurement of hand bone mineral density by DXA may be a useful and practical outcome measure in RA and may be predictive for radiographic progression or functional status in patients with early RA.

Key words: Rheumatoid arthritis; Hand bone density; Dual X-ray absorptiometry; Periarticular; Osteoporosis

Core tip: Periarticular osteoporosis or osteopenia affecting the hands is an early characteristic sign of bone damage in rheumatoid arthritis (RA). Dual X-ray absorptiometry (DXA) can be considered a reproducible, sensitive and non-invasive method to assess hand bone mineral density (BMD) in early RA. Quantitative measurement of hand bone loss by DXA may be a useful and practical outcome measure in RA and may have predictive value to determine radiographic progression or functional status in patients with early RA. Building up a reference population to obtain objective and accurate *T* and *Z* scores for hand BMD is needed.

Kilic G, Ozgocmen S. Hand bone mass in rheumatoid arthritis: A review of the literature. *World J Orthop* 2015; 6(1): 106-116 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/106.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.106

INTRODUCTION

Rheumatoid arthritis (RA) is a severe chronic inflammatory disease and periarticular osteoporosis or osteopenia of inflamed joints is the characteristic feature of the disease[1]. Periarticular bone loss affecting the small joints of the hands is an early feature antedating the bone damage in RA. Hand bone loss occurs earlier than generalized

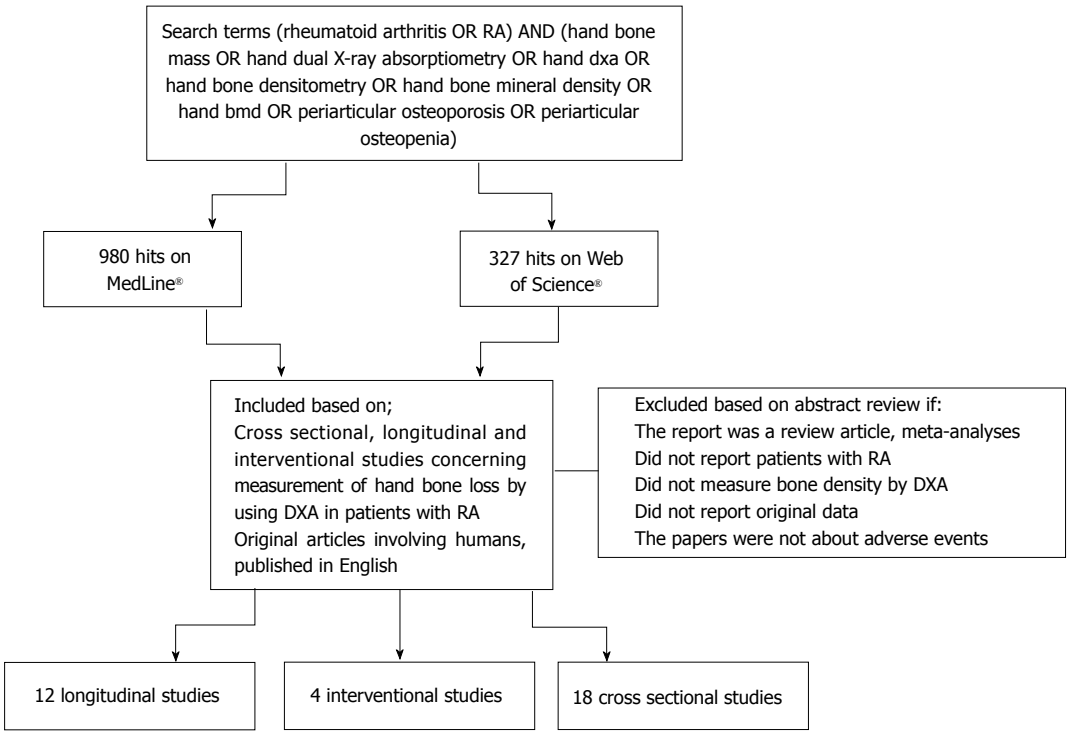

Figure 1 Flow chart. RA: Rheumatoid arthritis; DXA: Dual-X-ray absorptiometry.

osteoporosis and is associated with subsequent progressive joint destruction in patients with RA[2-4]. Therefore, precise quantification of hand bone loss may predict the severity and progression of joint destruction.

Recently, several imaging methods have been used to assess the peripheral bone mass, including plain X-ray[5], quantitative ultrasound (US)[6], peripheral quantitative computed tomography (pQCT)[7], magnetic resonance imaging[8], digital X-ray radiogrammetry[9] and dual X-ray absorptiometry (DXA)[10]. Among them, DXA can be considered an accurate, repeatable and sensitive method to assess hand bone mineral density (BMD) in early RA[11,12].

Until now, several studies have revealed the correlation of hand BMD with disease activity, functional capacity, radiographic progression or BMD at other sites in patients with RA[3]. A review of the literature documenting the role of hand DXA in the assessment of progression and joint damage in patients with early RA is necessary. Quantitative measurement of hand bone loss may be an outcome measure for the detection of joint destruction and disease progression in early RA. Therefore, this review will examine the published literature assessing hand bone mass in patients with RA, particularly those using the DXA methods.

SEARCH

The literature was searched for articles assessing hand bone mass in patients with RA. Studies in which hand bone mass was investigated by using DXA in patients with RA were eligible. Selection criteria consisted of original articles involving humans published in English. Articles were excluded if they were review articles or meta-analyses and did not measure bone density using DXA. In our search strategy, the following keywords were used: (rheumatoid arthritis OR RA) and (hand bone mass or hand dual X-ray absorptiometry or hand DXA or hand bone densitometry or hand bone mineral density or hand BMD or periarticular osteoporosis or periarticular osteopenia). The literature search was performed in PubMed® and Web of Science® databases between November 1993 and November 2013. Full texts of the selected articles were independently and systematically screened and data were extracted. For each trial, if applicable, information concerning sample size, study type, demographic characteristics of the patients, interventions, outcome measures and follow-up data was collected.

RESEARCH

Figure 1 shows the flow chart and the selection process. Thirty-four articles fulfilled the inclusion and exclusion criteria. 2131 patients with RA were reported within 18 cross-sectional studies, 12 longitudinal studies and 4 interventional studies. Table 1 shows the study design and characteristics of the studies.

Twelve cross-sectional studies compared patients with RA and controls. Ten studies showed that patients with RA had significantly lower hand BMD compared with matched healthy controls or patients with other rheumatic diseases[13-22]. Similarly, five longitudinal studies reported hand bone loss was higher in patients with RA than in matched healthy controls or patients with other rheumatic diseases, including spondyloarthropathies or

Table 1 Details of the studies included in the systematic reviews

Ref.	Study type	Sample size (M/F)	Mean/Median age	Disease duration (yr)	DXA equipment	DXA site	Coefficient variation BMD	Follow-up duration (yr)	Outcome	Conclusion
Florescu *et al*[19]	CS	RA: 10 HC: 10	63	15.3	Norland	MC bones (Ⅱ-Ⅴ)	0.9%-3.0%		There was a significant correlation between hand BMD and radiographic scoring methods	Hand BMD measurement may be a useful method for the detection and monitor of disease progression
Peel *et al*[34]	CS	RA: 70 F	64	3-45		WH, LS, femoral neck			Increased bone loss in patients with RA *vs* controls Hands: 22.7% Lumbar spine: 10.7% Femoral neck: 16.3% Total body: 11.3%	Significant correlation between hand BMD and BMD at other sites. Hand BMD correlated with grip strength and inversely related to ESR in patients with early RA
Deodhar *et al*[13]	CS	RA: 56 (22/34) Controls: 95 (46/49)	M: 64 F: 64	9	Hologic	WH	1%-3%		Mean total hand BMC (grams, M/F) RA: 81.7 /52.3 Controls: 90.9/62.2	Hand BMC correlated with disease severity but not with disease activity
Devlin *et al*[3]	CS	RA: 202 (61/141)	M: 59 F: 53	M: 1.6 F: 1.9	Lunar	LS Hip WH	0.6%		Hand BMD correlated with disease activity, functional capacity, lumbar and hip BMD	Hand bone loss can be used as outcome measure
Njeh *et al*[30]	CS	RA: 51 F Patients with osteopenia: 44 F HC: 52 F	Mean age 57.5		Lunar DPX-L	LS, Hip, WH			Mean Hand BMD (g/cm^2) in patients with RA: 0.415	Hand BMD was correlated with phalangeal ultrasound and hand functions but not CRP or ESR
Ozgocmen *et al*[22]	CS	RA: 30 F HC: 29 F	45.5		Lunar	WH II MC LS Hip	-		CI and C: MC ratio correlated with Ⅱ. MC midshaft and hand BMD	CI may predict cortical bone mass of the hand. C: MC ratio is a useful method for evaluating progression of wrist involvement
Alenfeld *et al*[14]	CS	RA: 41 (18/23) HC: 103 (35/68)	54	F: 2.1 M: 2	Lunar	WH Subcondral ROI	WH: 0.9 subcondral region: 2.7%-3.2%		Hand bone loss in the subregional regions is higher than total hand BMD	In early RA periarticular osteoporosis may be better assessed using detailed hand scan analyses
Ardicoglu *et al*[18]	CS	RA: 49 (9/40) HC: 34 (5/29)	49.1	5	Lunar	LS Hip WH			Hand BMD correlated with disease duration, CRP and radiographic scores	Hand BMD by DXA is a useful pratical and reproducible method

Harrison *et al*[20]	CS	RA: 17 (4/13) PsA: 15 (9/6)	RA:51 PsA:53	RA: 31 PsA: 27	Hologic	MCP, PIP, DIP joints	3.4%-6.6%	Periarticular BMD was significantly lower in patient with RA than PsA Periarticular BMD correlated with the number of swollen, tender joints in RA	Periarticular osteoporosis is associated with joint inflammation in RA but not PsA
Ozgocmen *et al*[47]	CS	RA: 15 F HS: 3 F	48.5	6.8	Lunar	WH, MCP	-	Flow patterns correlated with intra-articular bone and cartilage destruction	PDUS is a useful method for monitoring disease activity and measurement of therapeutic response
Jensen *et al*[48]	CS	RA: 11 female	53		Hologic	MC bones, forearm	0.65%-0.83%	There was a significant association between DXA-BMD and DXR-BMD	Periarticular bone loss can be detected better and earlier with DXR than DXA in patients with RA
Castañeda *et al*[15]	CS	EA: 22 (2/20) HC: 16 (3/13)	EA: 48.4 HC: 49.2	0.4	Hologic	WH MCP	MCP: 1.3% -0.7% WH: 1.4 %-0.9%	Whole hand BMD: (g/cm^2) HC: 0.355 EA: 0.349 MCP BMD: (g/cm^2) HS: 0.295, EA: 0.285	Measurement of BMD at MCP joints may be a useful method to assess the diagnosis or prognosis in patients with EA
Franck *et al*[21]	CS	RA: 421 (64/357) HC: 98 (31/67)	M: 56.11 F: 58.4	M: 4.8 F: 4.8	Hologic	LS, hip, forearm, WH, MCP Ⅱ-Ⅲ	Subregional scans: 0.9%-1.4% for short term, 1.5%-2.3% for mid-term	There was a significant correlation between WH BMD and its subregions, hip and forearm. Subregional BMD was correlated with CRP, bone resorption markers and grip strength	Measurement of hand and subregional BMD by DXA is accurate and reproducible method in RA
Murphy *et al*[49]	CS	RA: 4 SpA: 3	36.7	1.25	Hologic	MCP/PIP	0.73%-0.78%	The precision of MCP joints was greater than PIP joints	DXA can be used as a reliable measure for periarticular BMD
Alves *et al*[16]	CS	Established RA: 25 EA: 25 HS: 37	Established RA: 53 Early arthritis: 52		Lunar	WH, LS, hip, MCP and/or PIP joints mid MC to mid-phalangeal	0.45%-1.07%	Mean BMD of five ROI: Established RA: 0.321 to 0.372 Early arthritis: 0.321 to 0.382 HC: 0.342 to 0.401 Mean BMD of whole hand: Established RA: 0.387 Early arthritis: 0.392 HC: 0.420	Measurement of periarticular BMD is not a useful tool to discriminate between patients with early RA from HC

Zhu *et al*[7]	CS	RA: 100 F	53.4	9.1	Hologic	LS, hip, ultradistal radius			BMD assessed by HR-pQCT significantly correlated wth BMD at the peripheral and central skeleton	HR-pQCT is a useful method for evaluating periarticular bone loss at both cortical and trabecular bone
Moon *et al*[17]	CS	RA: 45 HC: 106	47.5		Lunar	Shaft and periarticular region of PIP, LS, hip			The ratio of shaft to periarticular BMD was higher in patients with RA	DXA assisted localized quantification and BMD ratio calculations are useful for assessing periarticular osteoporosis in early RA
Dogu *et al*[33]	CS	RA: 83	52.9	6.99	Lunar	WH	-		Hand BMD was correlated with HGS, TTP, radiological erosions but not DHI	HGS and TTP were most effective indicator of hand function
Deodhar *et al*[10]	LS	RA: 81 (33/48) HC: 95 (46/49)	Early RA: M: 53, F: 55 Late RA M: 65.5, F: 63	Early RA: 0.8 Late RA: 9	Hologic	WH		1	After 1 yr hand bone loss Early RA: M: 3.25%, F: 1.46% Late RA, no significant loss of hand BMD	Hand bone loss was highest in patients with early RA and correlated with disease activity
Daragon *et al*[25]	LS	Early RA: 15 (6/9) Other rheumatic diseases: 15 (7/8)	Early RA:42.7 Other rheumatic diseases: 48.8	0.4	Hologic	WH		1	There was no significant correlation between hand bone loss and clinical, radiological and biological parameters except for IFN alfa	Hand BMD by DXA may be useful tool for the early classification of inflammatory disease
Deodhar *et al*[26]	LS	Early RA: 40	-	< 2	Hologic	WH	2.3%	5	Percent change in BMD after 1 yr: -5.5, 2 yr: -7.5, 3 yr: -9.8, 4 yr: -9.9, and 5 yr: -10	Early loss in hand BMD (in the first six months) may be a prognostic marker for disease activity, functional status or poor functional outcome
Berglin *et al*[31]	LS	RA: 43(13/30)	Not available	0.6	Lunar	WH		2	Hand bone loss correlated with radiographic progression	Hand bone loss and radiographic progression were retarded by early treatment
Jensen *et al*[24]	LS	RA: 51 (10/41) Unclassified polyarthritis: 21 (3/18)	RA: 54 Unclassifiesd polyarthritis: 39	0.3	Norland	MCP, forearm		2	Hand BMD decreased only in patients with RA and associated with disease activity	DXR is better than DXA for detecting and monitoring periarticular osteoporosis of the MC bones

Haugeberg *et al*[4]	LS	Undifferentiated arthritis: 74 (9/65)	65	0.5	Lunar	LS Hip	1.07%	1	At the 1 yr follow-up, hand BMD loss; RA: -4.27 Inflammatory non-rheumatoid group: -0.49 Non-inflammatory group: -0.87	Hand DXA may be useful for determining the risk of progressive disease in RA
Haugeberg *et al*[36]	LS	RA: 79 (32/47)	49.7	0.7	Lunar	WH		0.9	Mean hand BMD loss 2.5% at 24 wk, 2.6% at 48 wk	Hand DXA is more sensitive than radiology can be used as outcome measure in early RA
Murphy *et al*[23]	LS	RA: 20 (8/12) SpA: 18 (11/7)	RA: 37, SpA: 33	RA: 0.4 SpA: 0.4	Hologic	WH LS Hip		1	Periarticular bone loss correlated with radiographic damage, disease activity and baseline TIMP-1 level	TIMP-1 may be use as a biomarker of periarticular bone loss in early RA
Hill *et al*[27]	LS	RA: 50 (12/38) Control: 30	57	0.75	Lunar	WH, LS, hip	1.1%	1	Hand BMD correlated with baseline CRP and radiographic score in RA	Hand BMD using DXA is a safe, reproducible procedure. It may predict radiological progression and disease activity
Bejarano *et al*[35]	LS	RA: 64 (27/37)	54.1	0.5		WH, lumbar spine, hip		6.4 yr	Follow-up change in hand BMD, -0.034	First year hand BMD loss was not associated with function or quality of life status but not long-term radiographic progression
Naumann *et al*[28]	LS	Early RA: 17 (4/13) Established RA: 35 (8/27)	Early RA: 55, Established RA with moderate disease activity: 58 Established RA with high disease activity: 53.5	Early RA: 0.2	Lunar	WH, MCP/ PIP, wrist, LS hip	Wrist: 0.75 WH: 0.78	1	There was a negative correlation between hand BMD and MCP joint synovitis in patients with high diasease activity. The best precision values of BMD were found for the wrist	Hand BMD measurement by DXA is highly reproducible method in patients with RA
Black *et al*[37]	LS	RA: 106 (29/77)	57	0.3	Lunar	WH		1	Lower hand BMD was associated with higher erosion scores	Hand BMD loss in the first 6 mo can predict early erosive change in patients with early RA
Haueberg *et al*[38]	IS	RA: 20 (7/13) IFX + MTX: 10	52.2	< 1	Lunar	WH, LS, hip		1	BMD (gr/cm^2) IFX treated group: WH: 0.42, spine: 1.14, T hip: 1.04, F neck: 1.03 Placebo: WH: 0.43, spine: 1.28, T hip: 1.06, F neck: 1.01	In the IFX treated group hand bone loss arrested at the hip but not at the hand and lumbar spine

Deodhar *et al*[39]	IS	Placebo: 13 Denosumab 60 mg treated group: 21 (7/14) Denasumab 180 mg treated group: 22 (5/17)	Placebo: 55.2 Denosumab 60 mg treated group: 57.7 Denasumab 180 mg treated group: 58.7	Placebo: 10.3 Denosumab 60 mg treated group: 12.6 Denasumab 180 mg treated group: 15.8	Lunar	WH	1	Mean change in hand BMD at 6/12 mo (%); denosumab 60 mg: 0.8/1 Denosumab 180 mg: 2/ 2.5 placebo: -1.2/-2	Denosumab increased hand BMD and decreased progression of bone erosion in RA
Haugeberg *et al*[29]	IS	MTX group: 19 (10/9) MTX + IAST: 21 (8/13)	MTX group: 56.2 MTX + IAST: 53.3	MTX group: 0.5 MTX + IAST: 0.4	Lunar	WH, MCP, hip, LS	1	In the first 3 mo, hand bone loss was lower in MTX + IAST treated group than MTX treated group. Hand bone loss associated disease activity, hand function and MRI synovitis score	IAST may protect against periarticular bone loss in inflamed finger joints in RA
Szentpetery *et al*[32]	IS	RA: 35 (11/24) PsA: 27 (12/15)	RA: 56 PsA: 44	RA: 8 PsA: 7	Hologic	WH, PIP/ MCP, hip, LS	3	Following anti-TNF therapy hip BMD decreased but spine and hand BMD unchanged. Periarticular BMD around PIP joints increased, MCP decreased	Anti TNF therapy increased bone formation without a change in bone resorption

CS: Cross-sectional study; CI: Cortical index; MC: Carpo:metacarpal; EA: Early arthritis; DXR: Digital X ray radiogrammetry; DXA: Dual X ray absorptiometry; HR-pQCT: High-resolution peripheral quantitative computed tomography; HGS: Handgrip strength; IAST: Intra-articular corticosteroid; HC: Healthy controls; IS: Interventional study; LS: Longitudinal study; PsA: Psoriatic arthritis; ROI: Region of interest; RA: Rheumatoid arthritis; SpA: Spondiloartropathy; TIMP-1: Tissue inhibitor of metalloproteinases 1; TTP: Three-finger pinch; vBMD: Trabecular volumetric bone mineral density; WH: Whole hand; LS: Lumbar spine; BMC: Bone mineral content; BMD: Bone mineral density; EA: Early arthritis; MTX: Methotrexate.

undifferentiated arthritis[4,10,23-25].

Hand bone mass and disease duration

Five longitudinal studies reported that hand bone loss occurred early in the disease duration in patients with RA[4,10,23,24,26]. A 5-year longitudinal study of hand bone mineral content (BMC) in patients with early RA indicated that the rate of hand bone loss measured by DXA was more pronounced in the first years of disease and then slowed. In this study, the predictors for bone loss over five years were identified as baseline disease activity, functional status and BMC loss within the first six months[26].

Hand bone mass and disease activity

Two cross-sectional[3,20] and seven longitudinal studies[4,10,23,26-29] reported that hand bone loss was significantly related to disease activity which was assessed by Disease Activity Score 28 (DAS-28), swollen joint count, CRP, Ritchie articular index or early morning stiffness in patients with early RA. However, Deodhar *et al*[13] underscored that hand BMC correlated with disease severity but not with disease activity in their pioneering cross-sectional study. Similarly, Njeh *et al*[30] showed that hand bone mineral density (BMD) correlated with functional capacity but not with CRP or ESR. On the other hand, Haugeberg *et al*[4] found that hand bone loss was associated with rheumatoid factor (RF) and mean CRP levels in their longitudinal study.

Hand bone mass and functional outcome

Five longitudinal[26,27,29,31,32] and four cross-sectional studies[3,18,33,34] indicated that hand bone loss correlated with functional status and health related quality of life (assessed using the outcome measures including Health Assessment Questionnaire scores, Short Form 36 (SF-36), hand function, grip strength or pinch strength) in early RA. However, 2 longitudinal studies failed to show a significant association between hand bone loss and functional status[4,35].

Hand bone mass and radiographic joint damage

Two cross-sectional studies revealed a significant correlation between BMC of the hand and radiographic joint damage[13,18]. Two longitudinal studies assessed the association between hand BMD and radiographic joint damage[27,36]. Haugeberg *et al*[36] showed that measurement of hand BMD by DXA was more sensitive than conventional radiographic scores for detecting early damage in patients

with RA. Four longitudinal studies identified the value of hand bone loss as a predictor for long term radiographic damage. A longitudinal study of 50 patients with early RA (whose hand BMD was measured at baseline, 6 and 12 mo) indicated that the baseline value of hand BMD was associated with radiographic scores at 12 mo[27]. Another longitudinal study consisting of 64 patients with RA confirmed the predictive value of hand BMD loss in the first year for the subsequent radiographic progression (6.4 year follow up)[35]. A longitudinal study by Black *et al*[37] showed hand BMD loss in the first 6 mo might be a predictor for erosions at 12 mo. Similarly, Berglin *et al*[31] found a significant correlation between hand bone loss and radiological progression over 24 mo follow up in patients with early RA. On the other hand, two studies failed to show a significant correlation between hand BMC loss and radiographic joint damage[25,26].

The effect of therapeutic agents on hand bone mass

Two studies have reported that anti-tumor necrosis factor (anti-TNF) treatment did not have a significant effect on hand bone loss[32,38] but reduced the bone loss at the hip[32]. Szentpetery *et al*[32] reported that a course of 3 years of anti-TNF treatment resulted in an increase in periarticular BMD at the proximal interphalangeal joints but not at the metacarpophalangeal (MCP) joints in patients with RA and psoriatic arthritis (PsA). A study by Haugeberg *et al*[29] revealed that intra-articular corticosteroid injection therapy (IAST) protected the inflamed joints against bone loss which was more pronounced in the MCP periarticular regions. A study by Deodhar *et al*[39] evaluated the effect of denosumab [a fully human monoclonal antibody against receptor activator of nuclear factor-kappa B ligand (RANKL)] on hand BMD and its correlation with erosion scores. Fifty-six patients with RA were randomly assigned to receive either placebo or one of two doses of denosumab (60 mg or 180 mg) every six months for one year. At 12 mo, mean hand BMD increased from baseline in both denosumab groups with a decreased progression of bone erosions.

Hand bone mass and bone turnover markers

Szentpetery *et al*[32] reported that baseline hand BMD inversely associated with bone turnover markers, including bone-specific alkaline phosphatase (bone ALP), procollagen type-I N-propeptide, C-terminal cross-linking telopeptides (CTX-I) and urinary N-terminal cross-linking telopeptide of type-I collagen (NTX-I) in patients with RA. Murphy *et al*[23] found a correlation between baseline serum levels of the tissue inhibitor of metalloproteinase 1 (TIMP-1) and periarticular bone loss after 12 mo follow-up in patients with early RA. Also the authors suggested that TIMP may be a predictive biological marker for periarticular bone loss. Daragon *et al*[25] showed that interleukin-1 (IL-1), IL-10 and TNF-α were not correlated with hand BMD, both in patients with RA and other rheumatic diseases.

DISCUSSION

In RA, bone involvement is characterized by focal articular bone loss (erosions), periarticular osteoporosis/osteopenia around inflamed joints and generalized osteoporosis affecting the axial and peripheral skeleton[40]. Periarticular osteoporosis or osteopenia affecting the hands is an early characteristic sign of bone damage and precedes the development of erosions in RA. Periarticular bone loss and erosions were considered as criteria in the revised 1997 American College of Rheumatology (ACR) classification criteria for RA[41]. Later, radiographic changes were excluded in the new 2010 ACR/European League Against Rheumatism classification criteria for RA due to the subjective evaluation of periarticular demineralization in the early stage of disease by conventional radiography[42].

Although pathogenesis of periarticular bone loss remains less clear, studies support that the periarticular bone loss may occur as a result of imbalance in bone remodeling. In RA, subchondral bone marrow and/or synovial inflammation inhibits bone formation by inhibiting the wingless signaling pathway and increases bone resorption by stimulating production of bone-resorbing cytokines, such as iIL-1, IL-6, IL-17 and RANKL[43,44].

Dual X-ray absorptiometry measurement of hand BMD can be considered an accurate, reproducible, sensitive, non-invasive method in early RA[11,12]. It is also a well tolerated and fast procedure. It has a small effective radiation dose and better precision value than conventional radiography. Hand BMD measurements by DXA have been suggested as a more sensitive method than radiological scoring for detecting bone damage in early RA[36]. DXA measurements provide quantitative results free of observer bias. On the other hand, there are many pitfalls using DXA on clinical application for measuring periarticular BMD in patients with RA. First, most elderly patients with RA have severe degenerative changes in the hands, including Heberden's and Bouchard' nodes, which may affect the result of hand BMD measurement and cause a higher result of BMC. Second, severe hand deformity in RA causes a change in hand position which results a wide variation in the hand BMD measurement but not hand BMC[13]. Third, hand bone loss seems to be the result of generalized plus local effect of the disease. Therefore, in patients with established RA, periarticular bone osteoporosis can be difficult to distinguish from generalized osteoporosis by using hand DXA alone. Moreover, it is also important to note the influence of normal age-related bone loss, especially in postmenopausal women. Finally, standard deviation (SDs) for hand BMD measurement by DXA is unknown. All of the studies included in this review compared DXA results with small reference populations. Further studies are needed to investigate SDs from the reference population to obtain objective and accurate results in T and Z scores for the hand[18].

Several studies support that hand bone loss occurs early in the disease process and more rapidly than at the hip and spine[4,10,23,24,26,34]. Ten studies demonstrated that hand bone loss was higher in patients with RA than matched healthy controls and patients with other rheumatic diseases[13-22].

Only a few studies examined the effect of several

therapeutic agents on hand bone loss assessed by DXA in RA. Several studies showed that anti-TNF drugs used in the treatment of RA reduces both disease activity and radiographic progression[45,46]. By contrast, limited data exist on the effect of anti-TNF treatment on periarticular bone loss in patients with RA. Two studies demonstrated that anti-TNF therapy (infliximab) did not have a significant effect on hand bone loss[32,38], whereas it reduced the bone loss in hip[32]. The mechanism of this failure has not been extensively investigated and is still an open question. The effect of RANKL blockade with denosumab on hand BMD was examined in the three treatment arms in a study: placebo or one of two doses of denosumab (60 or 180 mg). Mean hand BMD increased from baseline and progression of bone erosions decreased in both denosumab groups compared to placebo[39]. In RA, the effect of intra-articular corticosteroid injections into inflamed finger joints on hand bone loss was investigated in an interventional study comparing methotrexate (MTX) and IAST with MTX treatment for 1 year. The MTX and IAST treated group had a lower loss in periarticular hand BMD in the first 3 mo[29]. These data suggest that suppressing periarticular inflammation with a potent anti-inflammatory medication such as a corticosteroid may decrease periarticular inflammation, resulting in reduced periarticular bone loss.

Several longitudinal studies suggested that early hand bone loss may have predictive value to determine which patients with early RA will develop further radiographic progression or have poor functional status[26,27,31,35,37]. However, there are contrasting results. The discrepancy between results may be related to different radiological scoring methods, sample size, disease characteristics or therapetic approaches used.

CONCLUSION

Quantitative measurement of hand bone loss by DXA may be a useful and practical outcome measure in RA and may be predictive for radiographic progression or functional status in patients with early RA.

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P- Reviewer: El Maghraoui A, Mori K, Yamaguchi M
S- Editor: Wen LL **L- Editor**: Roemmele A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.117

World J Orthop 2015 January 18; 6(1): 117-126
ISSN 2218-5836 (online)

REVIEW

Current strategies for the restoration of adequate lordosis during lumbar fusion

Cédric Barrey, Alice Darnis

Cédric Barrey, Alice Darnis, Department of Spine Surgery, P Wertheimer Hospital, Hospices Civils de Lyon, University Claude Bernard Lyon 1, 69003 Lyon, France
Author contributions: Barrey C and Darnis A contributed equally to this work.

Correspondence to: Cédric Barrey, MD, PhD, Department of Spine Surgery, P Wertheimer Hospital, Hospices Civils de Lyon, University Claude Bernard Lyon 1, 59 Boulevard Pinel, 69003 Lyon, France. c.barrey@wanadoo.fr
Telephone: +33-6-86940037
Fax: +33-4-72357262
Received: December 30, 2013
Peer-review started: December 31, 2013
First decision: March 12, 2014
Revised: July 14, 2014
Accepted: July 27, 2014
Article in press: July 29, 2014
Published online: January 18, 2015

Abstract

Not restoring the adequate lumbar lordosis during lumbar fusion surgery may result in mechanical low back pain, sagittal unbalance and adjacent segment degeneration. The objective of this work is to describe the current strategies and concepts for restoration of adequate lordosis during fusion surgery. Theoretical lordosis can be evaluated from the measurement of the pelvic incidence and from the analysis of spatial organization of the lumbar spine with 2/3 of the lordosis given by the L4-S1 segment and 85% by the L3-S1 segment. Technical aspects involve patient positioning on the operating table, release maneuvers, type of instrumentation used (rod, screw-rod connection, interbody cages), surgical sequence and the overall surgical strategy. Spinal osteotomies may be required in case of fixed kyphotic spine. AP combined surgery is particularly efficient in restoring lordosis at L5-S1 level and should be recommended. Finally, not one but several strategies may be used to achieve the need for restoration of adequate lordosis during fusion surgery.

Key words: Lumbar lordosis; Pelvis shape; Pelvis incidence; Spinal fusion; Spine surgery; Sagittal balance

Core tip: Not restoring the adequate lumbar lordosis during fusion surgery may result in mechanical pain, sagittal unbalance and adjacent segment degeneration. The objective of this paper is to describe the current strategies and concepts for restoration of adequate lordosis during fusion surgery. The amount of lordosis to restore can be precisely evaluated from the analysis of spino-pelvic parameters. Technical tools during surgery involve patient positioning, release maneuvers, type of instrumentation used and surgical sequence. Finally, not one but several strategies may be used to restore the adequate lordosis during fusion surgery.

Barrey C, Darnis A. Current strategies for the restoration of adequate lordosis during lumbar fusion. *World J Orthop* 2015; 6(1): 117-126 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/117.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.117

INTRODUCTION

Lumbar fusion is a common surgical procedure for the

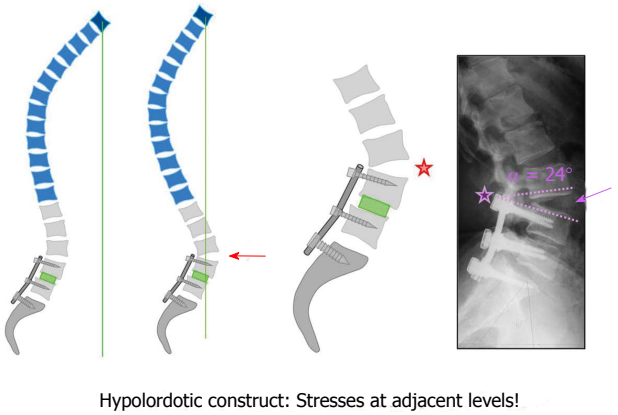

Figure 1 Hypolordotic lumbo-sacral fusion with hyperextension of the segment above the instrumentation. Failure to restore a good sagittal balance leads to chronic back pain and early degenerative changes at adjacent level(s).

management of degenerative and spinal deformities. Loss of lordosis after lumbar spine fusion can lead to chronic low back pain, positive sagittal balance with forward inclination of the trunk and adjacent segment degeneration. Identification and restoration of adequate lumbar lordosis for sagittal balance should be an everyday concern for the spine surgeon. However the challenge is to determine the correct amount of lumbar lordosis that each patient requires to maintain optimal sagittal balance. The development of posterior and anterior instrumentation has offered the advantage of a more accurate and more efficient restoration of the alignment of the lumbar spine and having good knowledge of the pelvic and spinal parameters is required to use it as effectively as possible.

WHY IS IT NECESSARY TO RESTORE LORDOSIS?

In 1973 Doherty[1] described a symptomatic fixed forward inclination of the trunk due to loss of normal lumbar lordosis following posterior spinal fusion for thoracolumbar scoliosis with Harrington instrumentation. Flatback syndrome, also known as fixed sagittal imbalance, was then described in 1977 by Moe *et al*[2] with a series of 16 patients with a loss of lumbar lordosis after thoracolumbar fusion. The most common cause of flatback syndrome is iatrogenic secondary to Harrington rod instrumentation[3-10] but there are many other iatrogenic causes such as hypolordotic lumbar fusion for degenerative spondylolysis, scoliosis or stenosis with instability. Failure to maintain lumbar lordosis during a fusion of a degenerative spine can result in accelerated adjacent degeneration, mechanical low back pain and loss of sagittal balance with forward inclination of the trunk, anterior displacement of the center of gravity and compensatory mechanisms such as cervical and thoracic segment hyperextension, knee flexion and hip extension[11-15]. These compensatory mechanisms have adverse effects such as chronic pain, disability and/or muscle fatigue[15]. Breakdown of the adjacent level has been identified as one cause of postoperative pain and disability[16-18].

The biomechanical effect of postoperative hypolordosis in lumbar fusion on instrumented and adjacent spinal segments has been described by Umehara *et al*[19] in 2000. Postoperative lumbar hypolordosis accelerate adjacent segment deterioration by loading the motion segment in a nonphysiologic way. The loss of lordosis in the instrumented segments not only affects the adjacent segments, but also increases the load on the posterior spinal implant. The tension in the anterior soft tissue structures decreases, increasing the implant load needed to balance the extension moment. To maintain good balance in the presence of a loss of lordosis, the posterior shear force on the proximal segments increases. This increases the extension moment on the lumbar spine and leads to an increased loading of the posterior implant, with a higher risk of loosening due to repetitive extension loading during activities of daily living. The loading of the posterior column in the segment above the instrumentation increases and may contribute to the degenerative changes (DDD, facet arthritis, listhésis) at the junctional level reported as long-term consequences of lumbar fusion (Figure 1).

Other factors are implicated in adjacent degeneration including rigid fixation, number of levels fused, and health of the adjacent level[19]. Guigui *et al*[20] showed that adjacent segment degeneration was significantly more common in patients treated earlier for degenerate disc disease than in younger patients with spondylolisthesis. Adjacent segment degeneration has been reported to be more frequent in females[21].

In 2001, Izumi *et al*[22] analyzed the sagittal lumbar alignment before and after posterior instrumentation and showed that in case of degenerative changes in the adjacent unfused segment the mean lumbar lordotic angles were decreased postoperatively by about 10°. Lazennec *et al*[23] in 2000 described the difficulty of achieving optimal lumbo-sacral alignment during fusion and showed statistically significant correlation between reduction of sacral inclination and back pain following lumbosacral fusion in the standing position because of undue stress on the sacroiliac joints and on the hips. In 2001, Kumar *et al*[24] reported 31 patients with radiographic evidence of adjacent level degenerative changes above the level of fusion in a series of 83 patients. The lowest incidence of adjacent segment degeneration was seen in patients with normal C7 sagittal plumb line and normal sacral inclination (8%). The difference between this group and the other groups with abnormality in either the plumb line or the sacral inclination or both was statistically significant.

It is difficult to determine the « good position » for lumbar fusion and the optimal degree of lordosis has not yet be defined[25]. Achieving a strong fusion in the optimal position requires understanding the relationships between the pelvic and spinal parameters in order to determine the theoretical lordosis for each individual (Table 1).

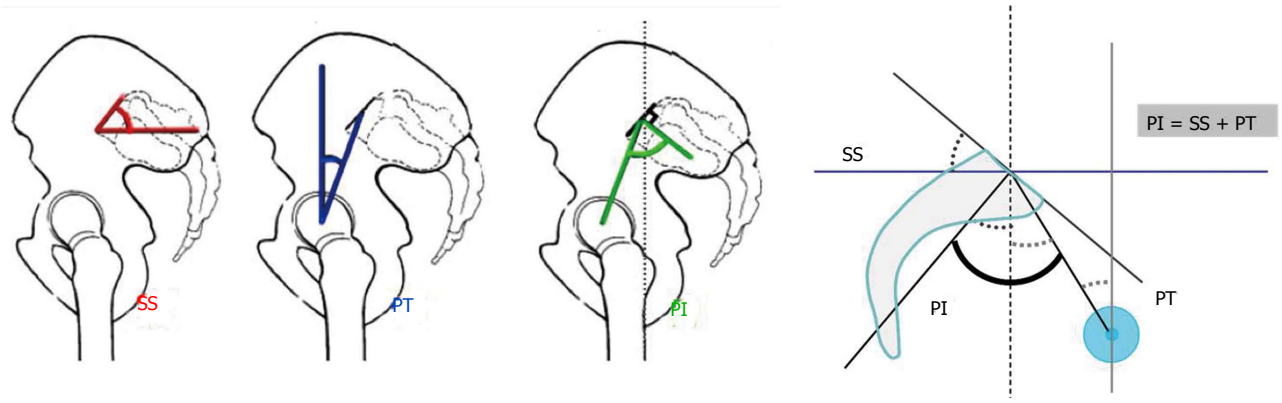

Figure 2 Duval-Beaupère's pelvic parameters. Sacral slope (SS), pelvic tilt (PT), pelvic incidence (PI) and mathematical relation between the parameters (PI = SS + PT).

Table 1 Consequences of hypolordotic construct

Inadequate restoration of lordosis (hypolordosis) during lumbar fusion exposes to	
Short term	Mechanical low back pain
	Anterior unbalance requiring compensatory mechanisms[15]
Long term	Adjacent segment degeneration

Table 2 Significance of spino-pelvic parameters

Anatomical	Pelvis	PI	Shape of the pelvis
Positional	Pelvis	SS	Inclination of the pelvis base
		PT	Position of the pelvis related to the femoral heads
	Spine	LL	Curve in extension above the pelvis to maintain the sagittal balance
		TK	Provide resistance and rigidity to the spine

PI: Pelvis incidence; SS: Sacral slope; PT: Pelvis tilt; LL: Lumbar lordosis; TK: Thoracic kyphosis.

HOW MUCH LORDOSIS IS IT NECESSARY TO RESTORE ? THE CONCEPT OF THE THEORETICAL LORDOSIS

The concept of the theoretical lordosis. Relationships between the components of the lumbo-pelvic complex. To determine the amount of lordosis to restore, we have to introduce the concept of theoretical lordosis deriving from the need for congruence between spinal and pelvic parameters.

Pelvic parameters

Relations between the shape and the position of the pelvis and lumbar lordosis have been initially described by Duval-Beaupère *et al*[26-29]. These authors proposed a pelvic anatomic parameter named pelvic incidence (PI) as the key factor for sagittal spinal balance, defined as the angle between the line perpendicular to the sacral plate at its midpoint, and the line connecting this point to the axis of the femoral heads. This pelvic parameter is constant for each individual after growth and determines the variable parameters of sacral slope (SS) and pelvic tilt (PT). Pelvic tilt is defined by the angle between the line connecting the midpoint of the sacral plate to the bi-coxo-femoral axis and the vertical line. Sacral slope is defined as the angle between the sacral plate and the horizontal line. Significance of these parameters in clinical practice is presented in Table 2.

A geometric construction by complementary angles showed that the anatomical parameter "pelvic incidence" is the algebraic sum of the "sacral slope" and "pelvic tilt" (Figure 2).

A significant relation exists between the pelvic and spinal parameters. The relation between lumbar lordosis and sacral slope has been well described by Stagnara *et al*[25] who established a linear increasing of lumbar lordosis (LL) with the increasing of the sacral slope. This strong correlation between SS and LL was confirmed in 2002 by Vaz *et al*[30] (r = 0.86). Duval-Beaupère demonstrated that pelvic incidence, which is the only independent and anatomical parameter, determines pelvic orientation and the spatial organization of the lumbar lordosis, which is closely correlated with it. A low value of pelvic incidence implies low values of pelvic parameters and a flattened lordosis; a high value implies well-tilted pelvic orientation and pronounced lordosis (Figure 3).

Legaye *et al*[28] found out that lumbar lordosis was closely related to the sacral slope (r = 0.86), which is strongly influenced by the pelvic incidence (r = 0.84), and established a predictive equation of the lordosis. Schwab *et al*[31] expressed it simply as "LL = PI + 9° (± 9)" based on healthy asymptomatic adults. In 2007, Barrey *et al*[32], through a comparative study, reported the pelvic parameters in a group of 154 healthy patients and found a mean pelvic incidence of 52°, sacral slope 40°, pelvic tilt 12°, and lumbar lordosis of 61°. Theoretical values of positional parameters, *i.e.*, SS, PT and LL, according to the PI are presented in Table 3.

Spinal parameters

A lot of parameters can be used to describe the sagittal spinal morphology: LL, thoracic kyphosis (TK), C7-plumb-line, spino-sacral angle (SSA) and spinal tilt (ST).

LL and TK

As mentioned by Roussouly *et al*[33], the sagittal profile

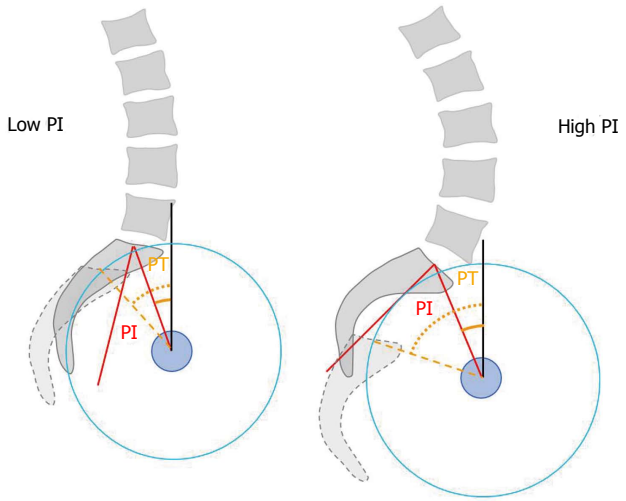

Figure 3 Low pelvic incidence is usually associated with slight sacral slope and flat lumbar spine, and high pelvic incidence with great sacral slope and more curved lumbar spine[32]. PI: Pelvis incidence; PT: Pelvis tilt.

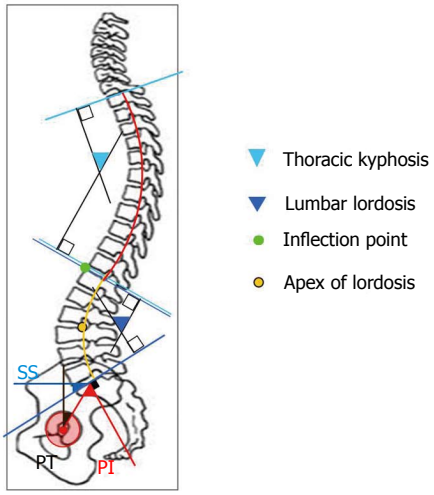

Figure 4 View of several spinal parameters. Lumbar lordosis (LL), Thoracic kyphosis (TK), Apex of the lordosis, Inflection point. PI: Pelvis incidence; PT: Pelvis tilt; SS: Sacral slope.

Table 3 Theoretical values for positional pelvis and spinal parameters related to pelvis incidence

PI class	PI (°)	PT_{th} (°)	LL_{th} (°)
I	< 38	4	PI + 18
II	38-47	8	PI + 13
III	48-57	12	PI + 9
IV	58-67	16	PI + 6
V	68-77	20	PI + 2
VI	> 78	24	PI - 5

PT: Pelvis tilt; LL: Lumbar lordosis; PT_{th}: Theoretical PT; LL_{th}: Theoretical LL. As examples, for PI measured to 40°, expected PT should be 8° and LL should be 53°; for PI measured to 52°, expected PT should be 12° and LL should be 61°; and for PI measured to 64°, expected PT should be 16° and LL should be 70°.

of the spine is usually characterized as being kyphotic between T1 and T12, and lordotic between L1 and L5, but this is not necessarily the case. The "thoracic" segment of the spine is located between T1 and the inflection point where the spine transitions from kyphosis to lordosis. The "lumbar" lordosis exists between the inflection point and S1. This determination of kyphotic and lordotic segments is independent of the anatomic location of the thoracolumbar junction at T12-L1. To characterize the lumbar lordosis in normal population, several parameters have to be taken into consideration: the position of the apex of the thoracic and lumbar curves, the position of the inflection point (transition between LL and TK), the number of vertebral bodies in each curvature, total kyphosis and lordosis in degrees, lordosis tilt angle, and the sacral slope (Figure 4).

Based on these considerations, Roussouly established a system to classify each patient as one of four types (Figure 5): Type 1 Lordosis. The sacral slope is less than 35°, which is usually associated with a low pelvic incidence. The apex of the lumbar lordosis is located in the center of L5 vertebral body. The lower arc of lordosis is minimal, decreasing toward zero as the sacral slope approaches the horizontal. The inflection point is low and posterior, creating a short lordosis with a negative lordosis tilt angle. The upper spine has a significant kyphosis of the thoracolumbar junction and thorax. In his series, the mean global lumbar lordosis of this group was 52°; Type 2 Lordosis. The sacral slope is less than 35°. The apex of the lumbar lordosis is located at base of the L4 vertebral body. The lower arc of lordosis is relatively flat. The inflection point is higher and more anterior, decreasing the lordosis tilt angle but increasing the number of vertebral bodies included in the lordosis. The entire spine is relatively hypolordotic and hypokyphotic. In his series, the mean global lumbar lordosis of this group was 52°; Type 3 Lordosis. The sacral slope is between 35° and 45°. The apex of lumbar lordosis is in the center of the L4 vertebral body. The lower arc of lordosis becomes more prominent. The inflection point is at the thoracolumbar junction, and the lordosis tilt angle is nearly zero. An average of four vertebral bodies constitutes the arc of lordosis. The spine is well balanced. In his series, the mean global lumbar lordosis of this group was 61°; Type 4 Lordosis: The sacral slope is greater than 45°, which is associated with a high pelvic incidence. The apex of the lumbar lordosis is located at the base of the L3 vertebral body or higher. The lower arc of lordosis is prominent, and the lordosis tilt angle is zero or positive. The number of vertebrae in a lordotic orientation is greater than 5, and a state of segmental hyperextension exists. In his series, the mean global lumbar lordosis of this group was 71°.

C7 plumb line, SSA and ST

As described by Roussouly *et al*[34], the C7-plumb-line is the vertical axis begining at the centroid of C7 and the SSA is defined as the angle between a line from the center of C7 to the center of the sacral endplate and the sacral endplate itself. The spinal tilt (ST) is defined as the angle between the line connecting the centers of C7 and S1

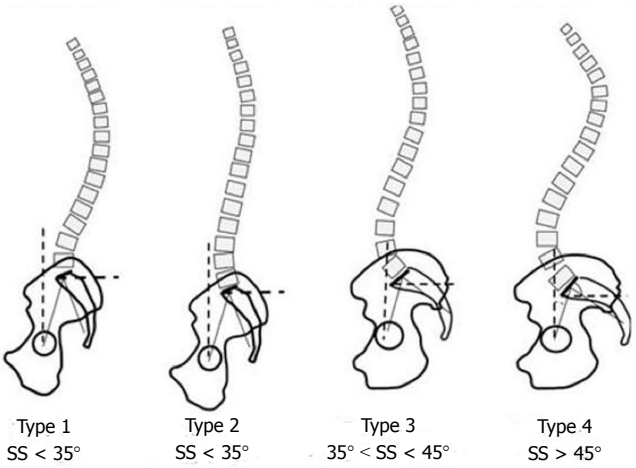

Figure 5 Roussouly's classification of sagittal profiles of the spine in four types[33].

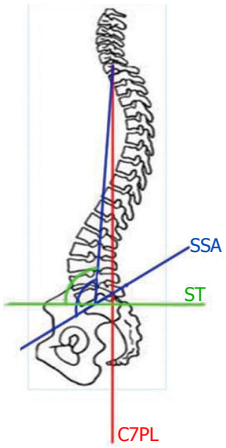

Figure 6 C7 plumb line, spino sacral angle and spinal tilt. C7PL: C7 Plumb Line; SSA: Spino sacral angle; ST: Spinal tilt.

Table 4 Amount of lordosis to restore related to the pelvis incidence and the length of spinal construct

PI	LL_{th}	Length of fusion				
		L5-S1	L4-S1	L3-S1	L2-S1	L1-S1
		40% of LL_{th}	67% of LL_{th}	85% of LL_{th}	97% of LL_{th}	100% of LL_{th}
40°	55°	22°	37°	47°	53°	55°
50°	60°	24°	40°	51°	58°	60°
60°	65°	26°	44°	55°	63°	65°
70°	70°	28°	47°	59°	68°	70°

PT: Pelvis tilt; LL_{th}: Theoretical Lumbat lordosis.

Table 5 Technical key points permitting to restore lordosis

Operative positioning	Avoid knee-chest position
Release	Allow for mobilization of the spinal segments
Instrumentation	Contouring of the rod Screw-rod connection Interbody implants
Spinal osteotomies	Indicated only when the spine is fixed in kyphotic position
Surgical sequence	AP sequence should be promoted

and the horizontal axis. There is a geometric association between ST, SSA, and SS: ST = SSA - SS (Figure 6). In a cohort of 153 patients without symptoms of spinal disease the mean SSA was 134.7° and the mean ST was 95.1°.

In 1998, Janik *et al*[35] hypothesized that a simple geometric model in the shape of an ellipse, from T12 to S1, would fit the lumbar lordosis. The elliptical model was approximately an 85° portion of a quadrant and suggested that about 70% of the lumbar lordosis was located between L4 and S1 (Figure 7).

Taking in account the theoretical lordosis for each individual related to the PI and also the normal distribution of the lordosis along the lumbar spine, we can calculate the amount of lordosis to restore according to the length of the construct (Table 4).

HOW TO RESTORE LORDOSIS DURING LUMBOSACRAL FUSION? TECHNICAL KEY POINTS

Tools and technical key-points to restore lordosis during lumbar fusion surgery are synthesized in Table 5.

Operative position

Different operative positions can be used in lumbar spinal surgery, depending on the type of the procedure. Decompressive procedures are optimally performed in positions incorporating less lordosis, improving access to the spinal canal and intervertebral discs and decreasing blood loss[36], as in the knee-chest position.

At the opposite, lumbar or lumbosacral fusions with internal fixation should be performed in an operative position which recreates physiologic lordosis. In 1996, Stephens *et al*[37] compared operative tables used commonly for spinal procedures in order to determine which positions reproduce "normal" lumbar lordosis. Ten volunteers without any history of lumbar surgery or symptomatology underwent lateral radiograph in the standing position and in three different kinds of operative position: prone position on the Jackson table, knee flexed at 15°, knee-chest position with hips flexed at 90° on the Andrews table, and intermediate position with hips flexed at 60° (Figure 8). The mean lumbar lordosis angle from L1 to sacrum was 51.7° in the standing position, 52° in the prone position on the Jackson table, 17° in the knee-chest position and 27.3° with the hips flexed at 60°. The decrease in lordosis was statistically significant in the knee-chest and the intermediate position compared with the standing position and the Jackson table.

Another study in 1995 by Peterson *et al*[38] showed that the "90-90" position on the Hastings frame was associated with significant reduction of total and segmental lordosis in the middle and lower lumbar spine. We therefore recommend positioning prone, as example on a Jackson table, maintained standing lumbar lordosis

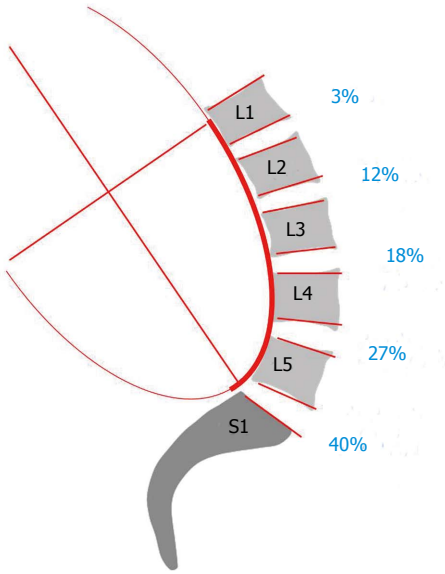

Figure 7 Sagittal lumbar curvature modeled by a portion of an ellipse. Note that 2/3 of the lumbar lordosis is located in the lower lumbar spine between L4 and S1 and that 85% of the lordosis is given by the L3-S1 segment.

and increased lumbo-sacral lordosis.

Release

Due to degenerative changes of the spinal segments (loss of disc height, facet arthritis, osteophytes, bony bridges, ligamentar hypertrophy…), mobilization of the spine and restoration of the optimal lordosis can be difficult to achieve. Therefore, release procedures allow for easier mobilization of the vertebra and thus facilitate realignment of the spine along the rod. The release maneuvers can be performed by posterior and/or by anterior approach involving different anatomical structures.

During posterior approach, release consists of: (1) resection of spinous processes and soft tissues retractions; (2) facetectomy involving the inferior facet but also the superior part of the superior facet; (3) complete foraminotomy when necessary; and (4) intervertebral distraction performed posteriorly through the disc space with intervertebral dilatators permitting to break some bony bridges.

During anterior approach, release consists of: (1) dissection of the anterior longitudinal ligament; (2) resection of osteophytes and bone bridges; and (3) thorough discectomy completed by dissection of the posterior longitudinal ligament when necessary.

Osteotomies

In case of rigid spine, fixed in kyphotic position, more aggressive techniques with osteotomies of the spine may be required. In the current chapter, the objective is not to describe in details such techniques but just mention that these techniques may be useful, not in routine, but in case of severe spinal deformity.

Traditional operative techniques in sagittal deformity correction involve a lengthening of the anterior column, shortening of the posterior column, or both. Posterior spine-shortening techniques include the Smith-Petersen and the pedicle subtraction osteotomies, while vertebral column resection is both an anterior and posterior excision[39]. These procedures are effective but require wide exposure of the spine and are associated with high blood loss and morbidity[40]. Alternatively, gains in lordosis can be achieved by anterior-column lengthening, releasing the anterior longitudinal ligament and placing interbody implants with an anterior approach, using the facets as a hinge point. Anterior release techniques in the treatment of deformity have been first described for adolescent idiopathic scoliosis[41-43] and are now performed in lumbar or lumbosacral fusion.

In a cadaveric study, Uribe *et al*[44] demonstrated that releasing the anterior longitudinal ligament increased segmental lordosis by 4.1° ± 2.7° and central disc height by 22.3% ± 15.4% compared with the intact disc.

Instrumentation

Technical aspects involving the instrumentation are represented by the shape of the rod, the screw-rod connection and the use of interbody implants. Posterior fusion techniques are commonly used to achieve solid arthrodeses and the use of instrumentation systems with pedicle screws and spinal rods has increased. The initial configuration of the spinal rod is usually straight and intraoperative contouring of the rods is almost always required in order to match the physiologic lordotic spinal curve, considering that the ultimate goal is to realign the instrumented spine along the rod. The amount of rod contouring depends on the amount and the type of the native lumbar lordosis of the patient. A patient with a high pelvic incidence and a pronounced lumbar lordosis requires an important rod contouring (Figure 9).

French benders are among the most common intraoperative contouring tools that deliver significant permanent curvature deformation. However, the contouring process affects the fatigue resistance of spinal rods, and ultimately, the mechanical integrity and fatigue resistance of the entire spinal construct[45]. Pre-lordosed rods can be used, conserving the integrity of the structure of the rod because of a different process of contouring.

Pedicle screw systems have been modified over the past years to reduce the incidence of screw breakage. Multiaxial pedicle screw designs allow deviation of the screw away from the perpendicular to the longitudinal rod, which facilitates application of a screw–rod system into the curved spine. Stanford *et al*[46] compared 6 multiaxial screw designs with static and dynamic mechanical testing and found that the static compression bending yield loads of the designs tested barely exceed the expected *in vivo* compression bending loads on a thoracolumbar pedicle screw construct incorporating three vertebral levels. Multiaxial designs introduced a site of reduced static compression bending yield strength at the rod-screw link in comparison with fixed screw designs. In 2007, Chen *et al*[47] studied the different performances between polyaxial and monoaxial pedicle screws in connection with rod contours of various lordotic angles (0°, 7°, 14° and 21°): the large segmental lordotic configuration can

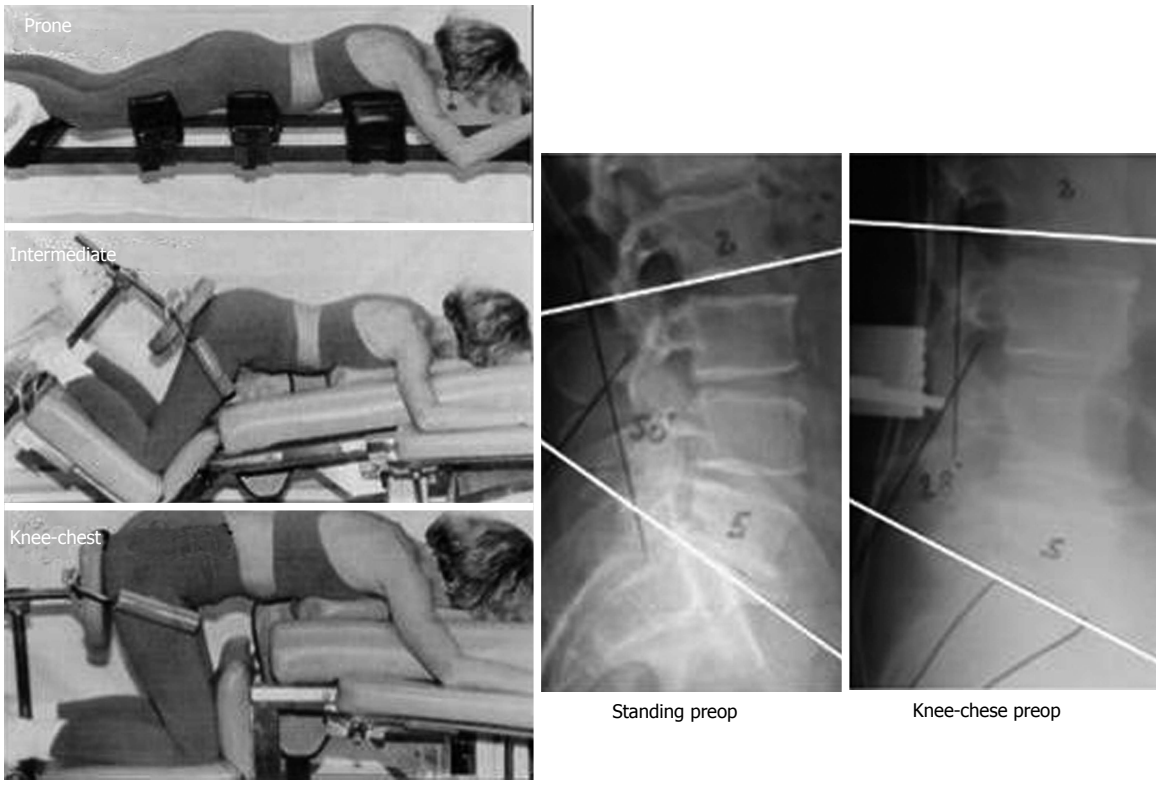

Figure 8 Different positions on operative table (Figures on the left coming from the work by Stephens *et al*[37]. Clinical case on the right: Loss of lumbar lordosis in knee-chest position with L2-S1 angle passing from 50° preoperatvely to 28° peroperatively).

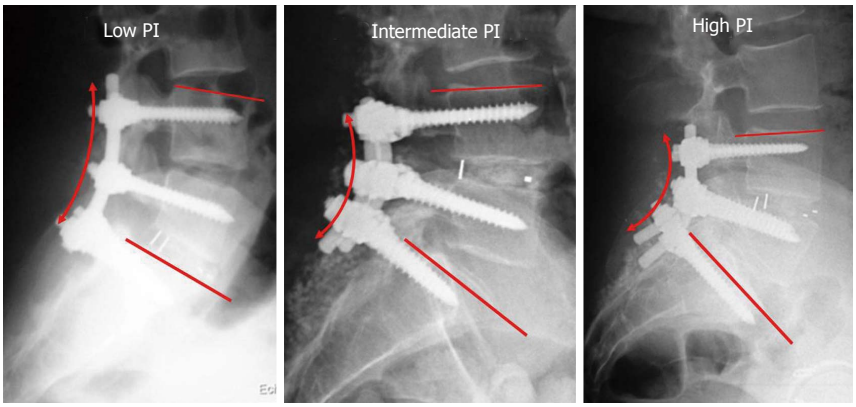

Figure 9 The importance of rod contouring depends on the spino-pelvic morphotype. PI: Pelvic incidence.

decrease the stiffness in the monoaxial screws. Polyaxial screws combined with an interbody cage fixation provide higher compression and flexion stiffness in 21° segmental lordosis and enhance the contact ratio of the interbody cage. However, to our knowledge there is no published data comparing the amount of lordosis restored between monoaxial and polyaxial screws. The angle between the screw and the rod is constant with the monoaxial screws (90°) whereas it is variable with the polyaxial screws. Because of this difference in the rod-screw connection, the amount of lordosis in the fusion may not be as important as the amount of rod contouring when using polyaxial screws (Figure 10).

Interbody fusion techniques have been developed to provide solid fixation of spinal segments while restoring a proper disc height and sagittal balance[48,49]. The interbody lumbar fusions may be achieved by anterior lumbar interbody fusion (ALIF), transforaminal lumbar interbody fusion (TLIF), posterior lumbar interbody fusion (PLIF), extreme lateral approach (XLIF) or a combined approach.

Segmental lordosis is a fundamental concern: at first, threaded interbody devices for lumbar fusion were placed under interbody distraction between parallel endplates and, as such, had no intrinsic ability to induce a lordotic contour, whereas for patients undergoing fusion with vertically oriented mesh cages combined with posterior compression instrumentation, there was a mean lordotic gain of 5°/segment[50]. Today, ALIF combined with posterior fixation

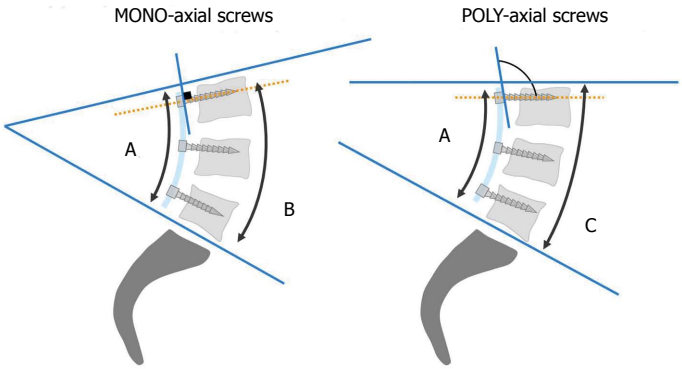

Figure 10 Impact of rod-screw connection on lordosis restoration: monoaxial *vs* polyaxial screws. With mono-axial screws, the connection between the screw and the rod is perpendicular, permitting therefore to position the spine approximately in a similar position compared to the rod. On the contrary, using poly-axial screws, the connection between the screw and the rod is angulated with the spine less lordotic compared to the rod. In the figure, although the contouring of the rod is similar for the two spines, the spine on the right, instrumented with poly-axial screws, is significantly less lordotic.

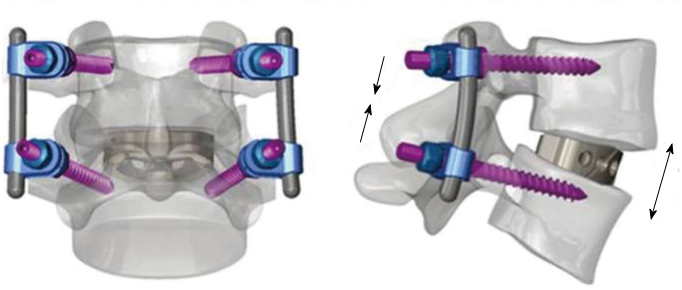

Figure 11 Posterior and lateral view of combined anterior/posterior arthrodesis using anterior lumbar interbody fusion cage inserted anteriorly and posterior pedicle-screw stabilization[55].

has become one of the standard operative procedures for degenerative disorders of the lumbosacral spine[51,52]. The ALIF procedure allows for thorough discectomy, appropriate cleaning of endplates and large bone grafts. Different studies have reported segmental lordosis gain measured over the fused segments from 2° to 11° with ALIF[53-55], 8° with PLIF[56], and 7° with TLIF[57]. The ALIF procedure uses high lordotic cages, allowing more correction of narrowed L5-S1 and L4-L5 discs than those observed in PLIF or TLIF procedure[55]. Restoring 5° to 6° is probable sufficient at L4-L5 level and above, but not enough at L5-S1.

Approach and surgical sequence

In the clinical setting of fusion at the lumbosacral junction, Soegaard *et al*[58] demonstrated that the circumferential fusion using the wedge-shaped cage and pedicle screws fixation restored lordosis, attained higher union rate, and had a better functional outcome than the instrumented posterolateral fusion. Combined anterior/posterior arthrodesis procedures are documented in the literature data, most authors focused on fusion success, without relating it to the sequence and details of anterior and posterior procedures[59-61]. In a recent study, Barrey *et al*[55] demonstrated that combined lumbo-sacral fusion was a safe and efficient surgical technique to obtain a high-quality fusion, restore a proper disc height and appropriate segmental lordosis and provide good clinical and functional outcomes. Lumbo-sacral fusion was achieved by combined approach, anterior then posterior, using anterior PEEK cage filled with BMP and posterior pedicle-screw stabilization. This surgical sequence combines an anterior distraction with an anterior release and the use of a high lordotic cage followed by a posterior pedicle-screw fixation with compression (Figure 11).

Surgery sequencing of this combined approach has also an impact on sagittal alignment and balance. In this study, the author begins with the anterior step, realigning the spine by the patient position: supine and slightly extension of lumbar spine, and then performs stabilization during the posterior step. Disc height and segmental lordosis L5-S1, L4-L5 and L4-S1 significantly increased postoperatively. Mean correction was approximately 11° for L5-S1 and 6° for L4-L5 and all levels instrumented with cages were fused at the last-time follow-up CT scan. This study suggests that combined AP surgery should be promoted particularly at L5-S1 level.

CONCLUSION

To conclude, need for restoration of lordosis during lumbar and lumbo-sacral fusion is now well-documented in the literature and well-admitted by spine surgeons. Instrument the spine in a lordotic position signifies to leave the spine in an economic, painless and balanced position.

Optimal lordosis is different for each individual and depends on the spino-pelvic organization of the subject. Analysis of the spino-pelvic parameters and, especially measurement of pelvis incidence, is a crucial step to determine the theoretical lordosis and therefore the amount of lordosis to restore. For harmonious types, we can now evaluate the amount of lordosis to restore according to the levels involved and the length of the construct.

Tools for the restoration of lordosis are not only represented by the instrumentation but also by patient positioning, release procedures and overall surgical strategy. Consequently, there are certainly not one but several surgical strategies permitting to achieve the same objective during lumbar fusion: restore the adequate lumbar lordosis.

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DOI: 10.5312/wjo.v6.i1.127

World J Orthop 2015 January 18; 6(1): 127-136
ISSN 2218-5836 (online)

REVIEW

Regeneration of the anterior cruciate ligament: Current strategies in tissue engineering

Thomas Nau, Andreas Teuschl

Thomas Nau, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology/AUVA Research Center, 1200 Vienna, Austria
Thomas Nau, IMSART-Institute of Musculoskeletal Analysis Research and Therapy, 1200 Vienna, Austria
Thomas Nau, Andreas Teuschl, The Austrian Cluster for Tissue Regeneration, 1200 Vienna, Austria
Andreas Teuschl, Department of Biochemical Engineering, University of Applied Sciences Technikum Wien, 1200 Vienna, Austria
Author contributions: Nau T contributed to the conception and drafting of the article and final approval; Teuschl A contributed to the drafting of the article and final approval.
Supported by The City of Vienna (MA 27 - Project 12-06); the Austrian´s Working Compensation Board (AUVA); the Austrian Research Agency FFG, Bridge-Project, No. #815471; and the New Tissue Project, No. FFG #818412.

Correspondence to: Thomas Nau, MD, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology/AUVA Research Center, Donaueschingenstraße 13, 1200 Vienna, Austria. office@traumanau.com
Telephone: +43-1-33110462
Fax: +43-1-33110460
Received: April 14, 2014
Peer-review started: April 15, 2014
First decision: June 18, 2014
Revised: June 19, 2014
Accepted: July 25, 2014
Article in press: July 29, 2014
Published online: January 18, 2015

Abstract

Recent advancements in the field of musculoskeletal tissue engineering have raised an increasing interest in the regeneration of the anterior cruciate ligament (ACL). It is the aim of this article to review the current research efforts and highlight promising tissue engineering strategies. The four main components of tissue engineering also apply in several ACL regeneration research efforts. Scaffolds from biological materials, biodegradable polymers and composite materials are used. The main cell sources are mesenchymal stem cells and ACL fibroblasts. In addition, growth factors and mechanical stimuli are applied. So far, the regenerated ACL constructs have been tested in a few animal studies and the results are encouraging. The different strategies, from *in vitro* ACL regeneration in bioreactor systems to bio-enhanced repair and regeneration, are under constant development. We expect considerable progress in the near future that will result in a realistic option for ACL surgery soon.

Key words: Anterior cruciate ligament; Tissue engineering; Orthopedic; Ligament regeneration; Stem cell

Core tip: This article reviews the current research strategies in anterior cruciate ligament tissue engineering and highlights the most promising strategies in this field.

Nau T, Teuschl A. Regeneration of the anterior cruciate ligament: Current strategies in tissue engineering. *World J Orthop* 2015; 6(1): 127-136 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/127.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.127

INTRODUCTION

Knee injuries frequently result in ruptured ligaments, typically through high-pivoting sporting activities such as skiing, football and basketball. In 2005, around 400000 physician office visits in the United States were related

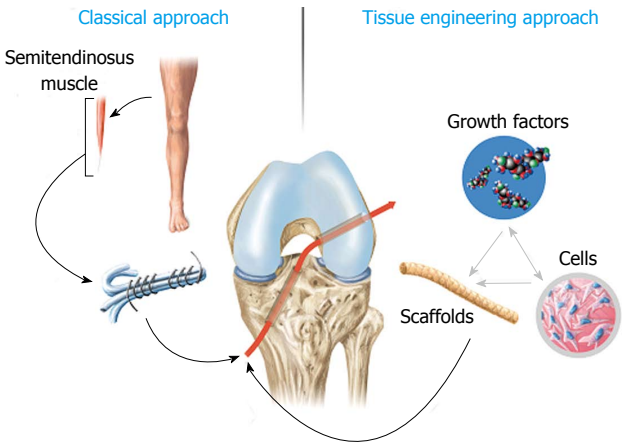

Figure 1 Comparison of the current clinical strategy in anterior cruciate ligament surgery to tissue engineering approaches. The current "golden standard" in the clinical routine is the use of autologous tissue grafts such as semitendinosus (depicted in the figure) or patellar tendon. In tissue engineering approaches, scaffolds alone or in a combined fashion with cells or growth factors are used to improve tissue regeneration.

to knee injuries[1]. The worldwide estimation of young sports players that require surgery following a knee injury lies between 17%-61%[2]. The anterior cruciate ligament (ACL), a main stabilizing structure of the knee, is one of the most commonly injured ligaments. In the United States alone, around 350000 reconstructive surgeries of the ACL are performed annually. According to the National Center for Health Statistics, the annual costs for the acute care of these injuries are around $6 billion[3].

Historically, the treatment of ACL injuries involved different strategies, from non-operative care to several surgical procedures[4]. Simple primary suturing in the 1970s was abandoned due to bad clinical results. Augmented ACL repair using natural as well as synthetic grafts leads to somewhat improved results. Synthetic grafts were popular in the 1980s but resulted in serious complications and bad clinical results. From the early 1990s onwards, ACL reconstruction with autograft or allograft material has become the method of choice for most surgeons (Figure 1). Despite the ongoing success of autografts, problems mostly associated with donor site morbidity remain, such as anterior knee pain, infrapatellar contracture, tendonitis, patellar fracture, muscle weakness and limited graft availability[5]. In terms of allograft material, the risk for transmissions of blood-borne diseases and the delayed biological incorporation were mentioned as the main disadvantages[6]. In addition, relatively high failure rates of ACL reconstruction, especially in young and active patients, have been reported for allografts[7]. An incidence of osteoarthritis as high as 50% within 7-14 years after injury and reconstruction of the ACL is still the main drawback of this surgical strategy. The development of osteoarthritis following ACL injury is not fully understood and may be caused not only by the limitation of the current grafts, but also by the initial joint trauma and the trauma caused by the surgeon. However, this has resulted in enormous ongoing research interest in that topic[8,9].

The regeneration of musculoskeletal tissues has become increasingly popular in the field of orthopedic research. Typically, structures that are injured or lost due to trauma and disease are the ideal candidates to be engineered. Tissue engineering as a multidisciplinary field includes strategies of engineering, material science and biology, with the aim of regenerating tissues that not only recreate the morphology, but also restore the normal function. In the late 1980s, Langer and Vacanti[10] first described the classic four basic components that are needed in tissue engineering: a structural scaffold, a cell source, biological modulators and mechanical modulators[10].

The ACL, with its limited healing capacity and the consequent need for reconstructive surgery, certainly is an appealing but also challenging structure for tissue engineering. In contrast to extra-articular ligaments, such as the medial collateral ligament, the intra-articular location of the ACL apparently prevents its primary healing. The disruption of the synovial sheath does not allow local hematoma formation crucial for the onset of the inflammatory response that would stimulate primary healing[11]. In addition, the complex three dimensional structure of the ACL, with different tensioning patterns throughout the knee path of motion, contributes to the difficulty of regenerating this ligament in terms of form and function.

It is the purpose of this article to review the current approaches in tissue-engineering of the ACL, to provide an overview of the current problems and limitations, and to present future directions of this evolving research technology.

SCAFFOLDS FOR ACL REGENERATION

Many different biomaterials have been introduced as a potential scaffold for ACL tissue engineering. Ideally, the scaffold has to be biocompatible and its mechanical properties should mimic the natural ACL as closely as possible. It also needs to be biodegradable to enable tissue ingrowth, which is crucial for the new ligament to form. Biological materials, biodegradable polymers and composite materials have all been or still are under evaluation for ligament regeneration[11].

Dunn *et al*[12] and Bellincampi *et al*[13] developed scaffolds made of collagen fibrils. They showed that ACL fibroblasts adhered to these scaffolds and remained viable, *in vitro* as well as *in vivo*. Unfortunately, after 6 wk the constructs were completely resorbed. Goulet *et al*[14] reported on the decreasing mechanical strength of collagen scaffolds seeded with ACL fibroblasts. Murray *et al*[15] demonstrated that a collagen-glycosaminoglycan composite scaffold supported cell growth and the expression of fibroblast markers. Several techniques have been explored to improve the mechanical properties of collagen-based scaffolds, including cross linking the collagen or a special braid-twist design[16-18]. However, despite considerable improvements of the mechanical properties, collagen-based scaffolds thus far have not been able to mimic the strength of the natural ACL.

Similar challenges regarding the mechanical strength have also been reported for other biological materials, such as alginate, chitosan and hyaluronic acid[19-25]. Many different composites of these materials have been explored and it has been shown that some of them may be an interesting option in terms of cell attachment and cell proliferation. However, the mechanical insufficiency of these biological materials remains a considerable problem for their routine practical use in ligament regeneration. To overcome the mechanical weakness, Panas-Perez *et al*[26] developed a collagen-silk composite and concluded that a scaffold with > 25% silk provides sufficient mechanical support very close to the properties of the native ACL.

The use of silk in ligament scaffolds is not restricted to combinations with other biomaterials. In various studies, its functionality in diverse tissue engineering approaches, especially in the musculoskeletal field, has been proven. The properties that make silk an attractive candidate as biomaterial are its remarkable strength and toughness compared to other natural as well as synthetic biomaterials[27-34]. The majority of studies dealing with silk as raw material for scaffold production use fibers from cocoons of the mulberry silkworm *Bombyx mori*. Due to biocompatibility issues, silkworm silk requires removal of the surface protein layer sericin, which can elicit adverse immune responses[35,36]. Once sericin is removed, the remaining silk fibroin fibers are non-immunogenic, biocompatible and capable of promoting cell adhesion, growth and, in the case of progenitor cells such as mesenchymal stromal cells (MSCs), differentiation. The classical way to remove this protein layer is to boil raw silk fibers in alkaline solutions such as sodium carbonate. Recently, Teuschl *et al*[36] successfully removed sericin from a compact and highly-ordered raw *Bombyx mori* silk fiber scaffold using borate buffer based solutions. The possibility of removing sericin after the textile engineering process eases the production of complex 3D structures in TE applications because the gliding properties of the silk fiber due to the gum-like sericin assist during textile engineering steps (*e.g.*, braiding and weaving). The pioneers in using silk fibers as raw material for ACL scaffolds are Altman and Kaplan, who demonstrated that the mechanical properties of their twisted fiber scaffolds match that of the native human ACL[37]. Moreover, Horan *et al*[38] demonstrated the processability of silk fibers with a huge number of different textile engineering techniques, enabling the generation of complex hierarchical structures with defined properties. Another characteristic that makes silk an attractive candidate for ACL tissue engineering is its slow rate of biodegradation (proteolytic degradation). Thus, ACL scaffolds made out of silk fibroin can provide the primary stability over an extended period of time, allowing ingrowing cells to rebuild neoligamentous tissue without exposing the knee joint to periods of instability. Moreover, the gradual transfer of stabilizing properties from the silk scaffold to the new forming tissue should allow a neotissue formation similar to the initial native tissue regarding collagen alignment, vascularization, *etc*.

In the literature, silk-based ligament grafts have been tested in animal models in only a few studies[26,39-41]. Historically, former ACL studies with synthetic materials have shown that the extrapolation of findings from animal data to humans needs large animal studies, like goat, sheep or pig models. To the best of our knowledge, only two studies have already tested silk-based ACL grafts in large animal studies with encouraging results[42,43]. In a pig model, Fan *et al*[43] demonstrated that their woven silk ligament scaffold in conjunction with seeded MSCs supported ligament regeneration after the 24 wk post implantation period. In conclusion, these very promising *in vivo* studies suggest that ACL scaffolds fabricated from silk fibroin have great potential for the translation into clinical applications. Moreover, clinical trials of silk-based ACL grafts proving functionality and safety in human knees have already been documented[44].

Apart from biological materials, synthetic biodegradable polymers have been introduced in ligament tissue engineering. Petrigliano *et al*[45] mentioned the advantages of synthetic polymers as proper selection and different manufacturing techniques allow for exact adaptation of the mechanical properties, cellular response and degradation rate[45]. Lin *et al*[46] used a scaffold composed of polyglycolic acid coated with polycaprolactone. Buma *et al*[47] worked with a braided polydioxanone scaffold in an *in vivo* animal study but reported an early loss of mechanical properties. Lu *et al*[48] compared different synthetic braided materials and concluded that poly L-lactic acid (PLLA) scaffolds had the best results in terms of mechanical properties as well as fibroblast proliferation. Laurencin *et al*[49] also developed a PLLA scaffold in a 3 dimensional braided fashion with distinct regions for the bony portions and the intra-articular portion of the construct. The same group consequently compared a different PLLA scaffold with different manufacturing techniques and demonstrated that a braid-twist scaffold had the most favorable viscoelastic properties[50,51]. In another study, a polyethylene glycol hydrogel was added to the PLLA scaffold which resulted in even better viscoelastic performance of the construct, but on the other hand, this also led to a decreased pore size of the scaffold which may negatively influence cell proliferation[52].

More recently, electrospinning has been used for the development of scaffolds for ligament tissue engineering[53]. This technique can be used to produce very thin fibers in the nanometer to micron range. This allows for a more exact adaptation of the mechanical properties. Some of the studies using this technique reported better cell proliferation and extracellular matrix production[53,54]. However, these techniques are under constant investigation and while early *in vitro* studies show interesting results, the overall biological and mechanical performance still has to be examined further to draw any conclusions for a later clinical use of these materials.

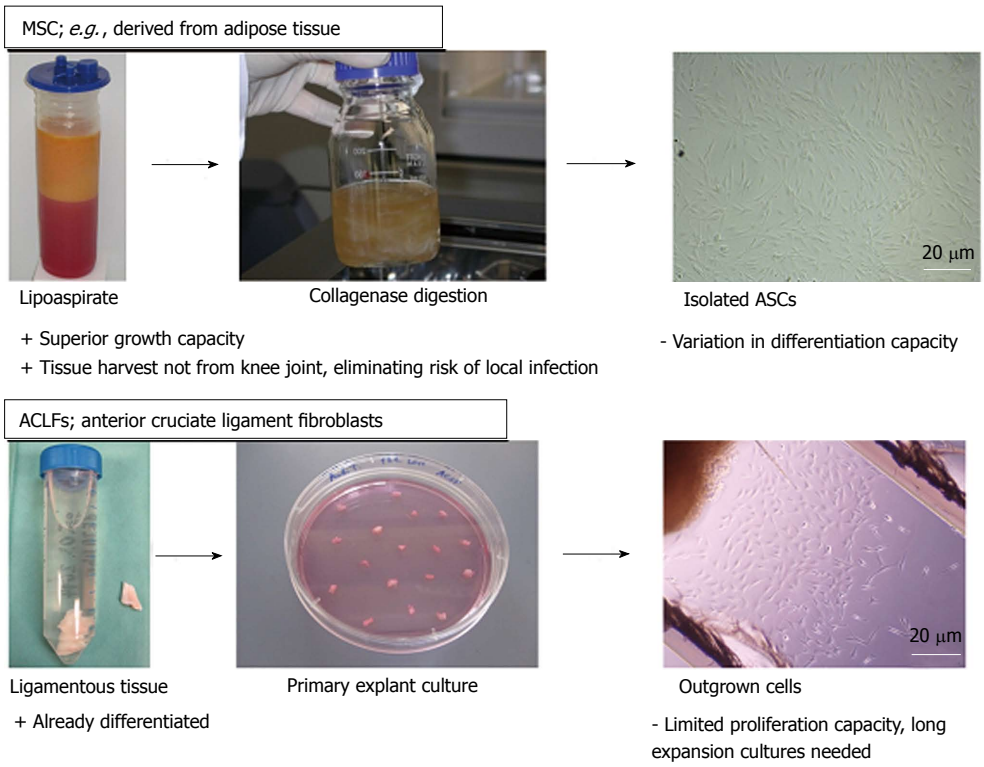

Figure 2 Overview of the main cell types used for anterior cruciate ligament tissue engineering approaches. Two different types of cells are mainly regarded as the primary choice for anterior cruciate ligament (ACL) regeneration: mesenchymal stem cells (MSC) and ACL fibroblasts. Since MSCs can be isolated from adipose tissue (in our studies in cooperation with the Red Cross Blood Transfusion Service of Upper Austria, Linz, Austria) or bone aspirates, their harvest is less delicate than cells isolated from ligamentous tissue. Further advantages of MSCs over ACL fibroblasts are their superior growth capacity and capability of differentiating into the appropriate cell types. Nevertheless, due to their origin, ACL fibroblasts would be the accurate cell type to build up neoligamentous tissue. ASCs: Adipose derived stem cells.

CELL SOURCES FOR ACL REGENERATION

Two different types of cells are mainly regarded as the primary choice for ACL regeneration: mesenchymal stem cells (MSC) and ACL fibroblasts[55].

MSCs are present in almost all tissue types of the body[56,57]. However, for cell therapeutic purposes, bone marrow and adipose tissue are regarded as the main feasible sources to isolate MSCs[58,59]. The potential of MSCs to differentiate into various mesenchymal lineages, including fibroblastic, osteogenic, chondrogenic and myogenic, was proven in numerous studies. Furthermore, MSCs have already been effectively applied to enhance repair in different musculoskeletal tissues, in particular in bone and ligaments (Figure 2)[40,60-62].

The use of ACL fibroblasts involves the risk of local infection in the knee during biopsy harvesting. From the view that the seeded cells should rebuild the ligament tissue by deposition of extracellular matrix, the appropriate cell type would be ACL fibroblasts since they are the native cell type in intact ligament tissue. Therefore, they are used as control cells for cell behavior such as protein expression, especially in *in vitro* studies. Interestingly, different studies have demonstrated that the ACL tissue contains populations of cells sharing MSC characteristics, such as clusters of differentiation markers or multipotency[63,64]. Although stem cells are present in the ACL tissue, their regenerative capacity is too restricted to be capable of healing ruptured ligaments. As ACL tissue can only be harvested reasonably in diagnostic arthroscopic procedures after ACL rupture, other ligament fibroblast sources have been discussed, such as the medial collateral ligament[65]. Nevertheless, the majority of studies involving cell therapy approaches in ACL tissue engineering uses mesenchymal stromal cells as a cell source since they can be obtained much more easily in higher numbers and, moreover, MSCs show higher proliferation and collagen productions rates compared to ligament fibroblasts[66,67].

From a cellular view, the knee joint comprises different sources of cells[68] (ligament tissue, synovium, *etc.*) that have been shown to participate during the ligament regeneration process, such as the above described ACL fibroblasts or MSCs that are natively recruited after ligament ruptures or tears. The activation and recruitment of regenerating cells can be augmented mechanically, for instance by the surgical procedure (*e.g.*, drilling of bone holes for the graft which gives access to the vasculature of bone tissue) or biochemically, by the use of growth factors or gene-based therapeutic approaches.

GENE-BASED THERAPEUTIC APPROACHES AND GROWTH FACTORS

Growth factors can either be directly applied *via* inserted cells (producing these biochemical signal molecules *in*

situ), *via* local delivery of growth factors or *via* gene-based therapeutic approaches where vehicles are encoding the chosen growth factor.

The most frequently used factors belong to proteins that directly affect the deposition of extracellular matrix proteins, such as the bone morphogenetic proteins (BMPs) or the degradation of ECM components assisting in remodeling impaired tissue. BMPs belong to the TGF-β superfamily. Their most prominent characteristic is to induce the differentiation of MSCs into the chondrogenic and osteogenic lineage. A special class of the BMPs, the growth and differentiation factors (GDF) 5/6 and 7, has been shown to be able to ectopically induce neotendon/ligament formation *in vivo*[69]. Furthermore, Aspenberg *et al*[70] (1999) demonstrated the enhanced regenerative effect of GDF 5 and 6 in an Achilles tendon rat model[70]. Interestingly, from a mechanistic point of view, the effects of GDFs depend on the mechanical loading of the injection site. Forslund *et al*[71] (2002) showed that the injection of GDF 6 in unloaded Achilles tendon defects led to the induction of bone formation[71], which in contrast was not observable in control groups of loaded tendons. This clearly indicates the interaction of the effect of growth factors and mechanical stimulation.

Other factors that have also been used to enhance the repair of tendon/ligament structures but are not directly associated with ECM turnover are insulin-like growth factor 1 (IGF1)[72,73], vascular endothelial growth factor (VEGF)[74], epidermal growth factor (EGF)[75] and platelet derived growth factor (PDGF)[76-79]. For instance, VEGF is well known to be a powerful stimulator of angiogenesis and the main function of IGF1 is mainly attributed to an anti-inflammatory effect[80] since functional analysis revealed a decreased recovery time but no biomechanical improvement in an Achilles tendon injury model.

An autologous and already clinically applied approach to augment tendon and ligament healing with growth factors is the use of platelet-rich plasma (PRP). PRP is obtained by plasma separation and constituents of platelets, blood proteins such as fibrin and a mixture of diverse growth factors (PDGF, VEGF, TGF-β, IGF, *etc*.) involved in general healing processes. Beside its autologous nature, another advantage generally attributed to PRP is its combination of growth factors in native proportions[81,82]. This feature of PRP is noteworthy as various studies have proven the synergistic effects of different growth factor combinations. Although beneficial effects of PRP have been demonstrated in cell culture studies as well as in *in vivo* models on tendon/ligament regeneration, the effectiveness of PRP in clinical use is still debated due to varying outcomes[81,83-87]. In a review by Yuan *et al*[87], these variances were mainly attributed to non-optimized treatment protocols.

Another strategy to trigger the healing capacity is to deliver therapeutic genes, either *in vivo* with vehicles or *ex vivo* in cells which are subsequently implanted. Wei *et al*[74] demonstrated that autologous graft remodeling in an ACL rabbit model can be enhanced by local administration of *TGFβ-1/VEGF165* gene-transduced bone MSCs, leading to superior mechanical properties compared to solely *TGFβ-1* gene transduced cells. In another very promising study by Hoffmann *et al*[88], MSCs were genetically modified to coexpress Smad8 and BMP2. These genetically modified MSCs enhanced the regeneration of the Achilles tendon in a mouse model. Taken together, the co-expression of growth factors is more efficient and potent than single gene therapeutic approaches.

MECHANICAL STIMULATION IN ACL REGENERATION

Mechanical stimuli and dynamic loading are necessary for ligaments to maintain their strength. In a number of studies, Woo *et al*[89] demonstrated that immobilization leads to weakened mechanical properties of ligaments[89-91]. From a mechanistic point of view, it is known that cells react to mechanical stimuli *via* integrin-mediated focal adhesions and cytoskeleton deformation[92-94]. Altman *et al*[95,96] demonstrated that mechanical stimuli are able to influence stem cell differentiation as well as the production of extracellular matrix (ECM). Mechanical strain resulted in the differentiation of MSCs into fibroblast-like cells, as seen by the upregulation of ligament markers tenascin-C, collagen types I and Ⅲ, and the formation of collagen fibers[95,97]. Petrigliano *et al*[98] showed that uniaxial cyclic strain of a three-dimensional polymer scaffold seeded with MSCs resulted in upregulated tenascin-C, collagen type I and Ⅲ. Berry *et al*[99] reported on the proliferative effect of uniaxial strain on young fibroblasts. Park *et al*[100] demonstrated that 8% cyclical strain in ligament fibroblasts leads to higher cell proliferation and collagen production compared to a 4% strain and unloaded controls. In their review, Leong *et al*[11] mentioned that despite the known fact that mechanical stimuli play an important role in ligament tissue engineering, the timing, direction and magnitude of the stimuli as well as the cell type can all be of significant influence on the cellular response. As an example, they discussed a study by Moreau *et al*[101] in which MSCs were stimulated immediately after seeding and showed an inhibited expression of collagen I and Ⅱ. In contrast, the opposite effect was observed when the mechanical loading was applied at the peak of MSC proliferation. Leong *et al*[11] mentioned that in case of ACL tissue engineering, additional investigation is required to elucidate the mechanotransduction pathways that are necessary for tissue formation and maintenance. They also stated that, to date, it is not known if any mechanical stimulation is required prior to implantation of tissue engineered ACL constructs.

FUTURE DIRECTIONS IN ACL REGENERATION

In a recent questionnaire study by Rathbone *et al*[102], 300 orthopedic surgeons were asked if they would consider a tissue engineered ACL if it were an available option.

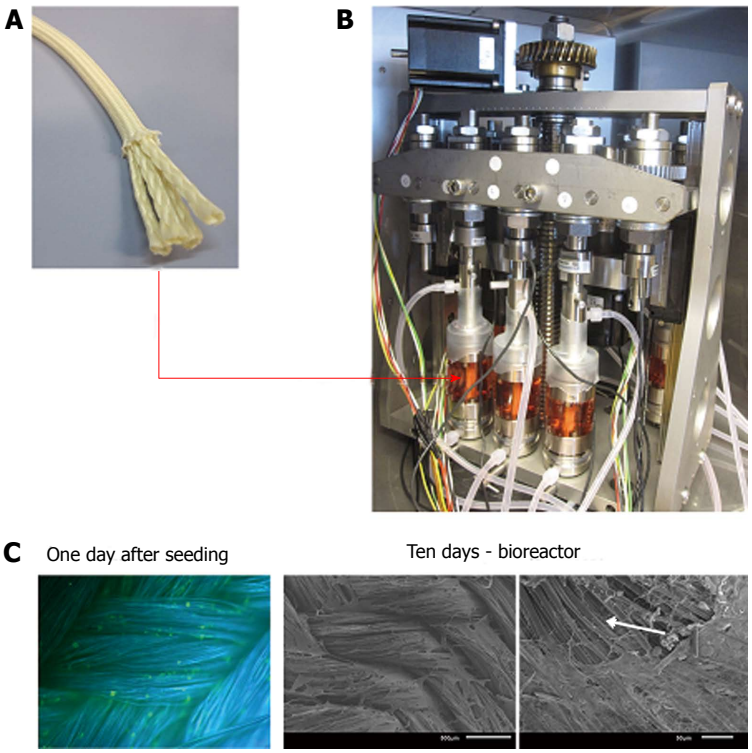

Figure 3 Adipose-derived stem cells cultured on silk-based ligament grafts (A) produce sheets of extracellular matrix proteins (C) under mechanical stimulation *via* a custom-made bioreactor system (B: design and construction in cooperation with the Technical University of Vienna, Institute of Materials Science and Technology). A: The silk-based anterior cruciate ligament (ACL) scaffold is produced of *Bombyx mori* silk fibers in a wire-rope design; B: The scaffold is seeded with ASCs for 24 h and then transferred into bioreactor and cultured under linear and rotational displacement for 10 d. The mechanically stimulated ACL scaffolds show sheets of extracellular matrix. The arrow in the bottom panel indicates an artefact of scanning electron microscopy preparation. In this area, the covering extracellular matrix sheet has been flushed away due to too intense flushing, allowing the view to the underlying silk fibers.

Eight-six percent answered positively if the construct demonstrates biological and mechanical success. For 63%, improved patient satisfaction was important and 76% of the participants mentioned that a tissue engineered ACL would be superior to any of the currently used autograft materials. It was also clearly stated that a fully load-bearing construct for implantation is needed and that several ACL tissue engineering strategies should address this need for mechanical integrity. This seems to be of crucial importance as the presently used ACL reconstruction techniques with autograft or allograft material provide an immediate load bearing environment. It seems obvious that, until the results of any regenerated ACL can compare with the current relatively successful autograft methods, patients are likely to prefer the autograft. As most surgeons do not require immobilization after reconstructive surgery, immobilization is likely to be unacceptable.

Another important aspect that will need consideration is the timing of the tissue engineering process and consequent implantation. In recent studies, our group focused on the mechanical stimulation of silk grafts with a custom-made bioreactor system[103] in order to increase the maturity of cell-loaded grafts prior to implantation (Figure 3). In accordance with a study by Altman *et al*[95], we triggered MSCs to produce layers of ECM on silk-based grafts. Our hypothesis is that the applied mechanical stimulation triggers the MSCs into ligamentous cells which in conjunction with the cells' own secreted ECM leads to more functionality of the cell/scaffold construct and therefore will superiorly fulfil its tasks once it is implanted.

Future studies using a combination of *in vitro* bioreactor engineering with consequent *in vivo* implantation are certainly needed to get a clearer picture of this complex topic. On the other hand, engineering mechanically appropriate scaffolds that are implantable at any time also seems to be a good option. Future research efforts may also demonstrate which cell type seeded on these scaffolds is the ideal candidate for direct *in vivo* implantation in this case. Furthermore, there is also some interest in exploring the regenerative potential of solely implanted scaffolds that would recruit *in vivo* cells, provided there is the appropriate mechanical and physiological environment. Just recently, Murray *et al*[104] proposed the strategy of repair and regeneration. Here, tissue engineering efforts are undertaken to overcome the obstacles to native ACL healing. This group proposed a bio-enhanced ACL repair technique that uses a collagen scaffold saturated with platelet-rich plasma. In a number of animal studies, they demonstrated improved mechanical and biological healing of the ACL[84,105-107]. In a recent randomized large animal trial, bio-enhanced ACL repair had equal results compared with ACL reconstruction. It was also shown that the knees treated with enhanced ACL repair had a lower rate of osteoarthritis in contrast to those treated with ACL reconstruction which developed osteoarthritis in 80% after one year[108]. Despite these interesting findings, it may be problematic to draw direct conclusions as osteoarthritis is not common a year after ACL injury in humans.

CONCLUSION

There is a growing research interest in the tissue engineering of the ACL and the clinical need seems obvious. Different strategies from *in vitro* engineering of ACL grafts to bio-enhanced repair and regeneration are followed. For the

surgical community, any type of engineered ACL may be a future option provided that it is easy to implant, does allow for at least the same aggressive rehabilitation protocol as currently used and will lead to better patient satisfaction and outcome.

ACKNOWLEDGMENTS

The authors want to thank Johannes Zipperle for his outstanding artwork.

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P- Reviewer: Finestone AS, Pappas E, Zheng N
S- Editor: Ji FF **L- Editor**: Roemmele A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.137

World J Orthop 2015 January 18; 6(1): 137-144
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Retrospective Study

Overweight and obesity in hip and knee arthroplasty: Evaluation of 6078 cases

Daniel Guenther, Stefan Schmidl, Till O Klatte, Harald K Widhalm, Mohamed Omar, Christian Krettek, Thorsten Gehrke, Daniel Kendoff, Carl Haasper

Daniel Guenther, Stefan Schmidl, Till O Klatte, Thorsten Gehrke, Daniel Kendoff, Carl Haasper, Orthopaedic Department, Helios-Endo Klinik Hamburg, Hamburg 22767, Germany
Daniel Guenther, Mohamed Omar, Christian Krettek, Trauma Department, Hannover Medical School (MHH), Hannover 30625, Germany
Till O Klatte, Department of Trauma, Hand, and Reconstructive Surgery, University Medical Center Hamburg-Eppendorf, Hamburg 20246, Germany
Harald K Widhalm, Department of Trauma Surgery, Medical University of Vienna, Waehringer Guertel 18-20, Vienna 1090, Austria
Author contributions: Guenther D, Krettek C and Haasper C designed the research; Guenther D, Schmidl S, Klatte TO, Widhalm HK and Omar M performed the research; Guenther D, Schmidl S, Klatte TO and Kendoff D analyzed the data; Guenther D, Haasper C and Gehrke T wrote the paper.

Correspondence to: Daniel Guenther, MD, Orthopaedic Department, Helios-Endo Klinik Hamburg, Holstenstr. 2, Hamburg 22767, Germany. guenther.daniel@mh-hannover.de
Telephone: +49-511-5322026
Fax: +49-511-5325877
Received: April 20, 2014
Peer-review started: April 20, 2014
First decision: June 6, 2014
Revised: July 9, 2014
Accepted: August 27, 2014
Article in press: August 31, 2014
Published online: January 18, 2015

Abstract

AIM: To evaluate a possible association between the various levels of obesity and peri-operative characteristics of the procedure in patients who underwent endoprosthetic joint replacement in hip and knee joints.

METHODS: We hypothesized that obese patients were treated for later stage of osteoarthritis, that more conservative implants were used, and the intra- and perioperative complications increased for such patients. We evaluated all patients with body mass index (BMI) $\geqslant$ 25 who were treated in our institution from January 2011 to September 2013 for a primary total hip arthroplasty (THA) or total knee arthroplasty (TKA). Patients were split up by the levels of obesity according to the classification of the World Health Organization. Average age at the time of primary arthroplasty, preoperative Harris Hip Score (HHS), Hospital for Special Surgery score (HSS), gender, type of implanted prosthesis, and intra-and postoperative complications were evaluated.

RESULTS: Six thousand and seventy-eight patients with a BMI $\geqslant$ 25 were treated with a primary THA or TKA. Age decreased significantly ($P < 0.001$) by increasing obesity in both the THA and TKA. HHS and HSS were at significantly lower levels at the time of treatment in the super-obese population ($P < 0.001$). Distribution patterns of the type of endoprostheses used changed with an increasing BMI. Peri- and postoperative complications were similar in form and quantity to those of the normal population.

CONCLUSION: Higher BMI leads to endoprosthetic treatment in younger age, which is carried out at significantly lower levels of preoperative joint function.

Key words: Adiposity; Total knee arthroplasty; Total hip arthroplasty; Obesity; Overweight; Prosthesis

Core tip: Our study demonstrates that total hip arthroplasty and total knee arthroplasty can be performed in all stages of obesity with low perioperative risk. We have to mention that good preparation is indispensable. Co-morbities should be assessed and the set-up should be related to high weight. Sometimes special operation-tables, beds, and crutches are required. Higher body mass index leads to endoprosthetic treatment in younger age, which is carried out at significantly lower levels of preoperative joint function.

Guenther D, Schmidl S, Klatte TO, Widhalm HK, Omar M, Krettek C, Gehrke T, Kendoff D, Haasper C. Overweight and obesity in hip and knee arthroplasty: Evaluation of 6078 cases. *World J Orthop* 2015; 6(1): 137-144 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/137.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.137

INTRODUCTION

The prevalence of overweight patients is steadily increasing in the general population. 67.1 % of men and 53.0% of women in our country have a body mass index (BMI) ⩾ 25 kg/m^2. 23.3% of men and 23.9% of women have a BMI ⩾ 30 kg/m^2[1]. The data of the world's population are similar to this[2]. As defined by BMI, 1 of every 3 Americans is overweight[3]. It is known that obesity has a negative influence on the formation of osteoarthritis[4]. An increased BMI leads to an increased risk of needing a joint replacement. Waist circumference and waist-to-hip ratio were less strongly associated with this risk[5]. Several studies have examined the influence of obesity on the need for endoprosthetic joint replacement[6,7]. However, to our knowledge, there is no study that evaluated the influence of the respective stage of obesity in a monocentric setting with large number of cases. If a decision for an endoprosthetic joint replacement was made, the kind of implant for artificial hip and knee arthroplasty is up to the individual surgeon.

Obese patients with severe osteoarthritis, axis deviation, and ligamentous instability are a major challenge for the surgeon[8]. These patients often lack the ability of postoperative partial weight bearing. There is no study in modern literature that deals with the influence of obesity on the choice of the individual implant.

There are studies showing that obesity is associated with an increased risk of infection and impaired wound healing[9]. However, a large number of morbidly obese people seem to consider that the benefits outweigh the risks[10].

The aim of this study was to evaluate if there is an association between the various levels of obesity and peri-operative characteristics of the procedure in patients who underwent total hip arthroplasty (THA) and total knee arthroplasty (TKA). Furthermore, it should be issued if an increasing BMI has an influence on the choice of the implant by the individual surgeon and whether the intra- and perioperative complications are increased or not. We hypothesized that obese patients were treated with later stage of OA and more advanced stage implants like cemented THA and constrained TKA.

MATERIALS AND METHODS

We evaluated all patients with a BMI ⩾ 25 kg/m^2 who were treated in the period from January 2011 to September 2013 in our institution for a primary THA or TKA. These patients were split up by stages of obesity according to the classification of the World Health Organization[2]. Data from the hospitals database were analyzed.

We evaluated the average age at time of primary arthroplasty. Furthermore data collection included the preoperative Harris Hip Score (HHS) for total hip arthroplasty[11], the Hospital for Special Surgery Score (HSS) for total knee arthroplasty[12], the gender, the type of implanted prosthesis, the comorbidities and the intra-and postoperative complications. The study was conducted according to the guidelines of the local ethics committee. Informed consent for this retrospective study was obtained from every single patient.

The data were processed with the statistical software package SPSS (version 20.0, SPSS Inc., Chicago, United States). Interference statistical analyses were performed for two independent samples using the Mann-Whitney *U* test. The Kruskall-Wallis test was used to check several independent samples. Multivariate analysis was performed to evaluate whether there is an independent association between the level of obesity, BMI, functional status (HHS/HSS), gender and age at THA/TKA. Logistic regression was performed to evaluate the association between BMI, gender, functional status and the used prosthesis type.

A power analysis was performed based on previously reported values of HHS and HSS following THA and TKA. It was determined that the available sample size was sufficient to detect a ten point difference in the scores between the groups with $\alpha = 0.05$ and a power of 0.95.

RESULTS

In the period from January 2011 to September 2013, 9742 primary hip or knee arthroplasties were performed in our institution. Six thousand and seventy-eight patients with a BMI ⩾ 25 kg/m^2 were treated with a primary hip or knee arthroplasty (62.4 % of total number of primary THA and TKA).

Table 1 presents the distribution of patients to the different stages of overweight and obesity. The dissemination of comorbidities was comparable between the different stages (Table 2). The age in which an endoprosthetic treatment was necessary decreased significantly ($P < 0.001$) by increasing overweight and obesity in both the hip and knee arthroplasty. In the higher stages of obesity, both HHS and HSS were at significantly lower levels at the

Table 1 Distribution of patients to the different degrees of overweight and obesity

BMI (kg/m^2)	25-29.9 total	(Overweight) percent	30-34.9 total	(Stage Ⅰ) percent	35-39.9 total	(Stage Ⅱ) percent	⩾ 40 total	(Stage Ⅲ) percent	Total amount
THA	1920	60.5%	899	28.3%	285	9.0%	70	2.2%	3174
TKA	1394	48.0%	961	33.1%	432	14.9%	117	4.0%	2904
THA and TKA	3314	54.5%	1860	30.6%	717	11.8%	187	3.1%	6078

THA: Total hip arthroplasty; TKA: Total knee arthroplasty; BMI: Body mass index.

Table 2 Comorbidities in total hip arthroplasty and total knee arthroplasty

BMI (kg/m^2)	25-29.9 total	(Overweight) percent	30-34.9 total	(Stage Ⅰ) percent	35-39.9 total	(Stage Ⅱ) percent	⩾ 40 total	(Stage Ⅲ) percent
Anemia	498	15.00%	273	14.70%	106	14.80%	27	14.40%
Cancer diseases	9	0.30%	6	0.30%	3	0.40%	1	0.50%
Congestive heart failure	86	2.60%	48	2.60%	19	2.60%	5	2.70%
Chronic pulmonary disease	629	19.00%	353	19.00%	136	19.00%	36	19.30%
Coagulopathy	23	0.70%	13	0.70%	5	0.70%	1	0.50%
Depression	497	15.00%	279	15.00%	108	15.10%	28	15.00%
Diabetes	1100	33.20%	616	33.10%	238	33.20%	67	35.80%
Fluid and electrolyte disorder	230	6.90%	130	7.00%	50	7.00%	15	8.00%
Gastro esophageal reflux disease	63	1.90%	35	1.90%	14	2.00%	6	3.20%
Hypertension	2550	76.90%	1431	76.90%	553	77.10%	148	79.10%
Hypothyroidism	497	15.00%	279	15.00%	108	15.10%	30	16.00%
Liver disease	13	0.40%	10	0.50%	4	0.60%	1	0.50%
Obstructive sleep apnea	695	21.00%	409	22.00%	150	20.90%	44	23.50%
Paralysis	3	0.10%	2	0.10%	1	0.10%	0	0.00%
Peripheral vascular disease	30	0.90%	17	0.90%	6	0.80%	2	1.10%
Psychoses	46	1.40%	26	1.40%	10	1.40%	2	1.10%
Pulmonary circulation disorders	20	0.60%	11	0.60%	4	0.60%	1	0.50%
Renal failure	73	2.20%	39	2.10%	16	2.20%	4	2.10%
Rheumatoid arthritis/collagen vascular disease	93	2.80%	54	2.90%	20	2.80%	5	2.70%
Valvular heart disease	80	2.40%	45	2.40%	17	2.40%	6	3.20%

BMI: Body mass index.

time of prosthetic treatment compared to overweight or obese stage I patients ($P < 0.001$) (Tables 3 and 4).

A correlation between anthropometric data (gender, BMI, stages of overweight/obesity) and functional scores (HHS/HSS) could be shown with the strongest negative correlation between BMI and functional scores in TKA as well as in THA. A correlation between anthropometric data and age of arthroplasty could be shown with the strongest negative correlation between BMI and age of arthroplasty in TKA and HHS and age of arthroplasty in THA (Tables 5 and 6).

In all stages of obesity, the surgeons used a similar distribution pattern of the different types of hip prostheses. In the super-obese population, more cementless alternatives were used instead of fully cemented or hybrid prostheses (Tables 7 and 8).

In the knee replacement surgery, the surgeons used a similar distribution pattern of implants in the overweight and obese stage I patients. With increasing BMI more bicondylar surface replacements and less hinge prostheses or constrained condylar knees (long stem) were used. The use of unicondylar knee replacement declined with increasing BMI (Tables 9 and 10).

The peri-and postoperative complications were similar in form and quantity to those of the normal population (Tables 11 and 12).

DISCUSSION

Our study shows that the time of primary implantation of a total hip or total knee arthroplasty is significantly influenced by the stage of obesity. In our study, patients who have had a higher BMI needed endoprosthetic joint replacement at a younger age. It is noticeable that the primary implantation was carried out at significantly lower function scores (HHS, HSS) with increasing BMI. This suggests that super-obese patients were treated much more cautiously than overweight or normal weight patients. In higher stages of obesity, more cementless total hip arthroplasties were carried out than fully cemented or hybrid alternatives. An explanation for that could be the shorter time of surgery for cementless arthroplasty. This can sometimes become necessary in this high-risk population such as multimorbid patients. Obesity is associated with multiple comorbidities such as type Ⅱ diabetes and cardiovascular disease[13].

It is known that obese patients have a high risk of formation of osteoarthritis. Due to the high weight-

Table 3 Pre-total hip arthroplasty comparison of the different study groups

BMI (kg/m^2)	25-29.9 (Overweight)	30-34.9 (Stage Ⅰ)	35-39.9 (Stage Ⅱ)	≥ 40 (Stage Ⅲ)	*P* value
Gender (percent male)	961/959 (50.0%)	445/454 (49.5%)	121/164 (42.5%)	34/36 (48.6%)	
Age at the time of Arthroplasty (years)	65.8 ± 11.0	63.7 ± 11.0	62.6 ± 10.6	58.9 ± 10.2	< 0.001
Harris Hip Score	47.1 ± 12.5	44.8 ± 12.4	42.2 ± 13.1	37.7 ± 12.2	< 0.001
Weight (kilograms)	80.7 ± 9.8	94.4 ± 11.5	107.8 ± 12.8	125.9 ± 18.2	< 0.001

BMI: Body mass index.

Table 4 Pre-total knee arthroplasty comparison of the different study groups

BMI (kg/m^2)	25-29.9 (overweight)	30-34.9 (Stage Ⅰ)	35-39.9 (Stage Ⅱ)	≥ 40 (Stage Ⅲ)	*P* value
Gender (percent male)	596/798 (42.7%)	368/593 (38.3%)	116/316 (26.8%)	33/84 (28.2%)	
Age at the time of Arthroplasty (yr)	68.2 ± 9.7	65.9 ± 9.3	64.2 ± 9.2	62.8 ± 7.0	< 0.001
Hospital for Special Surgery Score	55.7 ± 13.1	54.2 ± 13.3	50.6 ± 12.9	49.3 ± 13.8	< 0.001
Weight (kg)	79.9 ± 9.9	92.9 ± 11.5	103.7 ± 13.3	119.6 ± 16.5	< 0.001

BMI: Body mass index.

Table 5 Relationships between age at total hip arthroplasty, Harris Hip Score, body mass index, stages of overweight/obesity and gender

	Age at THA Regression coefficient	*P* value	HHS Regression Coefficient	*P* value
BMI	-0.178 (-0.226 to -0.13)	< 0.001	-0.201 (-0.256 to -0.146)	< 0.001
HHS	-0.217 (-0.232 to -0.202)	< 0.001		
Gender	0.112 (-0.268 to 0.492)	< 0.001	-0.099 (-0.537 to 0.339)	< 0.001
Overweight	0.139 (-0.251 to 0.529)	< 0.001	0.148 (-0.301 to 0.597)	< 0.001
Stage Ⅰ	-0.098 (-0.529 to 0.333)	< 0.001	-0.099 (-0.594 to 0.396)	< 0.001
Stage Ⅱ	-0.110 (-0.786 to 0.566)	< 0.001	-0.125 (-0.901 to 0.651)	< 0.001
Stage Ⅲ	-0.116 (-1.427 to 1.195)	< 0.001	-0.127 (-1.631 to 1.377)	< 0.001
Age at THA			-0.215 (-0.415 to -0.195)	< 0.001

BMI: Body mass index; THA: Total hip arthroplasty; HHS: Harris Hip Score.

Table 6 Relationships between age at total knee arthroplasty, Harris Hip Score, body mass index, stages of overweight/obesity and gender

	Age at TKA Regression coefficient	*P* value	HSS Regression coefficient	*P* value
BMI	-0.224 (-0.263 to 0.185)	< 0.001	-0.152 (-0.208 to 0.096)	< 0.001
HSS	-0.118 (-0.132 to -0.104)	< 0.001		
Gender	0.076 (-0.294 to 0.446)	< 0.001	-0.128 (-0.641 to 0.385)	< 0.001
Overweight	0.184 (-0.175 to 0.543)	< 0.001	0.115 (-0.39 to 0.62)	< 0.001
Stage Ⅰ	-0.129 (-0.529 to 0.271)	< 0.001	-0.063 (-0.623 to 0.497)	< 0.001
Stage Ⅱ	-0.181 (-0.715 to 0.353)	< 0.001	-0.138 (-0.885 to 0.609)	< 0.001
Stage Ⅲ	-0.130 (-1.051 to 0.791)	< 0.001	-0.100 (-1.386 to 1.186)	< 0.001
Age at TKA			-0.118 (-0.144 to 0.092)	< 0.001

BMI: Body mass index; TKA: Total knee arthroplasty; HHS: Harris Hip Score.

Table 7 Distribution pattern of implanted total hip arthroplasty

BMI (kg/m^2)	25-29.9 total	(Overweight) %	30-34.9 total	(Stage Ⅰ) %	35-39.9 total	(Stage Ⅱ) %	≥ 40 total	(Stage Ⅲ) %
Cementless short stem	535	27.9	253	28.10	76	26.7	20	28.6
Cementless standard stem	585	30.5	297	33.00	109	38.2	27	38.6
Hybrid (cemented/cementless)	43	2.2	22	2.40	8	2.8	3	4.3
Cemented THA	757	39.4	327	36.40	92	32.3	20	28.6
Total amount	1920		899		285		70	

THA: Total hip arthroplasty; BMI: Body mass index.

Table 8 Relationships between preferred prosthesis type, age at total hip arthroplasty, Harris Hip Score, body mass index, stages of overweight/obesity and gender

	Cementless short stem (Reference)		Cementless standard stem (Reference)		Hybrid (cemented/cementless) (Reference)		Cemented THA (Reference)	
	Regression coefficient B	*P* value	Regression coefficient B	*P* value	Regression coefficient B	*P* value	Regression coefficient B	*P* value
Cementless short stem								
BMI			-0.003 (-0.015 to 0.009)	0.826	-0.025 (-0.054 to 0.004)	0.389	0.002 (-0.013 to 0.017)	0.898
Age at THA			0.007 (0.002 to 0.012)	0.132	-0.061 (-0.075 to -0.047)	< 0.001	-0.171 (-0.179 to -0.163)	< 0.001
Gender			0.609 (0.513 to 0.705)	< 0.001	0.989 (0.737 to 1.241)	< 0.001	1.134 (1.023 to 1.245)	< 0.001
HHS			0.019 (0.015 to 0.023)	< 0.001	0.043 (0.033 to 0.053)	< 0.001	0.042 (0.037 to 0.047)	< 0.001
Cementless standard stem								
BMI	0.003 (-0.117 to 0.015)	0.826			-0.023 (-0.052 to 0.006)	0.432	0.004 (-0.010 to 0.018)	0.746
Age at THA	-0.007 (-0.012 to -0.002)	0.132			-0.068 (-0.082 to -0.054)	< 0.001	-0.178 (-0.185 to -0.171)	< 0.001
Gender	-0.609 (-0.705 to -0.513)	< 0.001			0.380 (0.13 to 0.63)	0.128	0.525 (0.419 to 0.631)	< 0.001
HHS	-0.019 (-0.023 to -0.015)	< 0.001			0.024 (0.014 to 0.034)	< 0.05	0.023 (0.019 to 0.027)	< 0.001
Hybrid (cemented/cementless)								
BMI	0.025 (-0.004 to 0.054)	0.389	0.023 (-0.006 to 0.052)	0.432			0.027 (-0.002 to 0.056)	0.353
Age at THA	0.061 (0.047 to 0.075)	< 0.001	0.068 (0.054 to 0.082)	< 0.001			-0.110 (-0.125 to -0.095)	< 0.001
Gender	-0.989 (-1.241 to -0.737)	< 0.001	-0.380 (-0.63 to -0.13)	0.128			0.145 (-0.105 to 0.395)	0.561
HHS	-0.043 (-0.053 to -0.033)	< 0.001	-0.024 (-0.034 to -0.014)	< 0.05			-0.001 (-0.011 to 0.009)	0.926
Cemented THA								
BMI	-0.002 (-0.017 to 0.013)	0.898	-0.004 (-0.018 to 0.010)	0.746	-0.027 (-0.056 to 0.002)	0.353		
Age at THA	0.171 (0.163 to 0.179)	< 0.001	0.178 (0.171 to 0.185)	< 0.001	0.110 (0.095 to 0.125)	< 0.001		
Gender	-1.134 (-1.245 to -1.023)	< 0.001	-0.525 (-0.631 to -0.419)	< 0.001	-0.145 (-0.395 to 0.105)	0.561		
HHS	-0.042 (-0.047 to -0.037)	< 0.001	-0.023 (-0.027 to -0.019)	< 0.001	0.001 (-0.009 to 0.011)	0.926		

TKA: Total knee arthroplasty; HHS: Harris Hip Score; BMI: Body mass index.

Table 9 Distribution pattern of implanted total knee arthroplasty

BMI (kg/m^2)	25-29.9 total	(Overweight) percent	30-34.9 total	(Stage Ⅰ) percent	35-39.9 total	(Stage Ⅱ) percent	⩾ 40 total	(Stage Ⅲ) percent
Bicondylar surface replacement	1246	89.40%	878	91.40%	403	93.30	116	99.10%
Long stem	60	4.30%	43	4.50%	22	5.00	1	0.90%
PFJ	10	0.70%	5	0.50%	3	0.70	0	0.00%
Unicondylar knee replacement	78	5.60%	35	3.60%	4	0.90	0	0.00%
Total amount	1394		961		432		117	

BMI: Body mass index.

related load on the skeleton, obese patients often have good bone quality. Yet in obese patients who have a lack of physical activity and sometimes hormonal disbalances, a poorer bone quality is frequently found. However, these patients often do not manifest complaints due to their low level of activity[14].

In the knee replacement surgery in stage Ⅲ obese patients, surgeons used almost no hinge prostheses or constrained condylar knees. Super-obese patients with a distribution pattern of pitfalls such as severe axis deviations and ligamentous instabilities are often preoperatively convinced to lose weight. Studies have shown that weight loss is effective for symptomatic relief in obese subjects with knee osteoarthritis independently of joint damage severity[15]. In this patient group, the risk of complications following joint replacement appears to be lower if bariatric surgery is performed first[16].

Isolated medial gonarthrosis seems to be much less common in this group of patients. Due to this fact, unicondylar knee replacements or osteotomies have not been performed at all in the super-obese population at our institution in this time period. Some studies mention that there is a significant increased risk for complications in the super-obese population[17,18]. Some authors determined that there is no increased risk in this population[19,20]. In our institution the peri-and postoperative complication rate was not increased significantly by increasing BMI. Sometimes total hip arthroplasties in obese patients were perceived by the surgeon to be significantly more difficult. However, in this cases neither increased risk of complications, operation time, or blood loss, nor suboptimal implant placements have been observed[21].

We have to mention that good preparation is indispensable. Co-morbities should be assessed and the set-up should be related to high weight. Sometimes special operation-tables, beds, and crutches are required. The long-time outcome after the duration of years will be interesting. Obese patients showed greater improvement according to functional outcome compared with non-morbidly obese patients. Morbid obesity does not affect 1-year outcomes in patients who have had a total knee arthroplasty[22]. TKA benefits were realized at all stages

Table 10 Relationships between preferred prosthesis type, age at total hip arthroplasty, Harris Hip Score, body mass index, stages of overweight/obesity and gender

	Bicondylar surface replacement (Reference)		Long stem (Reference)		PFJ (Reference)		Unicondylar knee replacement (Reference)	
	Regression coefficient B	*P* value	Regression coefficient B	*P* value	Regression coefficient B	*P* value	Regression coefficient B	*P* value
Bicondylar surface replacement								
BMI			0.023 (0.001 to 0.045)	0.299	0.085 (0.023 to 0.147)	0.172	0.133 (0.104 to 0.162)	< 0.001
Age at THA			-0.046 (-0.057 to -0.035)	< 0.001	0.158 (0.131 to 0.185)	< 0.001	0.043 (0.033 to 0.053)	< 0.001
Gender			-0.097 (-0.307 to 0.113)	0.642	0.447 (-0.06 to 0.954)	0.378	-0.277 (-0.477 to -0.077)	0.167
HSS			0.070 (0.063 to 0.077)	< 0.001	-0.056 (-0.077 to -0.035)	< 0.001	-0.047 (-0.056 to -0.038)	< 0.001
Long stem								
BMI	-0.023 (-0.045 to -0.001)	0.299			0.062 (-0.004 to 0.128)	0.348	0.110 (0.074 to 0.146)	< 0.05
Age at THA	0.046 (0.035 to 0.057)	< 0.001			0.204 (0.175 to 0.233)	< 0.001	0.089 (0.074 to 0.104)	< 0.001
Gender	0.097 (-0.113 to 0.307)	0.642			0.545 (-0.002 to 1.092)	0.320	-0.179 (-0.466 to 0.108)	0.532
HSS	-0.070 (-0.077 to -0.063)	< 0.001			-0.125 (-0.148 to -0.102)	< 0.001	-0.117 (-0.128 to -0.106)	< 0.001
PFJ								
BMI	-0.085 (-0.147 to -0.023)	0.172	-0.062 (-0.128 to 0.004)	0.348			0.049 (-0.019 to 0.117)	0.472
Age at THA	-0.158 (-0.185 to -0.131)	< 0.001	-0.204 (-0.233 to -0.175)	< 0.001			-0.115 (-0.143 to -0.087)	< 0.001
Gender	-0.447 (-0.954 to 0.06)	0.378	-0.545 (-1.092 to 0.002)	0.320			-0.724 (-0.1262 to -0.186)	0.178
HSS	0.056 (0.035 to 0.077)	< 0.001	0.125 (0.102 to 0.148)	< 0.001			0.008 (-0.015 to 0.031)	0.711
Unicondylar knee replacement								
BMI	-0.133 (-0.162 to -0.104)	< 0.001	-0.110 (-0.146 to -0.074)	< 0.05	-0.049 (-0.117 to 0.019)	0.472		
Age at THA	-0.043 (-0.053 to -0.033)	< 0.001	-0.089 (-0.104 to -0.074)	< 0.001	0.115 (0.087 to 0.143)	< 0.001		
Gender	0.277 (0.077 to 0.477)	0.167	0.179 (-0.108 to 0.466)	0.532	0.724 (0.186 to 1.262)	0.178		
HSS	0.047 (0.038 to 0.056)	< 0.001	0.117 (0.106 to 0.128)	< 0.001	-0.008 (-0.031 to 0.015)	0.711		

THA: Total hip arthroplasty; HHS: Harris Hip Score; BMI: Body mass index; PFJ: Patello-femoral joint.

Table 11 Surgical complications in total hip arthroplasty

BMI (kg/m^2)	25-29.9 total	(Overweight) percent	30-34.9 total	(Stage Ⅰ) percent	35-39.9 total	(Stage Ⅱ) percent	⩾ 40 total	(Stage Ⅲ) percent
Femoral fracture	8	0.2%	1	0.1%				
Femoral perforation	2	0.1%						
Trochanteric fracture	4	0.1%			2	0.3%		
Acetabular fracture					1	0.1%		
Acetabular perforation	11	0.3%	6	0.3%	3	0.4%	1	0.5%
Vascular leasion	1	0.0%						
Other complications	1	0.0%	2	0.1%				

BMI: Body mass index.

Table 12 Surgical complications in total knee arthroplasty

BMI (kg/m^2)	25-29.9 total	(Overweight) percent	30-34.9 total	(Stage Ⅰ) percent	35-39.9 total	(Stage Ⅱ) percent	⩾ 40 total	(Stage Ⅲ) percent
Femoral fracture			1	0.1%				
Femoral perforation	4	0.1%	2	0.1%	2	0.3%	1	0.5%
Condylar fracture	3	0.1%	1	0.1%				
Rupture of the patellar tendon					1	0.1%	1	0.5%
Vascular leasion	2	0.1%						
Nerval leasion	1	0.0%						
Wound healing disorders			1	0.1%				
Other complications	3	0.1%	4	0.2%	2	0.3%		

BMI: Body mass index.

of BMI, but at BMI ⩾ 40 kg/m^2, more rehabilitation and monitoring are recommended because of more patellar radiolucencies, poorer hamstring and quadriceps conditioning, and more patellofemoral symptoms[23].

There are limitations of this study. The multivariate analysis is limited by a limited availability of information on potential confounding factors and by a cross-sectional nature of the sample. Furthermore, there should be a long-time follow-up of our study population. The associated data should also be part of future publications.

We conclude that both the primary hip and knee arthroplasty can be performed in all stages of obesity with

a relatively low perioperative risk. A higher BMI leads to an endoprosthetic joint replacement at earlier times, which, however, is only carried out at significantly lower levels of joint function.

COMMENTS

Background

The prevalence of overweight patients is steadily increasing in the general population. It is known that obesity has a negative influence on the formation of osteoarthritis. An increased body mass index leads to an increased risk of needing a joint replacement.

Research frontiers

To the knowledge, there is no study that evaluated the influence of the respective stage of obesity in a monocentric setting with large number of cases.

Innovations and breakthroughs

Six thousand and seventy-eight patients with a body mass index (BMI) $\geqslant$ 25 kg/m^2 were treated with a primary total hip arthroplasty (THA) or total knee arthroplasty (TKA). Age decreased significantly ($P < 0.001$) by increasing obesity in both the THA and TKA. Harris Hip Score (HHS) and Hospital for Special Surgery Score (HSS) were at significantly lower levels at the time of treatment in the super-obese population ($P < 0.001$). Distribution patterns of the type of endoprostheses used changed with an increasing BMI. Peri- and postoperative complications were similar in form and quantity to those of the normal population.

Applications

We conclude that both the primary hip and knee arthroplasty can be performed in all stages of obesity with a relatively low perioperative risk. A higher BMI leads to an endoprosthetic joint replacement at earlier times, which, however, is only carried out at significantly lower levels of joint function. Good preparation is indispensable.

Terminology

According to the classification of the World Health Organization overweight is defined as BMI 25-29.9 kg/m^2, stage I obesity is defined as BMI 30-34.9 kg/m^2, stage II obesity is defined as 35-39.9 kg/m^2 and stage III obesity is defined as BMI $\geqslant$ 40 kg/m^2. HHS and Hospital for HSS are used to measure function in patients suffering from osteoarthritis of the hip or the knee, respectively.

Peer review

This retrospective study, conducted at a single medical center with high volume of total joint arthroplasty, showed some interesting findings. The study was well conducted with detailed data analysis. The conclusion is validated.

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P- Reviewer: Cui Q, Trkulja VA **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.145

World J Orthop 2015 January 18; 6(1): 145-149
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Observational Study

Cost of external fixation *vs* external fixation then nailing in bone infection

Khaled Mohamed Emara, Ramy Ahmed Diab, Khaled Abd EL Ghafar

Khaled Mohamed Emara, Ramy Ahmed Diab, Khaled Abd EL Ghafar, Orthopaedic Surgery, Ain Shams University, Cairo 0020, Egypt
Author contributions: Emara KM designed and wrote up the research; Diab RA collected the data and wrote up the research; Ghafar KAE collected the data.

Correspondence to: Dr. Ramy Ahmed Diab, Lecturer, Orthopaedic Surgery, Ain Shams University, 13 B Kornish el, Nile, Agha Khan, Cairo 0020, Egypt. ramydiab79@gmail.com
Telephone: +20-2-22055661
Fax: +20-2-22055662
Received: April 25, 2014
Peer-review started: April 27, 2014
First decision: May 14, 2014
Revised: May 29, 2014
Accepted: September 16, 2014
Article in press: September 17, 2014
Published online: January 18, 2015

Abstract

AIM: To study the cost benefit of external fixation *vs* external fixation then nailing in treatment of bone infection by segment transfer.

METHODS: Out of 71 patients with infected nonunion tibia treated between 2003 and 2006, 50 patients fitted the inclusion criteria (26 patients were treated by external fixation only, and 24 patients were treated by external fixation early removal after segment transfer and replacement by internal fixation). Cost of inpatient treatment, total cost of inpatient and outpatient treatment till full healing, and the weeks of absence from school or work were calculated and compared between both groups.

RESULTS: The cost of hospital stay and surgery in the group of external fixation only was 22.6 ± 3.3 while the cost of hospital stay and surgery in the group of early external fixation removal and replacement by intramedullary nail was 26.0 ± 3.2. The difference was statistically significant regarding the cost of hospital stay and surgery in favor of the group of external fixation only. The total cost of medical care (surgery, hospital stay, treatment outside the hospital including medications, dressing, physical therapy, outpatient laboratory work, *etc*.) in group of external fixation only was 63.3 ± 15.1, and total absence from work was 38.6 ± 6.6 wk. While the group of early removal of external fixation and replacement by IM nail, total cost of medical care was 38.3 ± 6.4 and total absence from work or school was 22.7 ± 4.1. The difference was statistically significant regarding the total cost and absence from work in favor of the group of early removal and replacement by IM nail.

CONCLUSION: Early removal of external fixation and replacement by intramedullary nail in treatment of infected nonunion showed more cost effectiveness. Orthopaedic society needs to show the cost effectiveness of different procedures to the community, insurance, and health authorities.

Key words: Cost; Fixator; Nailing; Infection

Core tip: Fifty patients with infected nonunion tibia (26 patients were treated by external fixation only, and 24 patients were treated by external fixation early removal after segment transfer and replacement by internal fixation). Cost of inpatient treatment, total cost of inpatient and outpatient treatment till full healing, and the weeks of absence from school or work were calculated and compared between both groups.

Early removal of external fixation and replacement by intramedullary nail in treatment of infected nonunion showed more cost effectiveness. Orthopaedic society needs to show the cost effectiveness of different procedures to the community, insurance and health authorities.

Emara KM, Diab RA, Ghafar KAE. Cost of external fixation *vs* external fixation then nailing in bone infection. *World J Orthop* 2015; 6(1): 145-149 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/145.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.145

INTRODUCTION

Chronic bone infection can be secondary to open fracture, or post-operative[1]. Treatment of infection requires radical debridement, bone stability, and reconstruction of the bone defect resulted from debridement or nonunion[2]. Ilizarov technique is one of the most effective techniques used in bone infection: for stabilization, limb reconstruction, and fracture healing[3].

Ilizarov technique and external fixation system has many advantages including versatility, and high success rate in treatment of bone deformity, and infection[4]. But the long duration of external fixation is associated with many complications including: pin tract infection, joint stiffness, disuse atrophy, psychological stress, long duration of absence from work, and many other complications[5].

There are several surgical techniques proposed to shorten the duration of external fixation in treatment of bone infection. That includes lengthening then nailing technique[6], and lengthening over nail[7], and hemicorticotomy[8], and many other techniques. On the other hand there are several biological techniques proposed to shorten duration of external fixation: for example early bone graft for the docking site[9], platelet rich plasma[10], bone marrow injection[11], and many other techniques.

The cost of treatment and medical care is an important issue all over the world, not only in poor countries[12]. This cost puts a huge burden on the financial, insurance and health authorities and also affect the productivity of the community[13,14]. The cost in treatment of bone infection is not only the direct hospital cost of multiple surgeries. Not only the cost of care required at home including wound dressing, physical therapy, *etc*. There is the economic burden on the patient family, and community due to days of absence from work or school[15,16].

There are not so many papers in the scientific orthopaedic literature deal with the cost effectiveness of different surgical techniques[17]. This study presents two techniques used in treatment of chronic bone infection and nonunion. Both techniques involve segment transfer by Ilizarov external fixation. In one technique the external fixation is removed early after eradication of infection and finishing segment transfer, and replaced by intramedullary nail[18-20]. The other technique is to continue with external fixation till full healing of the fracture, docking site, and distraction callus[21-23]. Both techniques showed comparable long term outcome[18].

The aim of the study is to compare the cost of the two different techniques including hospital and surgical cost, home care cost, and absence from work or school, and to define which would be more cost effective for the patient and the community.

MATERIALS AND METHODS

This is a retrospective study included 71 patients treated for infected nonunion tibia after open fracture, between 2003 and 2006. All cases were classified as type B 1 according to Paley *et al*[24] classification for nonunion (defect more than 1 centimeter after debridement with no leg shortening). Average duration of nonunion and infection was 13.4 mo (ranged between 9-27 mo). Age ranged between 19 and 45 years old. Out of the 71 patients 39 were treated by external fixation only till full fracture healing, while 32 patients were treated by external fixation at the early stages till segment transfer was finished then external fixation was removed and replaced by intramedullary nail.

Inclusion criteria in this study were infected nonunion fracture tibia, treated by Ilizarov technique, with follow-up more than 2 years. Cases excluded from statistical analysis were patients who needed unexpected surgery for complications, cases of more than one fracture and patients without enough information about the cost and bills of medical care inside and outside the hospital.

After the use of these inclusion and exclusion criteria 21 patients were excluded from statistical analysis. The group of external fixation only included 26 patients (25 male and one female). The group of external fixation then nailing included 24 patients (22 male and 2 female).

Technique

Patients with infected nonunion fracture shaft tibia. Surgical debridement resulted in a bone defect ranged between 3-5 centimeters. Application of Ilizarov external fixation system and corticotomy was done. After surgery post-operative regiment during the first 45-75 d included: follow-up of the wound, pin care, antibiotics according to culture and sensitivity, and segment transfer to reconstruct the bone defect start 10 to 14 d after surgery. Laboratory follow-up of all patients every 2 wk during this stage for decreasing erythrocyte sedimentation rate and C-reactive protein beside wound condition to ensure eradication of infection[25].

At this stage (45-75 d after first surgery) choices were given to patients including benefits and risks. One choice is to continue with external fixation till full fracture healing and consolidation of the distraction callus. This choice has the advantage of being safe with no need for another major surgery and less risk for recurrence of infection and this technique is classic and many literatures explained the long term outcome of this technique. But

the disadvantage is the longer duration of external fixation with more risk of pin tract infection, and joint stiffness, discomfort, and other complications of long duration of external fixation[18]. Patients who chosen this line of treatment had autogenous bone graft surgery at the docking site to avoid slow healing of the docking site with no internal fixation and continued with external fixation till full healing[21].

The other choice was removal of external fixation and replacement by intramedullary nail. The advantage of this choice is more comfort to the patient and easier physical therapy to regain range of movement and muscle strength. Disadvantage included risk of recurrence of infection due to implantation of hard ware, and risk of implant failure[18]. Patients who chosen this technique were taken to the operative theater for Ilizarov external fixation removal and replaced by Interlocking intramedullary nail and autogenous bone graft at the docking site.

Follow-up was done till complete healing in both groups with minimum 2 years follow-up. We reviewed all cost involved in medical care in both groups, and the days of absence from work or school till full return to normal life. None of the cases involved had permanent disability.

In this study, all records were reviewed to calculate the cost of surgery, hospital stay and cost of treatment after discharge, and days of absence from work or school.

Cost was calculated in local currency (Egyptian pound), according to prices of years 2003-2006. Comparison between the two homogenous groups makes this study applicable anywhere all over the world.

Statistical analysis

Continuous variables are expressed as mean and Standard Deviation. Categorical variables are expressed as frequencies and percents. Student t test was used to assess the statistical significance of the difference between more two study group mean. Fisher's exact test was used to examine the relationship between Categorical variables.

Pearson's correlation

Pearson's correlation was used to assess the correlation between two continuous variables.

All statistical procedures were carried out using SPSS version 15 for Windows (SPSSInc, Chicago, IL, United States).

RESULTS

There was no statistically significant difference between the two groups of patients regarding age, sex, size of the bone defect as shown in Table 1. Regarding the total hospital cost the group treated by external fixation was less than the group treated by replacement of external fixation by internal fixation, the difference was statistically significant. On the other hand, Duration of external fixation, total absence from work or school, and total cost of medical care was less in the group of early removal of external fixation and replacement by internal fixation, and showed statistically significant difference (Table 1).

DISCUSSION

The cost of hospital stay and surgery in the group of external fixation only was 22.6 ± 3.3, while the group of early external fixation removal and replacement by IM nail the cost of hospital stay and surgery was 26.0 ± 3.2. The difference was statistically significant.

The total cost of medical care (surgery, hospital stay, treatment outside the hospital including medications, dressing, physical therapy, outpatient laboratory work, *etc.*) in group of external fixation only was 63.3 ± 15.1, and total absence from work was 38.6 ± 6.6 wk. While the group of early removal of external fixation and replacement by IM nail total cost of medical care was 38.3 ± 6.4 and total absence from work or school was 22.7 ± 4.1. The difference was statistically significant regarding the total cost and absence from work in favor of the group of early removal and replacement by IM nail.

Cost of medical care is an important issue all over the world. Health authorities and insurance systems keep asking the medical community about the cost effectiveness of different surgical procedures[13]. The choice of method of treatment needs to give the best clinical outcome according to evidence based medicine[15], to be cost effective, and able to achieve the best comfort for the patient and the earlier return to normal life with least burden on medical service[16].

Planning to study cost effectiveness in different treatment modalities is difficult due to the difference in cost between different countries, and different places within the same country, and the change in cost over years, the type of currency used and inflation, *etc.* There are also the other medical and economic variables to be considered.

The cost of medical care can be different from a country to another. For example: Total hip replacement cost 47000 US Dollars in United States, 8500 US Dollars in Egypt or India, 12000 US Dollars in Singapore, and 10000 US Dollars in Malaysia, and 17 300 US Dollars in Mexico[26,27]. Also the rise of medical cost over years can make comparison difficult[28]. Even within the same country the cost of the same procedure can vary from a medical center to another[29]. This variability can affect the interpretation of the results in this study and the applicability of the data in other countries. Comparing two homogenous groups of patients treated at the same center during the same period of time, by different techniques decrease this effect.

Every medical procedure carries some risks. Medical community needs to justify using this procedure or that. To do so, we as medical doctors and orthopaedic surgeons should do studies that review the clinical effectiveness and financial effectiveness of different surgical procedures.

In this study two techniques were reviewed. Both techniques give good final clinical outcome. Treatment of infected nonunion by external fixation as the only method of stabilization can be effective, and safe. But long duration of external fixation showed many medical problems and complications. Also the long duration of

Table 1 Comparison between two groups as regard all studied parameters

	Group				*P*	SIG
	External fixation with nailing		External fixation only			
	Mean	± SD	Mean	± SD		
Age	27.42	6.42	27.62	6.41	0.913[1]	NS
Sex						
Male (*n*)	22	91.70%	25	96.2%	0.602[2]	NS
Female (*n*)	2	8.3%	1	3.8%		
Duration of external fixation	10.63	1.74	26.00	1.52	0.0001[1]	HS
Duration to healing	24.54	0.83	26.00	1.52	0.0001[1]	HS
Size of defect	4.13	0.74	4.04	0.77	0.688[1]	NS
Hospital cost	26.00	3.18	22.65	3.35	0.001[1]	HS
Total medical cost	38.30	6.40	63.35	15.08	0.0001[1]	HS
Total absence from work/school	22.71	4.10	38.58	6.59	0.0001[1]	HS

[1]Student *t* test; [2]Fisher exact test. Age in years; Duration of external fixation in weeks; Time to bone healing in weeks; Size of bone defect in centimeters; Hospital financial cost calculated in 1000 local currency; Total medical cost calculated in 1000 local currency; Total absence from work in weeks.

external fixation leads to delay in rehabilitation and longer absence from work or school, and showed a high total medical cost. This total cost is not only involving hospital cost, but involve the daily dressing, physical therapy, medications, and absence from work.

The other technique involves early removal of external fixation once infection is eradicated and segment transfer is finished, and replacement by intramedullary nail. This technique carries some risk for the recurrence of infection, and the higher cost of a second surgical procedure. But the total cost of medical care, and duration needed till retune to work is less.

The treatment of infected nonunion has many techniques. Ilizarov is only one of these techniques. And within Ilizarov technique there are many modifications. This study was not able to review all techniques. But the design of this study, and the data available was used to compare two of these techniques, although in the future there should be studies to review every orthopaedic procedure and to show the clinical and cost effectiveness of this procedure.

There can be differences between different countries regarding details of medical care. In some countries the cost of medications or hospital stay or implant can be more than the other, on the other hand physical therapy in one country can cost less or more than the other. And there are many details within the medical care that can make difference in the cost. That is why in this study the comparison between the costs of two homogenous groups may compensate this defect and makes this study useful to medical society all over the world not only in poor countries or rich. The currency used to calculate the cost was the 1000 local currency. And this defect was also compensated by the comparison of two homogenous groups.

Orthopaedic community should focus on cost beside clinical effectiveness of different medical interventions to prove to the financial authorities the rationale behind the high cost of some orthopaedicprocedures.

Some procedures can cost more money regarding hospital stay and surgery, but the total cost of medical care and absence from work can be less than another procedure that has less surgical cost.

Early removal of external fixation and replacement by internal fixation after eradication of infection and finishing segment transfer is more cost effective and allow earlier return to work than the classic technique of segment transfer by Ilizarov external fixation only.

COMMENTS

Background

The cost of treatment and medical care is an important issue all over the world, not only in poor countries. This cost puts a huge burden on the financial, insurance and health authorities and also affect the productivity of the community. The cost in treatment of bone infection is not only the direct hospital cost of multiple surgeries but also the cost of care required at home including wound dressing, physical therapy, *etc.* There is the economic burden on the patient family, and community due to days of absence from work or school.

Research frontiers

The choice of method of treatment needs to give the best clinical outcome according to evidence based medicine, to be cost effective, and able to achieve the best comfort for the patient and the earlier return to normal life with least burden on medical service. Every medical procedure carries some risks. Medical community needs to justify using this procedure or that. To do so, medical doctors and orthopaedic surgeons should do studies that review the clinical effectiveness and financial effectiveness of different surgical procedures.

Innovations and breakthroughs

There are not so many papers in the scientific orthopaedic literature deal with the cost effectiveness of different surgical techniques. This study presents two techniques used in treatment of infected tibial nonunion. Both techniques involve segment transfer by Ilizarov external fixation. In one technique the external fixation is removed early after eradication of infection and finishing segment transfer, and replaced by intramedullary nail. The other technique is to continue with external fixation till full healing of the fracture, docking site, and distraction callus. The aim of our study is to compare the cost of the two different techniques including hospital and surgical cost, home care cost, and absence from work or school, and to define which would be more cost effective for the patient and the community.

Applications

Treatment of infected nonunion by external fixation as the only method of stabilization can be effective, and safe. But long duration of external fixation showed many medical problems and complications. Also the long duration of external fixation leads to delay in rehabilitation and longer absence from work or school, and showed a high total medical cost. This total cost is not only involving hospital cost, but involve the daily dressing, physical therapy, medications, and absence from work. The other technique involves early removal of external fixation once infection is eradicated and segment transfer is finished, and replacement by intramedullary nail. This technique carries some risk for the recurrence of infection, and the higher cost of a second surgical procedure. But

the total cost of medical care, and duration needed till retune to work is less. Orthopaedic community should focus on cost beside clinical effectiveness of different medical interventions to prove to the financial authorities the rationale behind the high cost of some orthopaedic procedures. Some procedures can cost more money regarding hospital stay and surgery, but the total cost of medical care and absence from work can be less than another procedure that has less surgical cost. Future studies should be done to review every orthopaedic procedure and to show the clinical and cost effectiveness of this procedure.

Terminology

The cost of treatment and medical care include the cost of surgery, hospital stay, cost of treatment after discharge, and days of absence from work or school till full return to normal life. Segment transfer is a technique used to fill a bone defect, in which a bone corticotomy done in healthy bone and gradually transfer this bone segment to fpll the bone defect.

Peer review

This is an interesting article that looks at the economics of two commonly performed surgeries for infected non unions.

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P- Reviewer: Chen YK, Maheshwari AV **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.150

World J Orthop 2015 January 18; 6(1): 150-155
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Prospective Study

How are those "lost to follow-up" patients really doing? A compliance comparison in arthroplasty patients

Jung Keun Choi, Jeffrey A Geller, David A Patrick Jr, Wenbao Wang, William Macaulay

Jung Keun Choi, Jeffrey A Geller, David A Patrick Jr, Wenbao Wang, William Macaulay, Center for Hip and Knee Replacement, Department of Orthopaedic Surgery, NewYork-Presbyterian Hospital at Columbia University Medical Center, New York, NY 10032, United States

Author contributions: All authors meet ICJME authorship guidelines; Choi JK, Geller JA and Macaulay W designed the research; Choi JK, Geller JA and Wang W performed the research; Choi JK, Wang W and Patrick Jr DA analyzed data; Choi JK, Geller JA, Patrick Jr DA, Wang W and Macaulay W wrote the paper.

Correspondence to: William Macaulay, MD, Nas Eftekhar Professor of Clinical Orthopaedic Surgery, Center for Hip and Knee Replacement, Department of Orthopaedic Surgery, NewYork-Presbyterian Hospital at Columbia University Medical Center, 630 West 168th Street, New York, NY 10032, United States. wm143@columbia.edu
Telephone: +1-212-3058193
Fax: +1-212-3054024

Received: March 28, 2014
Peer-review started: March 31, 2014
First decision: May 14, 2014
Revised: May 30, 2014
Accepted: August 27, 2014
Article in press: August 29, 2014
Published online: January 18, 2015

Abstract

AIM: To determine whether there is a functional difference between patients who actively follow-up in the office (OFU) and those who are non-compliant with office follow-up visits (NFU).

METHODS: We reviewed a consecutive group of 588 patients, who had undergone total joint arthroplasty (TJA), for compliance and functional outcomes at one to two years post-operatively. All patients were given verbal instructions by the primary surgeon to return at one year for routine follow-up visits. Patients that were compliant with the instructions at one year were placed in the OFU cohort, while those who were non-compliant were placed in the NFU cohort. Survey mailings and telephone interviews were utilized to obtain complete follow-up for the cohort. A χ^2 test and an unpaired *t* test were used for comparison of baseline characteristics. Analysis of covariance was used to compare the mean clinical outcomes after controlling for confounding variables.

RESULTS: Complete follow-up data was collected on 554 of the 588 total patients (93%), with 75.5% of patients assigned to the OFU cohort and 24.5% assigned to the NFU cohort. We found significant differences between the cohorts with the OFU group having a higher mean age (P = 0.026) and a greater proportion of females (P = 0.041). No significant differences were found in either the SF12 or WOMAC scores at baseline or at 12 mo postoperative.

CONCLUSION: Patients who are compliant to routine follow-up visits at one to two years post-operation do not experience better patient reported outcomes than those that are non-compliant. Additionally, after TJA, older women are more likely to be compliant in following surgeon instructions with regard to follow-up office care.

Key words: Total joint arthroplasty; Revision joint arthroplasty; Functional outcomes; Patient compliance; Patient follow-up

Core tip: Following total joint arthroplasty, often patients

are non-compliant with the surgeon requested follow-up protocol. This study aims to determine if there is a functional difference between patients who actively follow-up in office and those who are non-compliant with the visit protocol. Based on our results, patient compliance to routine follow-up visits at 12-24 mo post-operation does not lead to better patient-reported functional outcomes than those who are non-compliant. Additionally, older women are more likely to be compliant in adhering to surgeon post-operative follow-up instructions.

Choi JK, Geller JA, Patrick Jr DA, Wang W, Macaulay W. How are those "lost to follow-up" patients really doing? A compliance comparison in arthroplasty patients. *World J Orthop* 2015; 6(1): 150-155 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/150.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.150

INTRODUCTION

Total hip arthroplasties (THA) and total knee arthroplasties (TKA) were initially designed to help relieve pain and improve function in people with debilitating joint pain. Outcomes from these surgeries are often determined through the use of patient reported, validated outcome tools[1-3]. Currently, total joint arthroplasty (TJA) has revolutionized the care of patients with end-stage arthritis of the hip and knee joint, by providing excellent long term results exceeding 20 years after surgery[4-6]. With future projections of close to 3.48 million TKAs and 572000 THAs occurring in the United States alone in the next 15 years, there is an increased importance on learning all criteria that make total joint replacement successful[7].

Following TJA, post-operative follow-up visits with the surgeon are the standard of practice in the United States; although, each surgeon often has his or her own protocol. In a survey of the American Association of Hip and Knee Surgeons membership, 80% of the respondents recommended that clinical and radiographic examinations following TJA should occur annually or biennially[8]. Regular follow-up visits, including radiographs, enable the surgeon to assess the result of a surgery and can rule out the possible need for revision, amongst other complications[9]. The delayed diagnosis of potential problems such as osteolysis, subsidence, component loosening, and infection can result in the need for a complex and costly revision surgeries[10,11], which often have less certain and worse outcomes than primary joint replacement[12].

As addressed, follow-up visits are also important for patient-reported outcomes based studies of TJA; however, despite recommendations from surgeons, not all patients that undergo TJA return to the office for routine examination. Since surgeons have been unable to estimate non follow-up patient outcomes, studies based on outcomes reported by patients who actively follow-up in the office may not be an accurate representation of TJA patients as a whole. Previous studies have reported that patients who are lost to follow-up are more likely to have worse outcomes and have had further surgical intervention at a second site than those patients who follow-up with their surgeon consistently[13,14]. Conversely, some other studies have shown varied and inconsistent results regarding lost to follow-up patients. Furthermore, most of these studies did not include complete pre-operative and post-operative outcomes for patients that followed-up in office (OFU) and those non-compliant with follow-up procedures (NFU)[15,16].

The purpose of this study was to determine whether there is a difference in functional outcomes between patients that follow-up annually in the surgeon's office with those who are generally non-compliant with follow-up.

MATERIALS AND METHODS

After receiving local institutional review board approval, we identified prospectively tracked patients who had received either a hip or a knee arthroplasty at our center. The patient cohort included primary and revision THA, primary and revision TKA, unicompartmental knee arthroplasties (UKA), bicompartmental knee arthroplasties (BCA), and metal-on-metal hip resurfacings (MOMHR). For those receiving staged, bilateral joint arthroplasties, only data collected from the first procedure were utilized. If a patient received a primary TJA and subsequently required a revision of another joint, he or she was excluded from the study to guarantee no duplication of patients. All procedures were performed by two fellowship trained, adult reconstruction orthopaedic surgeons.

From our CHKR registry, 588 patients, who were available for the annual follow-up visit, fit the inclusion criteria and were included into the study group. At the time of hospital discharge, all patients were given appointments at six weeks and three months post-operatively. Following the three month outpatient visit, each patient was given verbal instructions by his or her primary surgeon to return for another visit at one year post-operatively. At the one year visit, instructions were issued to return at two or three years post-operatively. When the patients checked out at each outpatient visit, each was given two possible options for future appointment scheduling: (1) immediately schedule the future appointment through the receptionist; or (2) contact the office by telephone at a later date to schedule the routine annual follow-up visit. For immediately scheduled appointments, the patient was given the date and time of the next appointment verbally and in written form. Patients with scheduled annual appointments were notified of their upcoming appointments through an automated calling system the day prior to the scheduled appointment.

Preoperative data collected included age, gender, comorbidities, body mass index (BMI), and preoperative diagnosis. Comorbidities collected for this report, verified through medical records, included: alcohol dependency,

Table 1 Active follow-up in the office and non-compliant with office follow-up visits baseline demographics *n* (%)

Group	OFU	NFU	*P* value
Number of patients	444	144	
Surgeon 1	179 (40.3)	51 (35.4)	0.295
Surgeon 2	265 (59.7)	179 (64.6)	
Age at procedure	62.4 ± 12.9	59.6 ± 13.3	0.026[a]
Length of stay (d)	3.1 ± 1.3	3.4 ± 2.1	0.217
Gender: female	250 (56.3)	67 (46.5)	0.041[a]
Comorbidities	324 (73.0)	112 (77.8)	0.252
Operative side: right	53.4%	50%	0.542
SF12 physical	30.4 ± 8.2	30.2 ± 7.2	0.778
SF12 mental	49.8 ± 11.4	47.9 ± 11.5	0.080
WOMAC pain score	44.9 ± 26.6	46.6 ± 27.8	0.506
WOMAC stiffness score	42.0 ± 25.1	43.3 ± 23.0	0.581
WOMAC function score	46.0 ± 21.6	48.2 ± 20.9	0.271
BMI (kg/m^2)	30.3 ± 7.0	29.9 ± 6.9	0.634
Diagnosis			0.734
Osteoarthritis	347 (78.2)	106 (73.6)	
Osteonecrosis	45 (10.1)	18 (12.5)	
Rheumatoid arthritis	44 (9.9)	17 (11.8)	
Other	8 (2.1)	3 (1.8)	
Operative procedure			0.541

[a]$P < 0.05$ *vs* OFU. WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; BMI: Body mass index; OFU: Active follow-up in the office; NFU: Non-compliant with office follow-up visits.

cancer, cardiac disease, endocrine disease (diabetes mellitus, hypothyroidism), gastrointestinal disease, hematologic disease, hepatobiliary disease, hypertension, infectious disease, neurological disease, osteoporosis, Parkinson's disease, documented psychiatric disorders, respiratory disease, smoking, steroid use, thromboembolic disease, and vascular disease. Also collected preoperatively and postoperatively were the Short Form 12 version 1 (SF12) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) patient questionnaires.

To determine postoperative follow-up compliance, we reviewed the electronic medical records of each patient who had undergone TJA. Patient cohorts were then divided into OFU and NFU based on compliance determination. Since patients are routinely compliant with the scheduled three month follow-up visit, these data were not analyzed in this study. Patients that returned to the outpatient office at one or two years post-operatively were included in the OFU cohort, with those not returning to the office included in the NFU group.

Between one and two years after TJA, follow-up questionnaires were collected *via* routine outpatient visits, mail, or telephone. All data collection, entry, and maintenance were performed using the Patient Analysis and Tracking System (PATS 4.0, Axis Clinical Software, Portland, OR). When the registry was initially reviewed at the start of the study, 206 patients did not have up to date follow-up information. These patients included those who had initially returned to the office, but were in-between biennial appointments. Patients with incomplete follow-up were then mailed the post-operative survey twice, with a minimum, four week interval between the two mailings. Remaining subjects were then contacted *via* telephone for interviews and/or sent more, repeated mailings until the remainder of the study group was eventually contacted.

Statistical analysis

To compare baseline characteristics among the groups, a χ^2 test was used to analyze non-parametric variables, while an unpaired *t* test was used for the parametric variables. Analysis of covariance was used to compare the mean of clinical outcomes after arthroplasty between groups, controlling for age, gender, BMI, length of stay, pre-operative diagnosis, comorbidities, procedure, and preoperative SF12 and WOMAC scores. Statistical data analysis was conducted using SPSS Statistics v. 17.0 (IBM Corporation, Armonk, NY, United States). *P* values $\leqslant 0.05$ were considered significant.

RESULTS

Final analysis of the entire 588 patient cohort included: 172 TKAs, 200 THAs, 17 revision TKAs, 37 revision THAs, 22 UKAs, 14 BCAs, and 130 MOMHR patients. After initial database analysis, 75.5% of the total cohort had followed-up in the office, giving the OFU cohort 444 subjects and the NFU group 144 subjects. Of the 206 patients that were contacted to update their follow-up information, 62.1% of the patients (128 of 206) responded to the first or second mailing. From the remaining 78 non-responsive patients, 44 additional patients responded to further mailings and telephone interviews. Of the final 34 patients, one patient refused further participation and 33 were non-responsive to any form of contact. The breakdown of the lost patients included six that were initially in the OFU group and 28 in the NFU group.

Baseline characteristics according to each of the two groups are presented in Table 1. We found that there was a significant difference in both age ($P = 0.026$) and gender ($P = 0.041$) between the OFU and NFU groups. The mean age (62.5 years old) and percentage of females (56.8%) were both higher in the OFU group than the corresponding mean age (59.8 years old) and female percentage (47.2%) in the NFU cohort. Length of hospital stay, comorbidities, surgeon, operative side, procedure type, diagnosis, SF12 and WOMAC scores were not significantly different between the two cohorts. The types of procedures in each cohort are broken down in Table 2.

In evaluating the clinical, functional outcomes of the two groups, the mean follow-up periods for the OFU and NFU cohorts are 19.44 ± 8.4 and 20.28 ± 8.64 mo, respectively. While adjusting for confounding variables, there were no significant differences in either the postoperative SF12 mental and physical scores or in WOMAC pain, stiffness, and function scores. Raw scores can be found in Table 3 and seen graphically in Figure 1.

DISCUSSION

Importance of follow-up

Post-operative follow-up visits have been an integral part of total joint arthroplasty practices. Several authors

Table 2 Comparison of active follow-up in the office and non-compliant with office follow-up visits by operative procedure *n* (%)

Groups	MOMHR	Primary BKA	Primary THA	Primary TKA	Primary UKA	Revision THA	Revision TKA	Total
OFU	94 (21)	12 (3)	148 (34)	130 (29)	23 (5)	28 (6)	9 (2)	444 (100)
NFU	36 (25)	2 (1)	52 (36)	31 (22)	10 (7)	9 (6)	4 (3)	144 (100)
Total	130	14	200	161	33	37	13	588

MOMHR: Metal-on-metal hip resurfacings; UKA: Unicompartmental knee arthroplasties; OFU: Active follow-up in the office; NFU: Non-compliant with office follow-up visits.

Table 3 Comparison of active follow-up in the office and non-compliant with office follow-up visits outcome scores at one year

Group	OFU	NFU	*P* value
SF12 physical	45.1 ± 11.2	46.2 ± 11.2	0.685
SF12 mental	53.4 ± 9.2	54.1 ± 9.5	0.283
WOMAC pain score	89.1 ± 19.6	88.8 ± 20.5	0.612
WOMAC stiffness score	73.1 ± 24.7	75.3 ± 25.7	0.657
WOMAC function score	80.4 ± 21.7	82.4 ± 21.6	0.849

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; OFU: Active follow-up in the office; NFU: Non-compliant with office follow-up visits.

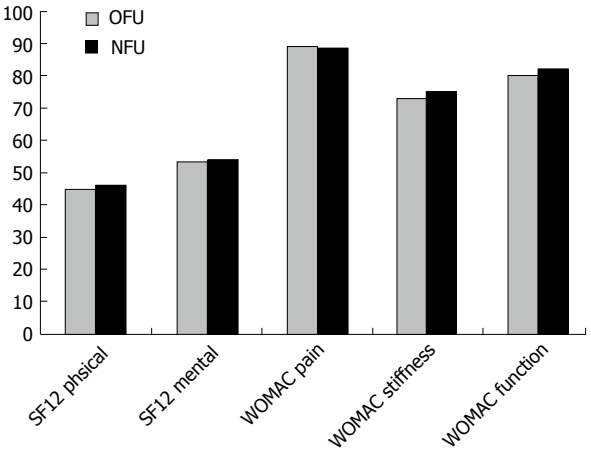

Figure 1 Comparison of postoperative follow-up SF-12 and Western Ontario and McMaster Universities Osteoarthritis Index scores between the active follow-up in the office and non-compliant with office follow-up visits cohorts. OFU: Active follow-up in the office; NFU: Non-compliant with office follow-up visits.

have suggested that even asymptomatic patients require follow-up care at least biennially following arthroplasty[8]. The reasoning behind this suggestion stems from the idea that even though some patients are asymptomatic, they may demonstrate radiographic or other signs of bone damage, which often require revision surgery despite the absence of symptoms[17]. While most cases of clinically significant osteolysis are typically identified at more than 6 years post-operatively, and with follow-up compliance expected to decrease over time, the detection of silent, clinical problems may be enhanced by early, regular, consistent follow-up visits. This strategy permits identification of potential complications at an earlier stage, and therefore, reduces the likelihood of complex revision procedures[18,19]. While some arthroplasty surgeons may conclude from presented data that routine follow-up visits are not necessary (or can be extended to every five years), anecdotally, at our urban, tertiary care center, we have found that when instructed to return every five years, patients are less likely to be compliant and do not return. From this information, we concur with Ries *et al*[20] that patients return every two to three years after the first annual follow-up visit.

Continual follow-up is also important for usage in post-operative outcome studies, as all such studies are limited by patient cooperation. If patients lost to follow-up have worse outcomes than those who continue to be assessed, as suggested by some authors, outcome studies, which do not account for these lost to follow-up patients, may give falsely optimistic results[13,14,21,22]. Therefore, extrapolations of the comparison between patients who did and did not consistently follow-up in office is essential to determining the real outcomes of an entire target population, particularly in long-term arthroplasty outcome studies.

Follow-up rate

Clohisy *et al*[23] showed that on the basis of a one-time verbal instruction, patient non-compliance with clinical follow-up after arthroplasty at one year post-operatively is up to 39%. Another study by Sethuraman *et al*[24] found that 45% of patients would prefer to not come into the office for routine evaluations at times greater than two years post TJA. This population based study, along with a separate study by de Pablo *et al*[25], showed that 15% of THA recipients self-reported receiving no post-operative follow-up radiographs, and only 42% of THA recipients had consistent follow-up over six years. The low office follow-up response rate observed in other studies corresponds well with our report. Our study showed that a large percentage (24.5%) of our patients did not visit the office for follow-up beyond their first year after arthroplasty. This low follow-up rate could be due to our simplistic follow-up protocol, which involves verbal instructions from the primary surgeon. If more intensive surgeon-directed instructions were given to patients, the rate of follow-up may possibly increase.

Baseline characteristics of patients

Many reasons are cited for the low rate of patient follow-up including: a change of residence, difficulty traveling, scheduling conflicts, doctor's office delays, or simply the patient feels good[23,24]. In previous studies, older patients, patients with lower income, and patients with a

lower education level were less likely to have consistent radiographic follow-up over six years post THA[25]. Additionally, these other studies demonstrated that younger patients and higher preoperative Harris hip gait scores were associated with follow-up compliance at two years post THA. Our study showed that the OFU and NFU groups had both different ages and gender proportions. Therefore, when comparing the mean clinical outcomes of the arthroplasties, we adjusted the age and gender through the use of analysis of covariance. One explanation for why younger men were less likely to be compliant with suggested follow-up is due to the desire to remain actively at work and not take the necessary time off to come into the office. This study was performed during a period of relative economic hardship in the surrounding area, which supports this speculation.

Follow-up outcome comparison

In a report by Dorey *et al*[15] on the influence of follow-up data loss on survivorship analysis in THA, they compared a cohort based on standard data collection with a 45% loss of follow-up to a cohort based on an almost complete data set with less than 10% loss of follow-up. The calculated survival rates for both groups were the same, leading Dorey *et al*[15] to conclude that the loss of follow-up data had little influence on analysis. Joshi *et al*[16] reviewed a series of 563 consecutive TKAs, and found no significant differences in revision rates or patient satisfaction between groups of patients who had or had not returned for follow-up office visits. An analysis by King *et al*[26] showed that there were no significant differences in Knee Society pain and function scores at a minimum of five years post-operative between follow-up and non-follow-up subjects. In contrast to these reports, Murray *et al*[14] published that patients lost to follow-up experienced worse outcomes in pain, range of motion, and radiologic features; however, these conclusions are based on the analysis of information derived from a patient's last visit rather than from an actual, final follow-up visit. Similar to previous studies, our analysis shows that there are no significant differences in clinical outcomes, SF12 and WOMAC post-operative scores between the OFU and NFU cohorts.

Limitations of the current study

One limitation of this study is investigator bias, which can occur during office visits or in telephone interviews[27-29]. McGrory *et al*[30] found that patient reported clinical scores following TKA were significantly different than those reported by physicians, although 97% of the responses were within one clinical grade of each other; however, no differences were noted in THA response. While investigator bias may have had a positive effect on the outcome of the OFU group, there were no significant differences in the patient reported, functional outcomes between the OFU and NFU cohorts. Another possible limitation is the inability to obtain a complete follow-up data set for our cohorts.

In conclusion, as observed in our two surgeon patient cohort from an academic, urban, tertiary care center, patients who do not visit the office for early route follow-up post TJA have similar outcomes to compliant patients, who routinely visit the office for follow-up. While we recommend to TJA patients to routinely follow-up in the office for both clinical and radiographical evaluations, our study shows that patients in our cohort were not negatively affected by non-compliance at early follow-up time periods of one to two years.

ACKNOWLEDGMENTS

The authors of this article would like to acknowledge Jonathan Nyce and Kalman Katlowitz for their assistance on this project.

COMMENTS

Background

Total joint arthroplasty (TJA) has drastically changed the care of patients with end-stage arthritis of the hip and knee, and is only becoming more prevalent in today's society, with more than 4 million TJAs expected to occur annually by 2030. Following TJA, adherence to post-operative follow-up visits allows surgeons to assess the results of a surgery, and to rule out possible needs for revision, amongst other complications. Delayed diagnoses of TJA complications often lead to less certain and worse outcomes. Currently, there is limited literature on the functional outcomes of those patients who adhere do not adhere to these follow-up protocols.

Research frontiers

With the expected increase in the number of total joint arthroplasties performed, adherence to post-operative protocols will be key to limiting poor outcomes. Previous research regarding functional outcomes of TJAs often only takes into account those patients who adhere to follow-up protocol timelines; however, without taking into account the non-compliant patients, these outcomes may not be an accurate representation of TJA patients as a whole. The study of functional outcomes of the follow-up non-compliant patient is necessary to determine overall TJA outcomes.

Innovations and breakthroughs

In previous studies regarding the outcomes of total joints, there have been varying reports on how successful patients who have been lost to follow-up have been doing. Additionally, other studies only include patients who report to the office as scheduled, creating an unintentional bias, by not providing the true, overall picture of the success of the surgery. Authors' study looks at the short-term, patient-reported functional outcome differences between those patients who were compliant to follow-up protocols to those that were non-compliant. Analysis of this data showed that in the short-term, non-compliant patients were not negatively affected with regard to functional outcomes.

Applications

This study shows that while it is important to have patients come back for routine, short-term follow-up to analyze for loose implants, infection, and heterotopic ossification, amongst other complications, there is no patient-reported functional outcome difference between compliant and non-compliant patients.

Terminology

Compliance - adherence of patients to the follow-up visit timeline as requested by the operating surgeon.

Peer review

This paper shows a well written research study on an important problem in monitoring total joint outcomes. The study highlights the facts that non-compliant patients are generally functioning at the same level as compliant patients, and that there may be future needs to monitor patient outcomes electronically in a way such that an office visit does not have to occur.

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P- Reviewer: Fisher DA, Malik MHA, Mugnai R
S- Editor: Wen LL **L- Editor**: A **E- Editor**: Wu HL

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.156

World J Orthop 2015 January 18; 6(1): 156-160
ISSN 2218-5836 (online)

META-ANALYSIS

Triangle tilt and humeral surgery: Meta-analysis of efficacy and functional outcome

Rahul K Nath, Chandra Somasundaram

Rahul K Nath, Chandra Somasundaram, Texas Nerve and Paralysis Institute, Houston, TX 77030, United States
Author contributions: Nath RK designed the study, performed the surgeries and revised the manuscript; Somasundaram C performed the literature search, statistical analysis and wrote the manuscript; both authors read and approved the final manuscript.

Correspondence to: Rahul K Nath, MD, Texas Nerve and Paralysis Institute, 6400 Fannin Street, Ste. 2420, Houston, TX 77030, United States. drnath@drnathmedical.com
Telephone: +1-713-5929900
Fax: +1-713-5929921
Received: December 25, 2013
Peer-review started: December 26, 2013
First decision: February 13, 2014
Revised: August 10, 2014
Accepted: September 4, 2014
Article in press: September 10, 2014
Published online: January 18, 2015

Abstract

AIM: To systematically review and analyze the overall impact and effectiveness of bony surgical procedures, the triangle tilt and humeral surgery in a comparative manner in permanent obstetric brachial plexus injury (OBPI) patients.

METHODS: We conducted a literature search and identified original full research articles of OBPI patients treated with a secondary bony surgery, particularly addressing the limitation of shoulder abduction and functions. Further, we analyzed and compared the efficacy and the surgical outcomes of 9 humeral surgery papers with 179 patients, and 4 of our secondary bony procedure, the triangle tilt surgical papers with 86 patients.

RESULTS: Seven hundred and thirty-one articles were identified, using the search term "brachial plexus" and obstetric or pediatric (246 articles) or neonatal (219 articles) or congenital (188 articles) or "birth palsy" (121 articles). Further, only a few articles were identified using the bony surgery search, osteotomy "brachial plexus" obstetric (35), "humeral osteotomy" and "brachial plexus" (17), and triangle tilt "brachial plexus" (14). Of all, 12 studies reporting pre- and post-operative or improvement in total Mallet functional score were included in this study. Among these, 9 studies reported the humeral surgery and 4 were triangle tilt surgery. We used modified total Mallet functional score in this analysis. Various studies with humeral surgery showed improvement of 1.4, 2.3, 5.0 and 5.6 total Mallet score, whereas the triangle tilt surgery showed improvement of 5.0, 5.5, 6.0 and 6.2.

CONCLUSION: The triangle tilt surgery improves on what was achieved by humeral osteotomy in the management of shoulder function in OBPI patients.

Key words: Meta-Analysis; Triangle tilt surgery; Humeral osteotomy; Obstetric brachial plexus injury; Birth palsy; SHEAR deformity; Shoulder function; Mallet score

Core tip: We systematically reviewed, analyzed and compared the surgical outcomes of 9 humeral surgery papers with 179 permanent obstetric brachial plexus injury patients (OBPI), and 4 of our secondary bony procedure, the triangle tilt surgical papers with 86 OBPI patients. We used modified total Mallet functional score in this analysis. Studies with humeral surgery showed improvement of 1.4, 2.3, 5.0 and 5.6 total Mallet score,

whereas the triangle tilt surgery showed improvement of 5.0, 5.5, 6.0 and 6.2. The triangle tilt surgery improves on what was achieved by humeral osteotomy in the management of shoulder function in OBPI patients.

Nath RK, Somasundaram C. Triangle tilt and humeral surgery: Meta-analysis of efficacy and functional outcome. *World J Orthop* 2015; 6(1): 156-160 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/156.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i1.156

INTRODUCTION

Bone deformities and their management in permanent obstetric brachial plexus injury children

Limitation to shoulder movement and function are the common secondary problems in permanent obstetric brachial plexus injury (OBPI) patients, as shoulder is the most frequently affected joint. If these infants do not receive early treatment, the chronic muscle imbalance leads to bone deformity and humeral head posterior subluxation.

To date, there has been no systematic evaluation of secondary bony surgical procedures that are involved in the treatment of shoulder function deficit in OBPI patients. Therefore, we attempted to systematically review and analyze the overall impact and effectiveness of bony surgical procedures, mainly the triangle tilt and humeral surgery in a comparative manner. The main goal of these secondary surgical procedures around the shoulder is to increase active abduction and external rotation in order to promote overall upper extremity functions.

Rotation/Derotational Humeral Osteotomy

Rotation osteotomy of the humerus has been described by several authors to treat the internal rotation contracture of the shoulder in OBPI[1-15]. Eng *et al*[2] reported that later surgical treatment with rotational osteotomy of the humerus seems to improve cosmesis but not function. Recently, Al-Qattan[9] has also shown that this procedure mainly improves the cosmetic appearance of children with total brachial plexus birth palsy. In addition, Al-Qattan *et al*[8] also found surprisingly, a significant ($P = 0.003$) decrease in shoulder abduction on long-term follow-up of his OBPI patients (the mean shoulder abduction was 135º, 146º and 109º measured pre-, early post- and late postoperatively, respectively). This technique has been used as a preferred procedure in older OBPI children[1,11,12,14], and shown to improve shoulder function[1,12], yet was not demonstrated as effective[8,9,13] procedure comparatively[16-18].

Waters *et al*[12], Waters *et al*[1] showed improvement of 5.0, and 5.6 in total Mallet score after humeral osteotomy. The efficacy and functional outcomes of the triangle tilt and humeral surgery are listed in Tables 1 and 2.

Triangle tilt surgery

The triangle Tilt is a novel osseous procedure, consists of osteotomy of the clavicle at the junction of the middle and outer thirds, osteotomy of the acromion at its junction with the spine of the scapula, ostectomy of the superomedial angle of the scapula and splinting of the limb in adduction, 5° of external rotation and full forearm supination.

Humeral surgeries do not address the SHEAR deformity[19] and its central influence in the pathophysiology of the medial rotation contracture, and the shoulder deformity. In our experience, successful restoration of position and function in failed humeral osteotomy patients has followed from surgically addressing the SHEAR deformity. It may be inferred that the SHEAR correction, the triangle tilt surgery is a more specific operation because it addresses the root cause of the medial rotation.

We have shown improvement of 5.0, 5.5, 6.0 and 6.2 Mallet score following short and extended-long term (5 years) follow-up of triangle tilt surgery respectively in OBPI patients, age between 0.9 and 17 year[16-18]. Further, the triangle tilt surgery is a salvage procedure in failed humeral osteotomy patients[16,20].

MATERIALS AND METHODS

We performed a search of the English language literature published up to December 2013 using mainly the Pubmed to identify full original research articles related to OBPI, using the following keywords "brachial plexus" and obstetric or pediatrics or neonatal or congenital or "birth palsy". We conducted search for also keywords specific to bony surgeries addressing the shoulder deformities in OBPI: "humeral osteotomy", "rotational/derotational osteotomy of the humerus", "humeral relocation", and "triangle tilt". Databases such as Scopus and Google scholar were also referred. We do not find any of the articles not published in Pubmed appeared in Scopus. If any such articles appear in Scopus, mostly they are either non-English or with animal experiments. Of all the articles, we found 9 studies with humeral and 4 with triangle tilt surgery, reporting pre- and post- operative or change in total Mallet score (Table 3).

Inclusion and exclusion criteria

Review articles, letter, technical and non-English language papers were excluded. Research articles using animal experiments and cadaver were also excluded. Articles reporting data from idiopathic or traumatic brachial plexus injuries in children were excluded as well (Table 4).

We included only articles using the triangle tilt and humeral surgery, reporting pre- and post- operative or change in total Mallet functional score in OBPI patients. 8 studies described the rotational osteotomy of the humerus with 166 patients, 1 described the relocation of the humerus with 13 patients, and 4 described triangle tilt surgery with 86 patients were included. Modified Mallet classification system was considered to assess the shoulder functions in this analysis (Table 1).

RESULTS

Seven hundred and thirty-one articles were identified, using the search term "brachial plexus" and obstetric or

Table 1 Bony surgical procedures and outcomes in obstetric brachial plexus injury patients

Name of the surgery	Ref.	No. of patients (age at surgery)	Follow-up (yr)	Surgical outcomes
Internal/external rotational/derotational osteotomy of the humerus	Abzug *et al*[13]	23 patients Mean age 10.1	2.2	13.8 ± 2.8, 16.1 ± 2.5 (P = 0.002), Mallet increased about 2.3
	Al-Qattan[7]	15 patients mean age 6.5	3	Mallet increased about 4.0
	Al-Qattan *et al*[9]	13 patients mean age 6 (4.5-9)	2	Improved the cosmetic appearance
	Al-Qattan[8]	17 patients mean age 6 (range 8-14) Recalled back to the clinic at a mean of 10 yr (range 8-14) after surgery. Mean age of 16, (range 13-20)	10	Found surprisingly, a significant (P = 0.003) decrease in shoulder abduction on long-term follow-up (the mean shoulder abduction was 135°, 146° and 109° measured pre-, early post- and late postoperatively, respectively)
	Waters *et al*[1]	16 patients mean age 8.4	3	Mallet improved 9.5 to 15.1 (P < 0.001)
	Waters *et al*[12]	27 patients mean age 7.6 range 2. 3-17	3.7	Mallet improved13 to 18 (P = 0.01). External rotation achieved with osteotomy was 64° (range, 35° to 90°)
	Pöyhiä *et al*[15]	5 patients	3.8	Mallet increased about 1.4 (P = 0.1)
	Kirkoset *al*[14]	22 patients mean age 10.0 age range 5-12	Vary, no mean	Increase in active abduction of the arm was 27 ° (range, 0 to 60), and the average increase in the arc of rotation was 25 ° (range, 5 to 85)
	Al-Zahrani[6]	12 patients age range 0.5 to 6	3.5 (1-5)	Cosmetic and functional improvement. ER improved 32° (20-40), abduction improved about 61° (60-70).
Relocation of the humerus	Pöyhiä *et al*[15]	13 patients	3.8	Mallet increased about 5.5 (P = 0.003)
Triangle Tilt surgery	Nath *et al*[16]	4 patients, mean age 10.2 (range 7.9-11.9)	< 1.0	Mallet improved 12.8 to 18.3 (P < 0.05)
	Nath *et al*[17]	40 patients, mean age 6.5 (range 2.2-10.3)	1.3	Mallet improved 13.6 to 18.6 (P < 0.000)
	Nath *et al*[20]	20 patients, mean age 5.0 (range 1.3-13)	1.5	Mallet improved about 6.0 (P < 0.001)
	Nath *et al*[18]	22 patients, mean age 5.8 (range 2.1-11.8)	5	Mallet improved 14.1 to 20.3 extended long term follow-up (5 yr, P < 0.0001)

Table 2 Improvement in functional score of triangle tilt and humeral surgery

Surgery	Ref.	Total Mallet improved
Humeral osteotomy	Abzug *et al*[13]	2.3 (P < 0.002)
Humeral osteotomy	Waters *et al*[1]	5.6 (P < 0.001)
Humeral osteotomy	Waters *et al*[12]	5.0 (P = 0.01)
Humeral osteotomy	Pöyhiä *et al*[15]	1.4 (P = 0.1)
Relocation of the humerus	Pöyhiä *et al*[15]	5.5 (P = 0.003)
Triangle tilt	Nath *et al*[16]	5.5 (P < 0.05)
Triangle tilt	Nath *et al*[17]	5.0 (P < 0.000)
Triangle tilt	Nath *et al*[20]	6.0 (P < 0.001)
Triangle tilt	Nath *et al*[18]	6.2 (P < 0.0001)

Table 3 Research articles in English only included

Search term	Pubmed	Scopus
"Brachial plexus" obstetric	731	620
"Brachial plexus" pediatric	246	176
"Brachial plexus" neonatal	219	226
"Brachial plexus" congenital	188	259
"Brachial plexus" "birth palsy"	121	115
Bony Surgery search		
Osteotomy "brachial plexus" obstetric	35	34
"Humeral osteotomy" "brachial plexus"	17	23
Osteotomy "brachial plexus" "birth palsy"	11	13
Osteotomy "brachial plexus" congenital	8	14
Osteotomy "brachial plexus" pediatric	10	8
Osteotomy "brachial plexus" neonatal	0	3
Triangle tilt "brachial plexus"	14	8

Table 4 Inclusion Criteria

Article parameters	Original full research paper with secondary bony surgical outcome of obstetric brachial plexus injury patients, English language publication, published till December 2013 in PubMed
Treatment options	Surgical-bony, humeral, triangle tilt
Patient age range	9 mo-18 yr old
Functional outcome	Improvement in total Mallet score

pediatric (246 articles) or neonatal (219 articles) or congenital (188 articles) or "birth palsy" (121 articles). Further, only a few articles were identified using the bony surgery search, osteotomy "brachial plexus" obstetric (35), "humeral osteotomy" and "brachial plexus" (17), and triangle tilt "brachial plexus" (14).

Of all, 12 studies reporting pre- and post- operative or improvement in total Mallet functional score were included in this study. Among these, 9 studies reported humeral surgery and 4 were triangle tilt surgery. We used modified total Mallet functional score in this analysis. Various studies with humeral surgery showed improve-

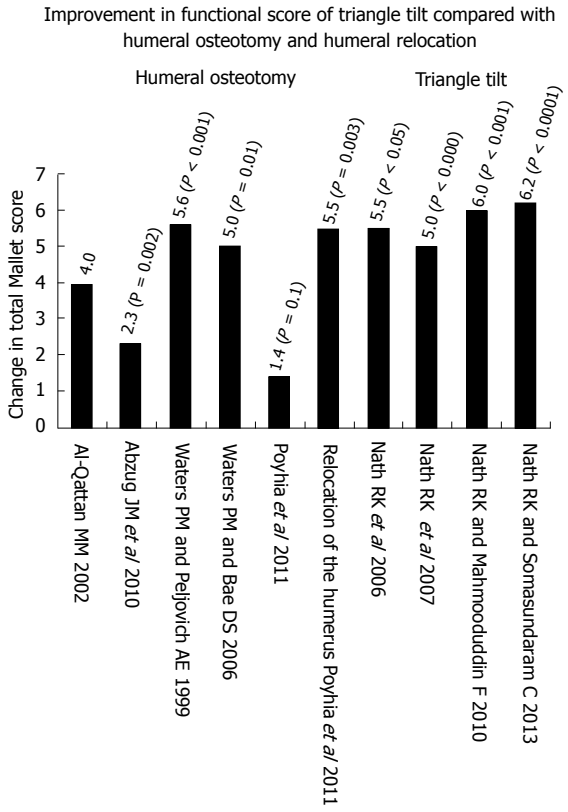

Figure 1 Improvement in functional score of triangle tilt compared with humeral osteotomy and humeral relocation.

ment of 1.4, 2.3, 5.0, and 5.6 total Mallet score, whereas the triangle tilt surgery showed improvement of 5.0, 5.5, 6.0 and 6.2 (Table 2 and Figure 1).

DISCUSSION

To our knowledge, this is the first attempt to review and analyze the surgical outcomes of the humeral and triangle tilt surgical procedures, that are involved in the management of shoulder function of OBPI patients. In examining restoration of shoulder function, the results of the meta-analysis suggest that the triangle tilt surgery improves on what was achieved by humeral osteotomy.

COMMENTS

Background

Limitation to shoulder movement and function are the common secondary problems in permanent obstetric brachial plexus injury (OBPI) patients, as shoulder is the most frequently affected joint. If these OBPI infants do not receive early treatment, the chronic muscle imbalance leads to bone deformity and humeral head posterior subluxation. To date, there has been no systematic evaluation of secondary bony surgical procedures that are involved in the treatment of shoulder function deficit in OBPI patients. Therefore, the authors attempted to systematically review and analyze the overall impact and effectiveness of bony surgical procedures, mainly the triangle tilt and humeral surgery in a comparative manner. The main goal of these secondary surgical procedures around the shoulder is to increase active abduction and external rotation in order to promote overall upper extremity functions.

Research frontiers

The authors systematically reviewed, analyzed and compared the surgical outcomes of 9 humeral surgery papers with 179 permanent OBPI, and 4 of this secondary bony procedure, triangle tilt surgical papers with 86 OBPI patients. The authors used modified total Mallet functional score in this analysis. Studies with humeral surgery showed improvement of 1.4, 2.3, 5.0 and 5.6 total Mallet score, whereas triangle tilt surgery showed improvement of 5.0, 5.5, 6.0 and 6.2. The triangle tilt surgery improves on what was achieved by humeral osteotomy in the management of shoulder function in OBPI patients.

Innovations and breakthroughs

Triangle tilt surgery, a novel osseous surgical procedure developed by the lead author and surgeon, improves on what was achieved by humeral osteotomy in the management of shoulder function in OBPI patients. This is the first report comparing the secondary bony surgical procedures in OBPI patients.

Applications

The triangle tilt surgery showed significant improvement of shoulder functions when compared to humeral surgery in OBPI patients.

Terminology

Meta-analysis, Triangle tilt surgery, humeral osteotomy, obstetric brachial plexus injury, Birth palsy, SHEAR deformity, Shoulder function, Mallet score. Triangle tilt surgery: This operative technique includes osteotomies of the clavicle, neck of the acromion and scapula in order to release the distal acromioclavicular triangle and allow it to reorient itself in a more neutral position into the glenoid.

Peer review

This is a review concerning the beneficial effect of the triangle tilt surgery and humeral surgery in permanent OBPI patients from the literature. The review was comprehensive and should be published.

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P- Reviewer: Canavese F, Pan HC, Schier R, Terzi R
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