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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (4): Hip

# Complications of hip fractures: A review

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## Abstract

Nowadays, fracture surgery represents a big part of the orthopedic surgeon workload, and usually has associated major clinical and social cost implications. These fractures have several complications. Some of these are medical, and other related to the surgical treatment itself. Medical complications may affect around 20% of patients with hip fracture. Cognitive and neurological alterations, cardiopulmonary affections (alone or combined), venous thromboembolism, gastrointestinal tract bleeding, urinary tract complications, perioperative anemia, electrolytic and metabolic disorders, and pressure scars are the most important medical complications after hip surgery in terms of frequency, increase of length of stay and perioperative mortality. Complications arising from hip fracture surgery are fairly common, and vary depending on whether the fracture is intracapsular or extracapsular. The main problems in intracapsular fractures are biological: vascularization of the femoral head, and lack of periosteum -a major contributor to fracture healing- in the femoral neck. In extracapsular fractures, by contrast, the problem is mechanical, and relates to load-bearing. Early surgical fixation, the role of anti-thromboembolic and anti-infective prophylaxis, good pain control at the perioperative, detection and management of delirium, correct urinary tract management, avoidance of malnutrition, vitamin D supplementation, osteoporosis treatment and advancement of early mobilization to improve functional recovery and falls prevention are basic recommendations for an optimal maintenance of hip fractured patients.

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**Key words:** Hip fracture; Complications; Morbidity; Mortality; Anesthesia

**Core tip:** Over 90% of hip fracture patients are older than 65-year-old and have preexisting medical comorbidities. Both factors have an important influence in its prognosis and treatment. Even with optimal care, elderly trauma patients suffer a higher morbidity and mortality rate when compared with the general population, and often demand for expensive hospital aftercare. Because of that, surgical treatment of hip fracture in these patients has exceptional clinical challenges, and needs strategies to optimize patient care. Acute orthogeriatric units, with medical co-management of these patients, offer the best chance for a successful outcome.

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## COMPLICATIONS OF HIP FRACTURES

### *Overall importance*

Nowadays, hip fracture surgery represents a large quota

**Table 1 Medical complications after hip fracture surgery**

| Medical complications | | Perioperative incidence | Intervention/recommendation[1] |
|---|---|---|---|
| Cognitive and neurological | Cognitive alterations | 10% | Preventive interventions in high-risk patients |
| | Postoperative delirium | 13.5%-33% | Preventive role of antipsychotics (haloperidol) |
| Cardiac and vascular | Arrhythmia | | Evaluation and care of patients with previous heart affectation |
| | Heart failure/Myocardial ischemia | 35%-42% | Restoration of fluid status to euvolemic. Beta-blockers if necessary |
| | DVT/PE | 27%/1.4%-7.5% | Thromboembolism prophylaxis<br>Early mobilization |
| Pulmonary | PPCs (exacerbation of chronic lung disease, atelectasis, respiratory failure, PE, ARDS) | 4% | Evaluation and care of patients with previous lung disease<br>Adequate postoperative fluid balance and pain control |
| | Hospital-acquired pneumonia | 7% | Thromboembolism prophylaxis<br>Timely diagnosis, adequate antibiotic treatment and accurate monitoring |
| Gastrointestinal | PGICs (dyspepsia, abdominal distension, reflexes ileum and constipation) | 5% | Adequate postoperative fluid, diet, pain and medication management |
| | Gastrointestinal postoperative stress ulcer/ gastrointestinal bleeding | 1.9% | Gastrointestinal bleeding prevention with pump inhibitors |
| Urinary tract | Urinary retention<br>Urinary tract infections | 12%-61% | Urinary catheters should be taken out as soon as possible, preferably within 24 h after insertion<br>Timely diagnosis and adequate antibiotic treatment<br>Preventive identification of pre, peri or postoperative medical or surgical risk factors |
| | AKI (prerenal, renal or postrenal) | 11% | Timely diagnosis, adequate treatment and accurate monitoring |
| Hematologic | Anemia | 24%-44% | Preventive identification of pre, peri or postoperative medical or surgical risk factors<br>Correct hemoglobin level to $\geqslant$ 10 g/dL before surgery<br>In anticoagulated patients, correct international normalized ratio to $\leqslant$ 1.5 preoperatively<br>Timely diagnosis, adequate treatment and accurate monitoring |
| Endocrino-metabolic | Protein-caloric malnutrition | 20%-70% | Nutritional supplements in peroperative period |
| | Diabetes | 17% | Maintain glucose levels between 100 and 180 mg/dL |
| | Vitamin D insufficiency-deficiency | | Vitamin D supplementation |
| Other | Pressure scars | 7%-9% | Early surgery fixation (within 24-48 h in stable patients)<br>Alternating pressure mattresses, pressure-relieving beds and equipment, aggressive skin care and proper nutrition, prevention-focused nursing |

DVT/PE: Deep vein thrombosis/pulmonary embolism; PPCs: Postoperative pulmonary complications; PGICs: Postoperative gastrointestinal complications; AKI: Acute kidney injuries. [1]Each patient needs a preoperative functional assessment, joint orthopedic-geriatric care is of benefit, reducing inpatient complications, length of stay and mortality.

of the orthopedic surgeon activity, and normally has associated major clinical and social cost implications[1]. Though hip fracture incidence has declined in many countries during the last decade, it still represents around 1/4 of the geriatric fractures that require hospital admission, and in spite of the enhancements in both surgical and medical services, its morbidity and mortality remains elevated[2]. Over 90% of hip fracture patients are older than 65 years old and have preexisting medical comorbidities. Both factors have an important influence in its prognosis and treatment[3]. Even with optimal care, elderly trauma patients suffer a higher morbidity and mortality rate when compared with the general population, and often demand for expensive hospital aftercare. Because of that, surgical treatment of hip fracture in these patients has exceptional clinical challenges, and needs strategies to optimize patient care. Acute orthogeriatric units, with a medical co-management of these patients, offer the best chance for a successful outcome[4-6], with some studies demonstrating a decrease in postoperative complications and mortality[7-9]. Early surgical fixation, the role of anti-thromboembolic and anti-infective prophylaxis, good pain control at the perioperative, detection and management of delirium, correct urinary tract management, avoidance of malnutrition, vitamin D supplementation, osteoporosis treatment and promotion of early mobilization to improve functional recovery and falls prevention are basic recommendations for an optimal care of hip fractured patients.

## Medical complications of hip fractures

Though a retrospective cohort study has reported that most patients have no medical problems after hip fracture repair[10], postoperative complications of this procedure are still relevant, and may affect around 20% of patients with hip fracture[11]. Cognitive and neurological alterations, cardiopulmonary affections (alone or combined), venous thromboembolism, gastrointestinal tract bleeding, urinary tract complications, perioperative anemia, electrolytic and metabolic disorders, and pressure scars are the most important medical complications after hip surgery in terms of frequency, increase of length of stay and perioperative mortality[6,12] (Table 1).

The American Society of Anesthesiologists (ASA)

classification can be a useful risk-stratification system for aged patients who have a hip fracture. In a retrospective study, medical complications were more usual in patients in ASA class 3 and 4 ($P \leqslant 0.001$) than those in ASA class 2, having respectively 3.78 and 7.39 times greater probability of suffering complications of this type[13]. With a similar clinical usefulness, a recent prospective study has demonstrated that advanced age (OR = 1.09), poor Barthel index (OR = 2.21) and low hemoglobin at admission (OR = 0.76) are factors associated with the development of medical inpatient complications[12].

### Cognitive and neurological complications

Cognitive complications appear in approximately 10% of patients after hip fracture surgery, being more common in elderly (> 65 years) than younger patients. Most of them suffer mild problems after surgery (inability to concentrate, write, read a book, *etc.*) but are able to overcome activities of daily living[14].

The physiopathology of postoperative cognitive problems has not been yet clearly elucidated. Probably, its responsible mechanisms are heterogeneous and multifactorial, and may be related to preoperative health status, level of cognition (cognitive reserve), the neurotoxic effects of anesthetic agents and perioperative events related to the surgery itself[15]. In this sense, the use of acrylic cement for prosthetic implantation can cause an inflammatory response that may possibly be associated with the occurrence of postoperative cognitive complications[16]. Upcoming research must be focused on actions to prevent and treat postoperative cognitive complications in patients at high-risk[14].

Postoperative delirium in patients with hip fracture appears normally after surgery, and affects 13.5% to 33% of these patients[17]. It has a variable presentation, and patients may reveal hyperactive, hypoactive, or mixed cognitive and motor statuses. While hyperactive patients present augmented psychomotor activity (pressured speech, irritability and uneasiness), hypoactive ones normally exhibit quiet appearance, carelessness, reduced mobility and trouble to answer simple questions about themselves and/or special-temporal orientation[18]. Hypoactive delirium may be misdiagnosed as depression or fatigue[14]. Causes of postoperative delirium are multifactorial and include advanced age, history of cognitive impairment, history of alcohol abuse, preoperative medication (especial attention to unrecognized benzodiazepine use), type of anesthetic used during surgery, infection, urinary retention and fluid or electrolyte disturbance[15,19]. Postoperative delirium amplifies the risk of poorer outcomes, medical complications, mortality and institutionalization in patients with hip fracture[6], being necessary to establish early prevention and treatment interventions to reduce its incidence in high-risk patients.

Regional anesthesia (especially spinal anesthetic with very light sedation) probably reduces the incidence of delirium early after surgery[20]. Supplemental oxygen (3-4 L/min) continually till day 2 post-surgery, or while patient's oxygen saturation is not $\geqslant$ 95% without oxygen, have proven to reduce delirium risk[21]. Because pain can contribute to delirium, an adequate postoperative analgesia minimizing the use of sedative drugs and anticholinergic medications seems to decrease its risk. It is necessary to take in count that narcotics also produce sedation and may contribute to its appearance. Though the preventive role of certain medications (antipsychotics, sedatives and cholinesterase inhibitors) has not been yet clearly elucidated[6], some studies have proven that low doses of haloperidol are effective in delirium prevention in this patient population.

### Cardiac and vascular complications

A report of the American College of Cardiology and the American Heart Association (ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery) estimates at less than 5% the risk of cardiac complication in postoperative after orthopedic major surgeries, but the 1-year recorded mortality exceeds 20% in patients with hip fracture[22].

The main reasons of in-hospital cardiac related mortality after hip fracture are heart failure and myocardial ischemia, which normally come out quick after fracture in patients with previous heart affectation[23]. The general incidence of perioperative myocardial ischemia in aged patients suffering hip fracture surgery has been informed to be 35% to 42%[24]. Deep venous thrombosis (DVT) is one of the principal causes of perioperative morbidity and mortality. In lack of thromboembolism prophylaxis, the prevalence of venography-detected proximal DVT ascend to 27% of patients[25]. The incidence of fatal pulmonary embolism oscillates between 1.4% to 7.5% of patients within 3 mo of hip fracture surgery[25]. Thromboembolism prophylaxis reduces the rate of DVT by approximately 60%[26]. Regional anesthesia significantly reduces as well these complications, probably in relation with its capability to generate peripheral vasodilatation and to maintaining venous blood flow in the lower extremities, as well as to promote a local inhibition of platelet aggregation and stabilization of endothelial cells[27].

### Pulmonary complications

Postoperative pulmonary complications (PPCs) were defined as anomalies of the lung resulting in an identifiable disease with adverse impact in the clinical course of the patient[28]. They are quite common (4% of patients) and suppose an increase length of stay, morbidity and mortality, in patients who had undergone hip fracture surgery. For those reasons, PPCs occurrence may predict long-term survival, particularly among patients older than 70-year-old[28]. Clinical important PPCs after hip fracture surgery comprise exacerbation of chronic lung disease, atelectasis, respiratory failure, pneumonia, pulmonary thromboembolism and acute respiratory distress syndrome[28].

A high number of PPCs risk factors have been identified, such as disorders of central nervous system, medication reducing alertness, treatment with dopamine antagonists, *etc.* Adequate postoperative fluid balance

and pain control may help to diminish PPCs by enabling earlier ambulation and improving the patient's ability to take deep breaths. Hospital-acquired pneumonia has a high incidence and an important clinical relevance in-between PPCs, being currently the second most frequent nosocomial infection[6]. In addition to other PPCs risk factors, this entity is associated to immunosenescence, a change in the immune response associated with increased age, which causes higher rates of infection and impaired wound healing[29]. Moreover, age-related changes of the lung epithelium contribute to the higher susceptibility to chest infections, since fibrillation frequency and clearance of the respiratory epithelium decrease with higher age[28]. If a chest infection occurs after hip fracture surgery, timely diagnosis, treatment and accurate monitoring are required[21].

### Gastrointestinal complications

Common postoperative gastrointestinal complications after hip fracture surgery include dyspepsia, abdominal distention, reflexes ileum and constipation[6]. Gastrointestinal postoperative stress ulcer and secondary bleeding are well documented as a medical complication after hip surgery[6], especially in patients with a history of previous gastroduodenal ulcers. Prevention of gastrointestinal bleeding with pump inhibitors, antacids, *etc*. is extremely important in this clinical situation, in order to minimize the morbidity and mortality associated with it.

### Urinary tract complications

The most common postoperative urinary tract complications after hip surgery are urinary retention, urinary infections and acute kidney injuries[6].

Controlled trials have found that patients who had scheduled intermittent catheterization immediately after surgery or their catheter removed the morning after surgery, had lower rates of urinary retention[30]. For those reasons, urinary catheters should be removed as soon as possible, though the evidence is already limited[6].

Urinary tract infections are the leading cause of nosocomial infection and affect 12% to 61% of all patients with hip fractures[31]. Urinary tract infections are considered an important delirium factor risk, and are responsible to prolong the hospital stay for another 2.5 d and even a higher mortality rate[21]. Urinary catheters are the single most important risk related to this type of postoperative infection. Therefore, indwelling catheters should be preferably removed within 24 h after insertion[32].

The incidence of acute kidney injuries (AKI) among aging patients undergoing arthroplasty for femoral neck fractures ranges from 16% to 24.4%[33]. Postoperative AKI (prerenal, renal or postrenal acute failure) is often multifactorial and may be related to pre, peri or postoperative medical or surgical factors (age, emergency surgery or longer preparation time, dehydration, malnutrition, nephrotoxic drug use, including NSAID, type of surgical procedure, chronic obstructive pulmonary disease, congestive heart disease, peripheral vascular occlusive disease, chronic kidney disease, *etc*.)[33].

If an AKI occurs after hip fracture surgery, timely treatment and accurate monitoring are required, in order to minimize the risk of permanent kidney damage[33].

### Hematologic complications

The prevalence of perioperative anemia in hip fractured patients ranges from 24% to 44%, being even higher if consider only the postoperative one (51% to 87%)[34].

Oscillation of hemoglobin during a hip fracture hospital stay can be attributed to several causes. Preoperative ones are normally related to the fracture itself, because blood loss from a hip fracture can be up to 500 mL[35], while intraoperative ones comprise fluid shifting and significant blood loss during surgery. Postoperative anemia can happen from repeated phlebotomy or hemodilutional anemia[34].

Perioperative anemia has been consistently connected to adverse events in patients undergoing hip fracture surgery. It is related to other medical complications and increased hospitalization duration, rate of readmission and death. Risk factors linked up with this bigger rate of complications include age, inadequate pre-fracture functional level, cardiovascular or pulmonary diseases, low hemoglobin, fracture type, anesthetic type (neuraxial anesthesia and associated sympathetic blockade reduces intraoperative bleeding even under normotensive conditions), length of surgery, and the degree of intraoperative bleeding[15]. Values of hemoglobin concentration $\leqslant$ 10 g/dL at admission are an independent predictor of increased mortality at 30 d in patients with hip fractures[36].

### Endocrine-metabolic complications

Malnutrition, which is in general prevalent among the elderly population, is even more frequent among patients hospitalized for hip fracture, with rates ranging from 20% to 70%[6]. Malnutrition affects many organs and corporal systems, causing sarcopenia and impairing mental, cardiac and immune function. Consecutively, patients with a protein-caloric malnutrition have higher medical and surgical complication rates (including pressure scars and perioperative infectious complications), lower functional capability and a higher mortality[6,37].

Lower values of Body Mass Index and/or triceps skinfold, albumin, retinol binding protein and cholesterol are related to malnutrition and increase in a dependent way the risk of mortality in institutionalized elderly patients[38]. Men with hip fractures have normally inferior nutritional status than women, which may be one of the factors that explain their increased mortality[38]. Several studies have found a lower acute mortality in patients with hip fracture whom a nutritional supplement is administered in the perioperative period[6].

Diabetes, either type 1 or 2, is frequent in patients with hip fracture. In fact, type 2 diabetics are 70% more likely to suffer this type of fracture. Diabetes decompensation is a quite common preoperative complication of patients that undergo hip fracture surgery, and is associated with both increased risk of asymptomatic coronary heart disease and perioperative infection.

### Other complications

Pressure scars result from an imbalance between extrinsic mechanical forces acting on skin and soft tissue, and the intrinsic susceptibility to tissue to collapse. Acute hip fractures are their most frequent causes. Close to 35% of decubitus ulcers occur at the conclusion of the first week of hospitalization.

Risk factors of pressure scars include age, malnutrition, history of smoking and systemic illnesses[34]. The use of foam or alternating pressure mattresses, special beds and equipment to relieve pressure, aggressive skin care, nursing focused on prevention, and good nutrition help prevent the evolution to ulceration[34].

### Per and postoperative mortality

Hip fracture has an overall 1 year mortality rate that varies from 14% to 36% among patients aged 65 or above, being higher among men and women, especially after 5 to 10 years after fracture[15,39], and in addition, the survivors have a shorter life expectancy[34]. Mortality is significantly influenced by preoperative cognitive state, medical comorbidities and mobility. Dementia, chronic obstructive pulmonary disease, chest infection, heart failure, anemia, abnormal sodium (low or raised), elevated urea, elevated creatinine and malignancy, have all been described as risk factors for increased mortality in the months following a hip fracture. Patients with an acute heart failure or a postoperative chest infection had a high 30-d mortality of 65% and 43%, respectively[6]. However, postoperative complications increase short and long-term mortality[3].

From the anesthetic and surgical point of view, patients with a high ASA score and patients treated non-operatively have a higher mortality rate[40]. Patients operated within 48 h appear to have a better outcome than those with a delayed surgical intervention. However, in medically unstable patients, a delay of surgery does not result in a statistically significant difference in mortality compared to patients treated surgically[15].

The Nottingham Hip Fracture Score has been validated as a useful tool to predict hip fracture mortality at 30 d. Independent predictors of mortality in patients with hip fracture included masculine sex, age > 86-year-old, two or more comorbidities, anemia, and a mini mental test score ⩽ 6 of 10[36].

Clinical and surgical decision making may be personalized to each patient according to an accurate mortality risk assessment[13]. Complication and mortality scoring systems may allow a better informed discussion between doctors and patients.

### Anesthetic complications of hip fractures

The incidence of anesthetic complications during hip fracture surgery is influenced not only by the anesthetic technique used, but also by patient comorbidities, the delay between admission and operation, and the surgical technique employed.

A number of meta-analyses report that an operative delay of over 48 h leads to increased morbidity (*e.g.*, pressure scars, pneumonia, thromboembolic phenomena) and even to increased mortality[41-43].

The most frequently-encountered anesthetic complication is arterial hypotension, defined as a preoperative drop in mean arterial blood pressure of more than 30%, or a presurgical pressure reading of 60-70 mmHg[44]. Arterial hypotension has been reported in 15%-33% of patients during the first 20 min after spinal anesthesia induction. This form of anesthesia prompts a sympathetic nervous system block, leading to decreased venous return and thus to impaired peripheral vascular resistance. But hypotension may arise independently of the anesthetic technique used: patients are often hypovolemic due to a fracture-induced loss in blood volume, to the ingestion of diuretics, or to inappropriate fluid intake resulting from immobility, dementia or other causes. All these factors can enhance the hypotensive effect of anesthetics.

Around 25% of hip fracture patients display at least one episode of cognitive dysfunction during hospitalization[42]. A systematic review published by Cochrane in 2004 suggests that the use of spinal anesthesia may reduce the incidence of postoperative confusion. Since spinal anesthesia is also associated with a lower incidence of deep venous thrombosis, recent meta-analyses recommend this as the technique of choice for hip fracture repair, as long as it is not contraindicated[42,43].

Another complication which, though much less common, may prove fatal, is the use of bone cement, which can give rise to the so-called bone cement implantation syndrome (BCIS)[42,45]. Clinical features of this poorly-understood syndrome include hypoxia, hypotension, cardiac arrhythmias, lung hypertension, and a decline in cardiac output. The cardiopulmonary complications of BCIS can be reduced through modern cementing techniques, appropriate anesthesia interventions, and adequate patient preparation, as well as by avoiding the use of cement altogether.

In short, it is impossible to apply a single protocol for hip fracture repair, valid for all patients. The protocol has to be adjusted to reflect patient comorbidities, with a view to minimizing complications. It would seem to be generally accepted, nonetheless, that hip fracture surgery should be performed within 48 h of the patient's admission to hospital, and that the patient should be provided with an appropriate analgesic, bearing in mind that in most cases the best analgesic is surgical treatment[42].

### Surgical complications of hip fractures

Complications arising from hip fracture surgery are fairly common, and vary depending on whether the fracture is intracapsular or extracapsular. The main problems in intracapsular fractures are biological: vascularization of the femoral head, and lack of periosteum -a major contributor to fracture healing- in the femoral neck. In extracapsular fractures, by contrast, the problem is mechanical, and relates to load-bearing.

Though age, comorbidities, ASA classification and delay in surgery are correlated with both medical and surgical postoperative complications and a significantly prolonged hospital stay, there is not a well-designed study

**Figure 1 Intracapsular fracture.** Non-union.

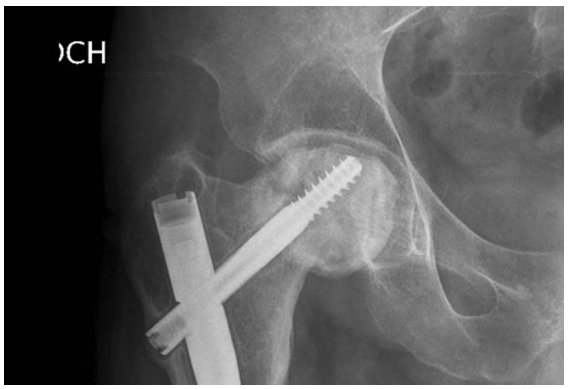

**Figure 2 Femoral head necrosis.**

**Figure 3 Total hip arthroplasty.** Dislocation.

**Figure 4 Acetabular erosion.**

that demonstrates a relation between precisely medical complications with particularly surgical ones. Nevertheless malnutrition and diabetes seem to be clearly related to deep infections. Despite the fact that osteoporosis and poor bone quality are related to some surgical complications, the most frequent concomitant osteoporotic fractures (radial and humeral fractures) seem not influence in length of hospitalization, in-hospital mortality, complication rate, and function[46].

### *Intracapsular fractures*

Two major complications may arise following treatment of an intracapsular fracture by osteosynthesis: non-unions and avascular necrosis.

Factors influencing the appearance of non-unions include patient age, degree of displacement, fracture line, degree of comminution and quality of reduction; non-unions are reported in between 10% and 45% of patients undergoing osteosynthesis[47] (Figure 1).

Avascular necrosis of the femoral head occurs in 9%-18% of patients, between two and eight years post-fracture; risk factors include the degree of fracture displacement, patient age and delay in surgical treatment[48-50] (Figure 2).

In view of the high complication rates recorded among patients undergoing osteosynthesis, often leading to repeat surgery, several works have compared arthroplasty with osteosynthesis to treat intracapsular fractures. The results indicate significantly ($P < 0.001$) lower complication and reoperation rates in patients undergoing arthroplasty[47,48]. A number of authors therefore recommend arthroplasty for the treatment of all intra-articular fractures in elderly patients. However, arthroplasty to treat the femoral neck fracture is associated with a number of complications. Dislocation (Figure 3) is most commonly seen in total hip arthroplasty. Acetabular erosion often occurs in active patients undergoing hemiarthroplasty (Figure 4); to avoid this complication, many experts recommend total arthroplasty in these patients[51]. Thigh pain is more frequently reported in uncemented arthroplasty[52]. Moreover, though uncemented arthroplasty may result in higher hip scores, it appears to carry an unacceptably high risk of later femoral fractures[53] (Figure 5).

### *Extracapsular fractures*

A number of postoperative complications have been reported following surgery for extracapsular fractures. The three most common are screw cut-out, femur fracture and implant failure.

Screw cut-out (Figure 6) occurs in between 1.1% and 6.3% of patients treated for an extracapsular fracture, and accounts for 85% of fixation failures[54]. The main causes of cut-out are fracture instability[55], and especially, the incorrect placement of the lag screw. The greatest predictor for the appearance of cut-out is the distance

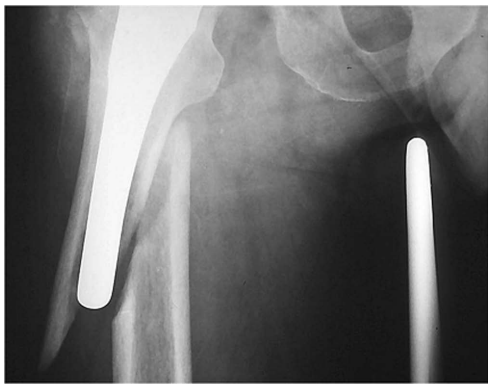

**Figure 5 Uncemented hip arthroplasty.** Femoral fracture.

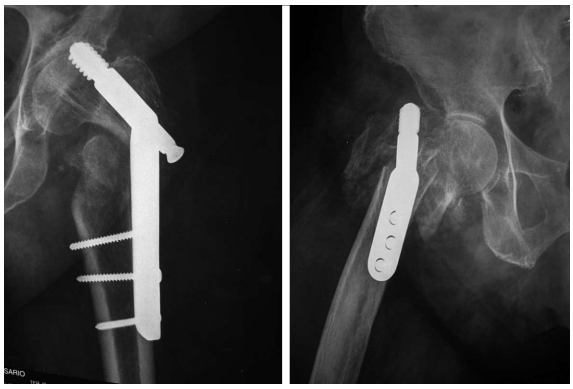

**Figure 6 Cut-out.**

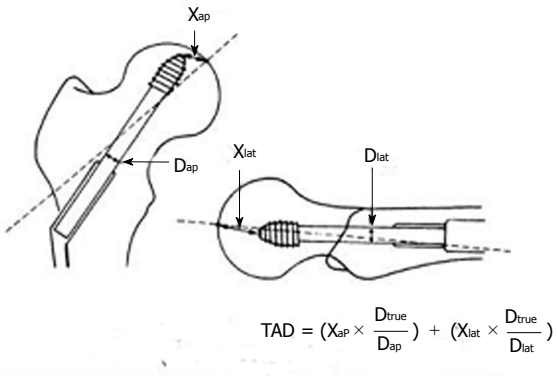


**Figure 7 Tip-apex distance.**

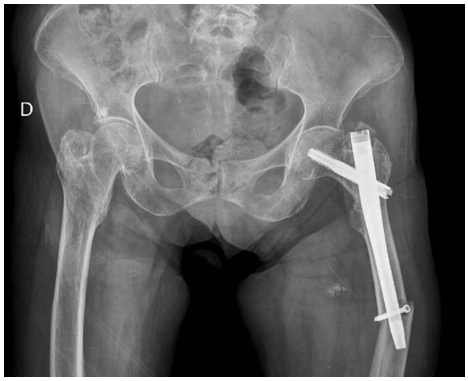


**Figure 8 Femoral fracture in intramedullary nail.**

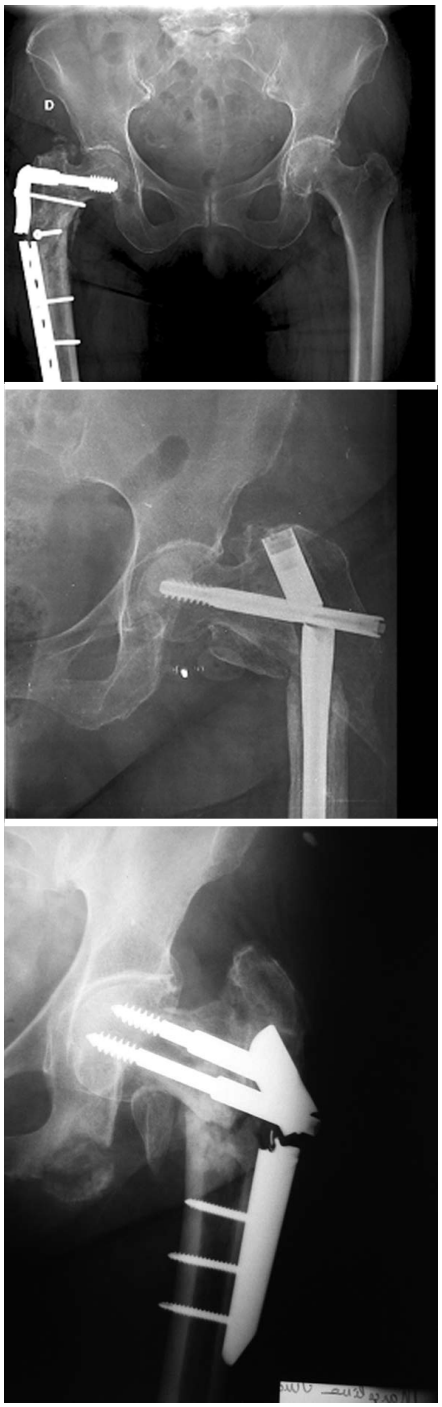


**Figure 9 Different implant failures.**

from the screw tip to the subchondral bone. Baumgaertner *et al*[56], have demonstrated the importance of screw placement and tip-apex distance (TAD) (Figure 7): when TAD was greater than 35 mm, the cut-out rate was 30%, while when TAD exceeded 45 mm, the cut-out rate rose to 60%. The best results have been reported with a TAD of less than 5 mm[49]. Equally important is the positioning of the lag screw in the femoral head, the ideal position being center-center; any other position of the screw tip leads to a higher cut-out rate, which a reportedly rise to 58%[49]. To avoid serious implant failure due to screw cut-out is largely conditioned by the ability of the surgeon

**Figure 10 Excessive screw sliding.**

to positioning the lag screw in the femoral head.

Femoral shaft fracture occurs much more frequently in patients treated with intramedullary nails, and particularly with first-generation nails with a larger distal diameter; according to one meta-analysis, these nails were associated with a femoral fracture rate of 5.3%[57] (Figure 8). Second-generation intramedullary nails, with reduced distal diameter and reduced valgus offset, have prompted a considerable decline in the incidence of femoral fractures[58]. Special mention should be made of reverse obliquity intertrochanteric fractures, in which extramedullary devices are associated with a failure rate of 36%, compared to only 5% for intramedullary nails, since the latter offer improved load-bearing capacity[59]. It should be borne in mind that reverse obliquity fractures of the proximal femur have biomechanical characteristics different from those of other intertrochanteric fractures. It is not yet clear whether nail length influences healing in these fractures[60].

Implant failure usually appears as a result of poor fracture reduction, mechanical stress or fracture instability, but may also be caused by technical error. Implant failure is more common when there is greater rigidity of the fraction fixation device (Figure 9).

Other complications are less frequently reported. Excessive screw sliding (Figure 10) has been linked to impaired postoperative mobility: patients with > 187 mm of sliding display the least postoperative mobility[54]. Thigh pain appears mainly in patients receiving first-generation intramedullary devices, and is linked to the use of two distal interlocking screws. Non-unions are much less common in extracapsular than in intracapsular fractures, and are reported mainly in severely comminuted fractures with bone loss.

## CONCLUSION

Even with optimal care, elderly trauma patients suffer a higher morbidity and mortality rate when compared with the general population, and often demand for expensive hospital aftercare. Because of that, surgical treatment of hip fracture in these patients has exceptional clinical challenges, and needs strategies to optimize patient care. Preoperative early clinical assessment helps to identify patients at high-risk and to prevent unnecessary delays. Orthogeriatric units, with a medical co-management of these patients, offer the best chance for a successful outcome, reducing length of stay, in-patient problems and mortality, allowing the patient to recover his previous ambulatory state.

Further research is necessary to evaluate those interventions and recommendations that improve medical management of aged patients with hip fractures, in order to achieve a reduction in morbidity and mortality in these at risk population.

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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (4): Hip

# Current concept in dysplastic hip arthroplasty: Techniques for acetabular and femoral reconstruction

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## Abstract

Adult patients with developmental dysplasia of the hip develop secondary osteoarthritis and eventually end up with total hip arthroplasty (THA) at younger age. Because of altered anatomy of dysplastic hips, THA in these patients represents technically demanding procedure. Distorted anatomy of the acetabulum and proximal femur together with conjoined leg length discrepancy present major challenges during performing THA in patients with developmental dysplasia of the hip. In addition, most patients are at younger age, therefore, soft tissue balance is of great importance (especially the need to preserve the continuity of abductors) to maximise postoperative functional result. In this paper we present a variety of surgical techniques available for THA in dysplastic hips, their advantages and disadvantages. For acetabular reconstruction following techniques are described: Standard metal augments (prefabricated), Custom made acetabular augments (3D printing), Roof reconstruction with vascularized fibula, Roof reconstruction with pedicled iliac graft, Roof reconstruction with autologous bone graft, Roof reconstruction with homologous bone graft, Roof reconstruction with auto/homologous spongious bone, Reinforcement ring with the hook in combination with autologous graft augmentation, Cranial positioning of the acetabulum, Medial protrusion technique (cotyloplasty) with chisel, Medial protrusion technique (cotyloplasty) with reaming, Cotyloplasty without spongioplasty. For femoral reconstruction following techniques were described: Distraction with external fixator, Femoral shortening through a modified lateral approach, Transtrochanteric osteotomies, Paavilainen osteotomy, Lesser trochanter osteotomy, Double-chevron osteotomy, Subtrochanteric osteotomies, Diaphyseal osteotomies, Distal femoral osteotomies. At the end we present author's treatment method of choice: for acetabulum we perform cotyloplasty leaving only paper-thin medial wall, which we break during acetabular cup impacting. For femoral side first we peel of all rotators and posterior part of gluteus medius and vastus lateralis from greater trochanter on the very thin flake of bone. This method allows us to adequately shorten proximal femoral stump, with possibility of additional resection of proximal femur. Furthermore, several advantages and disadvantages of this procedure are also discussed.

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**Key words:** Hip; Arthroplasty; Dysplasia; Reconstruction; Techniques; Acetabulum; Femur; Osteoarthritis; Developmental dysplasia of the hip

**Core tip:** Total hip arthroplasty (THA) in adult patients with developmental dysplasia of the hip is technically demanding procedure. In this paper we present a vari-

ety of surgical techniques available for THA in dysplastic hips, their advantages and drawbacks, ending with the author's treatment method of choice.

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## INTRODUCTION

Developmental dysplasia of the hip (DDH) is common cause of secondary hip osteoarthritis[1]. The prevalence of DDH varies among different ethnic groups; from 5.4 to 12.8% in the Danish population, 1.8% in Koreans, 2.4% in Turkish people and 7.3% in Singaporeans[2]. The aetiology of DDH is multifactorial, involving both genetic and intrauterine environmental factors. The group of patients at risk includes those with one or combination of the following risk factors: female gender, first born, positive family history or ethnic background, breech delivery, oligohydramnios, torticollis, and lower-limb deformity[3]. Despite new-born screening programs[4], some cases are missed, or incorrectly treated. These patients develop secondary osteoarthritis and eventually end up with total hip arthroplasty (THA) at younger age. Due to changed anatomy of dysplastic hips, THA in these patients is technically very demanding procedure[5-7]. Functional results after THA in dysplastic hips are often not excellent[8,9]. At the beginnings of modern arthroplasty it was considered that THA in these patients is not possible[10]. Better surgical techniques were developed over time to achieve a painless, stable and long-lasting hip endoprosthesis customized to increased functional needs of these young patients. In this paper we present a variety of surgical techniques available for THA in dysplastic hips, their advantages and drawbacks, ending with the author's treatment method of choice[7].

## ANATOMY AND BIOMECHANICS OF DYSPLASTIC HIP

Anatomy of dysplastic hip is usually significantly altered. Acetabulum and femur are underdeveloped and femur is often displaced. Hip biomechanics is altered and there is no ideal stimulation for development of proper acetabulum and proper femoral head. Different morphological alterations are seen, not only on femur and acetabulum but also on pelvis[11-13]. In simplest degrees of dysplasia acetabulum is just a little bit shallower with lover acetabular angle but in the most complex cases of dysplasia acetabulum is underdeveloped, shallow and lacking bone stock medially. Since femoral head is situated more proximal (dislocated), a new acetabulum (neoacetabulum) is

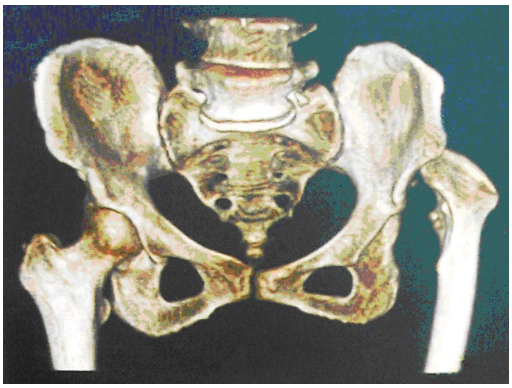

**Figure 1 On the right side hip is normally developed and on the left side the acetabulum is underdeveloped, shallow and lacking bone stock medially and at the level of normal (ideal) acetabular roof.** The femoral head is more proximal (dislocated) with increased anteversion, shorter neck and narrower and straighter femoral canal.

formed (Figure 1). Pelvic bone stock is rearranged and there is more bone thickness available more posteriorly in relation to the level of the true acetabulum[13]. Acetabular retroversion represents additional problem. Incidence of acetabular retroversion in dysplastic hips ranges from 1 in 6 according to Li *et al*[14] to 1 in 3 according to Mast *et al*[15]. Dysplastic femur has increased anteversion, shorter neck and narrower and straighter femoral canal[16,17]. Femoral head is elliptic which causes incongruity of the hip joint[17]. All of mentioned alterations in dysplastic hip anatomy are responsible for functionally "weaker" hip joint unable to withstand increased load. In short, dysplastic hips are incongruent, centre of rotation is displaced, hip abductors and flexors are shortened and weakened. If dysplasia is one-sided, pelvic disbalance is often present with limping and leg length discrepancy. All of these factors can increase forces in hip joint, which can cause quicker deterioration of cartilage and bone tissue with earlier onset of osteoarthritis of the hip joint[10,18].

## CLASSIFICATION OF DYSPLASTIC HIP

There are different classifications of dysplastic hips in adults. Those classifications are developed so that different treatments can be compared and so that the surgeon can plan and prepare operation and predict outcome based on the degree of dysplasia. Since in majority of the cases the diagnosis is formed based on the clinical exam and X-rays, most common classifications are based on X-rays of the pelvis and the hips. The most common is classification according to the Crowe[19] with 4 different degrees of dysplasia (Figure 2). There are more recent classification like Eftekhar[20] and Hartofilakidis *et al*[11,21] which take into account both femoral and acetabular side. Hartofilakidis *et al*[11] acknowledged importance at the acetabular side for operative treatment so in 1988 he based his classification on relations between femoral head and acetabulum and the difference between true and false (neo) acetabulum[11]. Then, in 2008, he additionally developed his classification by adding subtypes regarding to

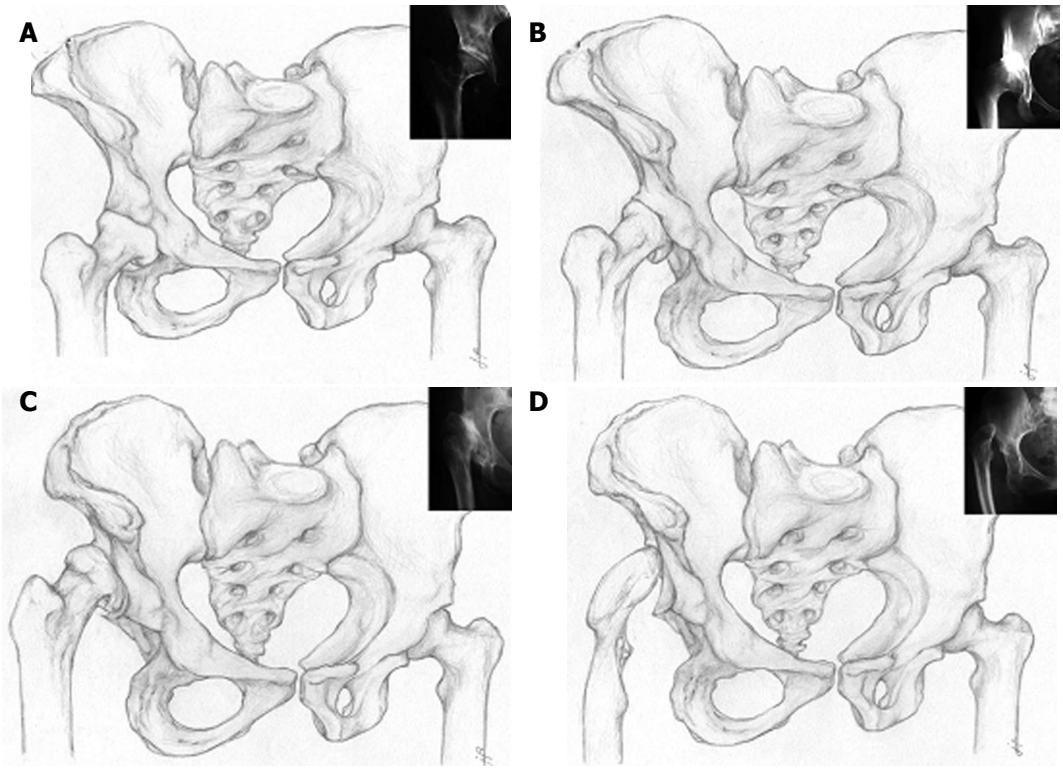


**Figure 2 Left hip is normal, right hip is dysplastic.** A: Crowe type 1-proximal head subluxation is less than 50% of vertical diameter of the femoral head (less than 10% of the pelvic height); B: Crowe type 2-proximal head subluxation is between 50% and 75% of vertical diameter of the femoral head (between 10% and 15% of the pelvic height); C: Crowe type 3-proximal head subluxation is between 75% and 100% of vertical diameter of the femoral head (between 15% and 20% of the pelvic height); D: Crowe type 4-proximal head dislocation with proximal movement of the femoral head for more than 100% of vertical diameter of the femoral head (head is moved proximally for more than 20% of the pelvic height).

the shape of the acetabulum[12]. This classification is very useful for surgeon but requires additional education and is more complicated. Special imaging modalities, including computed tomography (CT) of the hip, may be useful in complex hip arthroplasty. CT provides 3-dimensional information about anterior and posterior column deficiencies, socket size, thickness of the anterior and posterior walls and medial bone stock (thickness) at the level of the ideal acetabular roof which help us in preoperative planning[22]. Although Crowe classification is based on two-dimensional analysis of the pelvic X-ray and on, basically, just a vertical displacement of the femoral head, it is still predominant classification due to simplicity and availability.

## OPERATIVE TECHNIQUES IN DYSPLASTIC HIP ARTHROPLASTY

Secondary osteoarthritis due to DDH occurs at a younger age because of abnormal anatomy (an average of 53 years according to Hartofilakidis *et al*[23]). The key point of surgical treatment is to ensure long-term stability of the endoprosthesis by restoration of anatomical and biomechanical relationships. This is not an easy task because total hip arthroplasty in DDH is technically demanding due to deficient acetabular bone stock, abnormal femoral anatomy with increased neck-shaft angle and valgus orientation, increased anteversion, muscle contracture and leg-length discrepancy[10,24]. Despite an initial discouraging statement that THR should be avoided in patients who have DDH, various techniques have been developed to approach this problem[10]. The surgeon has to address several issues. Distorted anatomy of the acetabulum and proximal femur is always a challenge. Then there is a leg length discrepancy. And finally, since majority of patients are at younger age, the soft tissue balance is of great importance (especially the need to preserve the continuity of abductors) to maximise postoperative functional result[7,25]. Technical options are numerous (Table 1).

### *Surgical alternatives to THA*

There are also alternatives to THA in dysplastic hips such as pelvic osteotomies[14,26]. Pelvic osteotomies may provide excellent results for patients with early or no osteoarthritis and with moderate or no pain. The purpose of the pelvic osteotomy is to obtain an increased acetabular weight-bearing surface for the femoral head either by reshaping the acetabulum or by enlarging its margins. Different types of osteotomies are described in literature[14,26]. In the past, procedures such as the Chiari osteotomy or shelf augmentation of the acetabulum were used to treat adolescent and adult hip dysplasia but today realignment osteotomies would be used since they result with the reposition or acetabulum into a more favorable position over the femoral head and improve load distri-

**Table 1 Different operative treatment options for total hip arthroplasty in secondary hip osteoarthritis in developmental dysplasia of the hip**

| Techniques for acetabular reconstruction | Techniques for femoral reconstruction |
|---|---|
| Standard metal augments (prefabricated) | Distraction with external fixator |
| Custom made acetabular augments (3D printing) | Femoral shortening through a modified lateral approach |
| Roof reconstruction with vascularized fibula | Transtrochanteric osteotomies |
| Roof reconstruction with pedicled iliac graft | Paavilainen osteotomy |
| Roof reconstruction with autologous bone graft | Lesser trochanter osteotomy |
| Roof reconstruction with homologous bone graft | Double-chevron osteotomy |
| Roof reconstruction with auto/homologous spongious bone | Subtrochanteric osteotomies |
| Reinforcement ring with the hook in combination with autologous graft augmentation | Diaphiseal osteotomies |
| Cranial positioning of the acetabulum | Distal femoral osteotomies |
| Medial protrusion technique (cotyloplasty) with chisel | |
| Medial protrusion technique (cotyloplasty) with reaming | |
| Cotyloplasty without spongioplasty | |

bution. Their main advantage is that the femoral head is covered with hyaline cartilage instead of fibrocartilage. Their disadvantage is the complexity of the operations. Some of them are used only when the triradiate cartilage is open like Pemberton and Dega osteotomies. Others are single innominate osteotomy of Salter, the triple innominate osteotomies of Steel, Carlioz, and Tönnis and the periacetabular osteotomy of Ganz. The major disadvantage is that when there is advanced osteoarthritis of the dysplastic hip only THA can completely relieve the pain and restore the function of the hip joint.

### Acetabular reconstruction

The major concern with total hip arthroplasty in DDH is the containment and incorporation of the acetabular cup. Placement of the cup is technically difficult because normal anatomic landmarks are obscured. There is a need for fine balance in adjusting the cup size, inclination, cup anteversion and coverage. A compromise can be made by setting acetabular component away from the ideal centre of rotation, but in such a way to ensure a good stability of the endoprosthesis. High placement of the acetabular component has been proposed (Figure 3A). Russotti *et al*[27] reports good long-term results with "high hip centre" acetabulum placement. Kaneuji *et al*[28] shows no differences in polyethylene wear with rotation centre placed 20 mm proximal from the figure of tears. However, according to Bicanic *et al*[29] one has to take into account that for every millimetre of proximalisation, load on the hip increases for about 0.1%. At this level bone stock is usually insufficient and the lever arm for body weight remains much longer than that of the abductors, resulting in excessive loading of the hip joint. In addition, at this level, shearing forces acting on the acetabular component may lead to an early loosening, and in unilateral cases a proximally placed acetabular component contributes to limping and limb-length discrepancy[23,30,31]. Placement of the acetabular component in the anatomical position and augmentation of the superior segmental defect with structural autologous graft (autograft) or allograft has also been proposed (Figure 3B). Cementless acetabular cups with 30% to 40% of uncoverage may be acceptable[32-34], more than that should be covered. Some authors recommend spongioplasty of the acetabular roof for smaller uncovered areas (Figure 3C)[35]. For larger defects structural autograft or allograft can be used. Autografts can be free or vascularized. For vascularized autografts it is expected to better integrate with iliac bone (Figure 3D)[36]. Usually vascularised iliac graft is used, although Fujiwara reported good outcome of acetabular roof reconstruction with free vascularized fibular graft[37]. Long-term survival rates of such bone grafts proved to be different in various studies. While some authors report good long-term results of free auto- or allografts[24,38,39] and vascularized autografts[37,40-42], others warn about graft resorption and secondary instability of acetabular component in structural bone grafting[43-45]. Acetabular bone stock deficiency can be managed with specially constructed acetabular components or using special 3-dimensional porous materials which simulates bone structure and allow faster and better endoprosthesis–bone integration (Figure 3F)[46-48]. For that purpose trabecular metal is used in form of acetabular cup or trabecular metal augments. That is manly used in revision surgery, but can be useful in dysplastic hip THA[48,49]. Potential advantage of trabecular metal is to avoid the use of structural bone grafts, avoid the need for custom shaped implants and provide excellent bone ingrowth on small contact area. Major disadvantage is potential difficulty if the cup should be removed because of infection. Oblong-shaped cementless implant (oblong cup) can be used for acetabular reconstruction. Abeyta *et al*[50] presented satisfactory long-term results in using oblong cup for reconstruction of the acetabulum. The reinforcement ring with the hook in combination with autologous graft augmentation has been designed for cases with severe bone-stock deficiencies (Figure 3E)[51,52]. This technique enables reconstruction of the anatomic hip centre by positioning the hook around the inferior margin of the acetabular floor (incisura acetabuli). The hook does not act as a fixation device but helps prevent high or lateral placement of the ring and helps adequate coverage of the polyethylene liner, regardless of the degree of anatomical deformity. Pitto *et al*[53] presented how reinforcement ring with hook

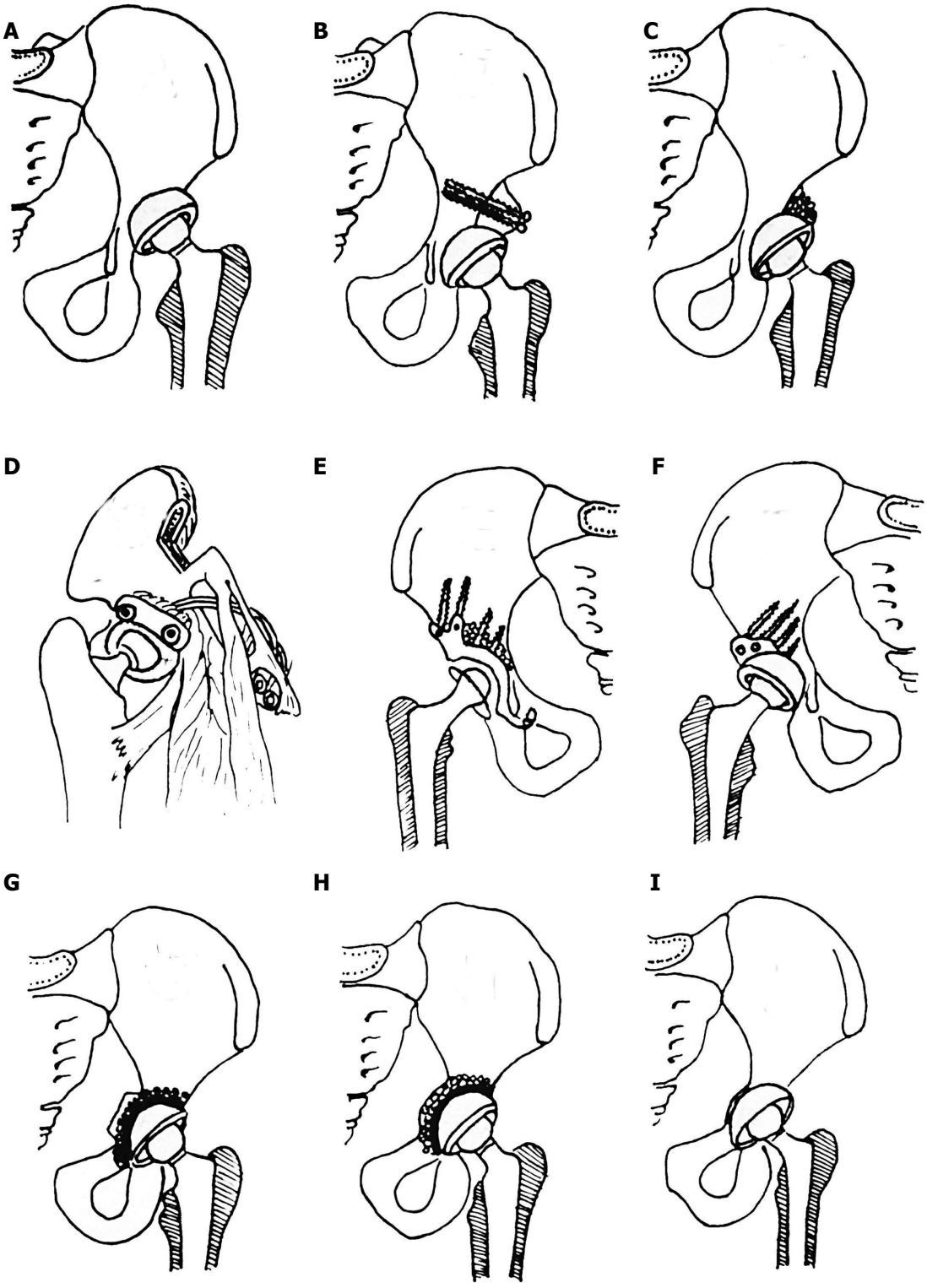


**Figure 3 Different options for acetabular reconstruction.** A: Higher placement of the acetabular cup; B: Placement of the acetabular component in the anatomical position and augmentation of the superior segmental defect with structural autograft or allograft fixed with screws; C: Placement of the acetabular component in the anatomical position and spongioplasty of the acetabular roof for smaller uncovered areas (30%-40%); D: Anatomical position of acetabular cup and augmentation of the superior segmental defect with vascularised iliac graft; E: Reinforcement ring with the hook in combination with autologous graft augmentation for cases with severe bone-stock deficiencies. Anatomic hip centre is reconstructed by positioning the hook around the inferior margin of the acetabular floor. The hook prevents high or lateral placement of the ring and helps adequate coverage of the polyethylene liner, regardless of the degree of anatomical deformity; F: Acetabular bone stock deficiency can be managed with specially constructed acetabular components or using special 3-dimensional porous materials which simulates bone structure and allow faster and better endoprosthesis-bone integration. For that purpose trabecular metal (tantalum) is used in form of acetabular cup or trabecular metal augments. Oblong-shaped cementless implants can be used for acetabular reconstruction; G: Cotyloplasty with chisel - intentional medial wall fracture using osteotome with cup placement beyond the ilioischial line with bone grafting; H: Cotyloplasty with reamer - first, perforation of the medial acetabular wall with a reamer is performed, then acetabulum is filled with a large amount of autogenous cancelous bone graft and cup is cemented in position without pressure; I: Cotyloplasty without spongioplasty - implantation of porous-coated cementless acetabular components without spongioplasty.

provides adequate stability in poor bone-stock settings and prevents bone graft resorption showing good mid-term results of this kind of treatment. According to fact that medialisation of acetabular cup decreases hip load and that satisfactory supero-lateral support of the component with host bone is a better option, a method named cotyloplasty was introduced. Later, in 2008 Bicanic *et al*[29] proved that every millimetre of lateral displacement of the acetabular cup (relative to the ideal centre of rotation) results with an increase of 0.7% in hip load, and for every millimetre of proximal displacement an increase of 0.1% in hip load should be expected (or decreased if displacement is medial or distal). That suggest acetabular placement as far medially as possible for optimal results. Cotyloplasty is a technique that involves making a perforation of the medial wall of a shallow acetabulum and then inserting an acetabular cup with the medial aspect of its dome beyond the Kohler's line. In 1976, Dunn *et al*[54] presented a method that involved intentional medial wall fracture using osteotome with cup placement beyond the ilioischial line, avoiding bone grafting but still achieving cemented acetabular cup stability (Figure 3G). At the meeting of the Greek Orthopaedic Association in 1984, technique of cotyloplasty for the preparation of the acetabulum was reported by Hartofilakidis *et al*[11]. This method involved the use of a T-handle curette to enlarge the socket. When the acetabulum was large enough they fracture the paper-thin medial wall using a deepening reamer. Acetabulum was filled with a large amount of autogenous cancelous bone graft and cup is cemented in position without pressure. Hartofilakidis *et al*[11,12] modified this method by perforating the medial acetabular wall with a reamer instead of an osteotome and called the technique cotyloplasty (Figure 3H). Satisfactory reports were published later concerning the results of implanting cemented cups using cotyloplasty. Dorr *et al*[55] reported good results when implanting porous-coated acetabular components using this technique. Cotyloplasty has advantages over other techniques of fixing an acetabular component in a dysplastic acetabulum. This technique has advantages over superior cup placement because it usually restores the normal hip joint biomechanics, it restores the leg length discrepancy and it has less chance of impingement that may lead to dislocation. Major disadvantage of the cotyloplasty is that it is difficult to control the amount of the medial wall fracture and complication such as fracture-dislocation of the cup inside the pelvis can occur.

### Preoperative skeletal traction

According to fact that long term stability of the prosthesis with better abductor function and leg-length equalization is best achieved by placing the endoprosthesis near the normal anatomic level, some authors suggests iliofemoral distraction to reduce high congenital dislocation of the hip before THA[56,57] (Figure 4A). Grill was the first to describe the application of distraction between the ilium and femur before open reduction for DDH in children[58]. Lai *et al*[56] used Wagner's apparatus for distraction, and showed how laxity after distraction and close-to-normal position of the femur to the acetabulum made THA much easier than in those performed without distraction. Operative time, blood loss, and surgical complications were reduced, and the functional results were as good as those of ordinary THA. Holinka *et al*[57] modified surgical procedure according to Lai *et al*[56], with immediate femoral head resection and extensive soft tissue release prior to distraction and showed satisfying five-year results in unilateral and bilateral Crowe type IV high hip dislocations. Complications, such as pin tract infection, peroneal nerve palsy, cup protrusions are described for such procedures[57].

### Femoral reconstruction

According to the Crowe classification, arthroplasty procedures performed on dysplastic hips that belong to Crowe I or Ⅱ class allow positioning of femoral head in optimal hip rotation centre without performing any of the femoral shortening procedures. In contrast, arthroplasty procedures performed on Crowe Ⅲ or Ⅳ dysplastic hips commonly require one of the femoral shortening procedures. However, here we have to emphasize that this is not a real "clear cut" division whether to perform femoral shortening or not since in Crowe I and Ⅱ dysplastic hips the complex deformities and variations of the dysplastic femur may be present and thus require femoral shortening procedure.

After placement of the acetabular component in anatomic position femur often becomes too long and needs to be shortened. Thus, shortening femoral osteotomies are developed, which further allow both: (1) hip arthroplasty without sciatic nerve stretching; and (2) correction of the proximal femoral anteversion. After these procedures are performed, abductor mechanism of the hip is restored with equal final leg length[59]. Femoral procedures can be roughly divided according to the level of procedure: proximal femur, femoral shaft and distal femoral procedure.

One of the most commonly performed procedures on proximal femur during THR includes trochanteric osteotomies. Trochanteric osteotomies in total hip arthroplasty were first introduced by Charnley[60] in 1972. Over long period of time several modifications of the initial procedure were developed such as changes in shape of skin incision, different approach to the hip, instrumentation etc. These procedures are nowadays reserved mainly for complex primary hip arthroplasty procedures (including arthroplasty in DDH) or complex revision procedures of THR. Trochanteric osteotomies have several major advantages. First, they provide excellent visualization of both, femur and acetabulum, *i.e.*, whole operating region. Second, by performing trochanteric osteotomy abductor mechanism of the hip is preserved and easily repositioned back to original position, altogether resulting in stable hip without risk for dislocation. An example of modified trans-trochanteric approach technique was

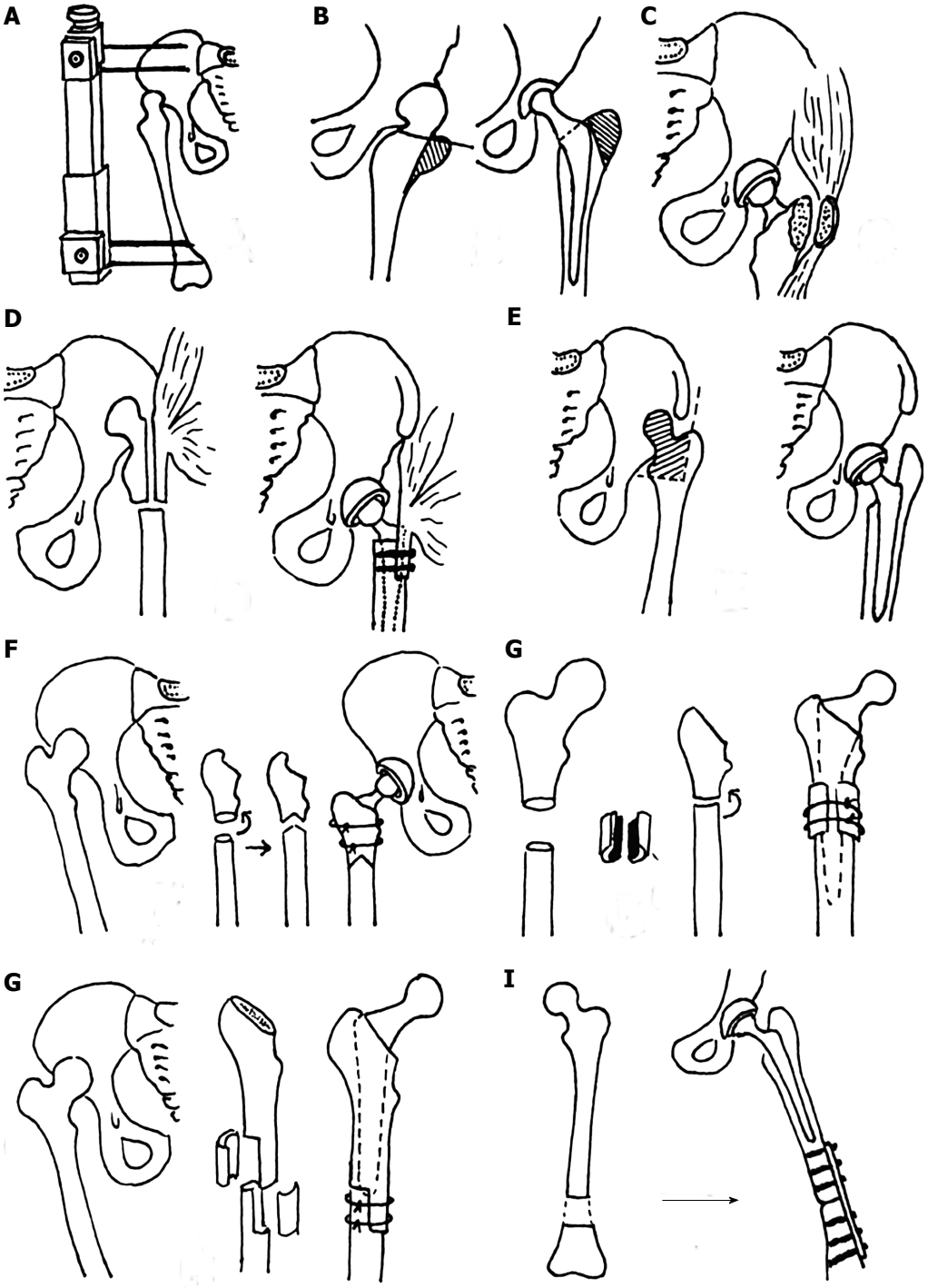


**Figure 4 Different types of femoral reconstruction options.** A: Wagner's apparatus for preoperative skeletal traction to reduce high congenital dislocation of the hip before total hip arthroplasty; B: Trochanteric osteotomy in total hip arthroplasty; C: Delimar *et al*[7] modification of the direct lateral approach to the hip. Anterior half of the continuous tendon is detached either by cautery or with a chisel. If the chisel is used, a thin layer of bone from the greater trochanter remains attached to the continuous tendon of the gluteus medius and the vastus lateralis. The posterior half of the continuous tendon of the gluteus medius and the vastus lateralis is always detached with the chisel leaving a bone flake of at least 2 to 3 mm thickness attached to tendons. In that way, the abductor muscles are stripped from the greater trochanter and there is no trochanteric osteotomy during the approach, which allows preservation of the continuity of the abductor muscles; D: Paavilainen's procedure of metaphyseal shortening osteotomy combined with distal sliding of the greater trochanter with intact attachment of the abductor muscles; E: Progressive femoral shortening at the level of lesser trochanter; greater trochanter remains intact, thus providing better functional results; F: Combined procedure of femoral subtrochanteric shortening with derotational double-chevron osteotomy. Transverse osteotomy was first performed, followed by rotational alignment in order to correct anteversion. Later, double chevron osteotomy was performed. Such method allows intraoperative derotation and shortening adjustment; G: Subtrochanteric osteotomy - modified technique; osteotomy sites were covered with onlay grafts of the excised fragments and fixed with two cerclage wires; H: Diaphyseal step-cut shortening osteotomy performed after reaming and stabilized with two to three cerclage bands with or without bone grafting. After stabile fixation, intramedullary reaming is done until optimal cortical contact is achieved, especially distal to the osteotomy site; I: Distal femur shortening procedure. First, total hip arthroplasty with acetabulum in anatomic position is performed followed by the femoral shortening that is done distal to stem so that the first screw of the plate would be more than 2 cm from the stem. Later, plate fixation of the femoral osteotomy site was performed.

presented by Kerboull *et al*[61] in 2007. These authors describe transtrochanteric approach as a method which allows easier hip dislocation with good visualization of the operating region and preserved hip abductory mechanism. This approach was also offered as one of the solutions in treatment of severe femoral deformities present in DDH. Namely, transtrochanteric approach allows performance of corrective osteotomies in the area of femoral metaphysis. Such procedure together with reposition of abductory muscles provide near-optimal anatomic relations in operated hip[61] (Figure 4B). Despite these evidences this approach is still controversial and under debate because of unclear conclusion about relatively high rate of around 6% of nonunion of greater trochanter after such procedures[61-64]. Paavilainen *et al*[32] reported procedure of femoral shortening on proximal femur during THR in DDH in 1990 - method included a cementless THR procedure where the acetabular cup is placed in anatomic position together with proximal femur shortening osteotomy with distal sliding of the greater trochanter (Figure 4D). Thorup *et al*[65] reported in 2010 a follow-up of 1.5 to 10 years after Paavilainen procedure on 19 hips with relatively low rate of complications reported after this procedure. Lesser trochanteric osteotomies represent method of progressive femoral shortening at the level of lesser trochanter in order to provide optimal positioning of acetabular cup in anatomic centre in patients with DDH (Figure 4E). Major advantage of this procedure is the fact that greater trochanter remains intact, thus providing better results and potentially lower rate of complications[66]. Bao *et al*[66], 2013 evaluated the efficacy of lesser trochanteric osteotomy for femoral shortening in total hip arthroplasty in treatment of 28 cases of Crowe Ⅳ DDH. After follow-up period of 55.3 mo method was proven to be safe and effective since complications were rare - sciatic nerve palsy was reported in two hips and positive Trendelenburg sign in two hips at the final follow-up. According to report of Bao *et al*[66] lesser trochanteric osteotomy could serve as valuable solution for femoral shortening in DDH; however, larger groups with longer follow-up are needed in order to bring up propper conclusion. In 2008 we described a modification of the direct lateral approach to the hip, which enables excellent exposure of both, femur and acetabulum and presents an optimal approach through which it is easy to shorten the proximal femur and neutralize leg length discrepancy[7] (Figure 4C). First, anterior half of the continuous tendon is mobilized either by cautery or with a chisel. If the chisel is used, a thin layer of bone from the greater trochanter remains attached to the continuous tendon of the gluteus medius and the vastus lateralis. The posterior half of the continuous tendon of the gluteus medius and the vastus lateralis is always detached with the chisel leaving a bone flake of at least 2 to 3 mm thickness attached to tendons. In that way, the abductor muscles are stripped from the greater trochanter and there is no trochanteric osteotomy during the approach, which allows preservation of the continuity of the abductor muscles. This approach eliminates the necessity for osteotomies of the trochanter and transverse cuts or detachment of the abductor muscles, thus reducing incidence of relatively often complications related to those method[7].

Shortening procedures performed on femoral metaphysis (subtrochanteric osteotomies) are the most frequently used procedures for femoral shortening in DDH. Double Chevron osteotomy was first described by Becker *et al*[67] in 1995, where total hip arthroplasty was combined with a femoral subtrochanteric shortening derotational double-chevron osteotomy in DDH. First results were promissing, but method of Becker and Gustilo did not allow any intraoperative changes and required complex and detailed preoperative planning that was sometimes hard to perform during surgery. Several modification of the first technique were reported so far, such as the one from Li *et al*[59] where transverse osteotomy was first performed, followed by rotational alignment in order to correct anteversion. Later, after vertical alignment (length) double chevron osteotomy was performed at the site of the previous transverse osteotomy (Figure 4F). Such method allowed more precise (intraoperative) derotation and shortening adjustment. Several authors with several differences in techniques described transverse subtrochanteric osteotomies. First, Reikeraas *et al*[68] presented transverse osteotomy in 25 cases, with the use of 4 cemented stems and 21 noncemented stems. The torsional stability was not performed with any fixation. Surprisingly, at 3-7 years later 96% satisfactory results were reported, with no revision procedures or mechanical complications and only 1 delayed union and 1 varus malunion. Similar to this procedure, Yasgur *et al*[69] reported in 1997 modified techique with enhanced torsional stability with noncemented fully porous-coated stems, press-fit into the diaphysis and augmented with allograft struts and cables on 9 patients. After 2-7 years period 1 patient suffered nonunion of the osteotomy site and one had failure of a distally ingrown porous device, which required revision. Later on, Masonis *et al*[70] supported the use of a transverse subtrochanteric femoral osteotomy in high DHH with secondary arthritis. 5 years after the procedure was performed a follow-up report was published where authors concluded that the transverse osteotomy union rate was identical to the report using a step-cut method[71]; with one important advantage - it allows intraoperative adjustment of femoral anteversion correction. On the other side, cemented total hip arthroplasty with subtrochanteric transverse osteotomy for Crowe group Ⅳ HDD was described by Kawai *et al*[72] in 2011. Authors descibed procedure where shortening osteotomy sites were covered with grafts of the excised fragments fixed with cerclage wires (Figure 4G). Authors presented good short-term results without significant complications. Bruce *et al*[73] reported in 2000 a femoral shortening technique with use of straight cylindrical prosthesis that acts as an intramedullary nail. Such prosthesis provides stability control of the distal fragment. First, femoral osteotomy was performed with prosthesis *in situ*, then,

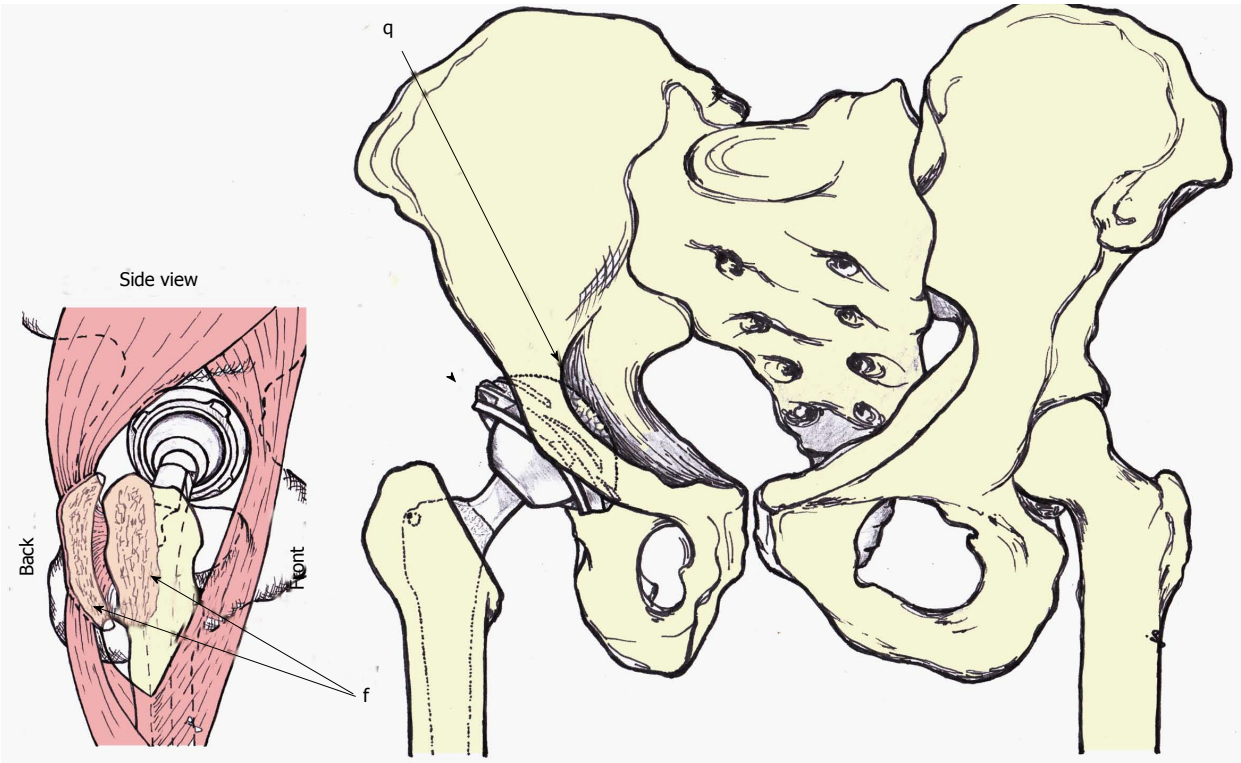


**Figure 5 Anterior-posterior and latero-lateral (side) view of the author preferred method of treatment.** Anterior-posterior view - acetabular cup is medialized (cotyloplasty) so that the dome of the cup is protruding beyond Kohler's line inside the pelvis (q marked with single arrow). Superolateral part of the cup is uncovered by the bone (marked with arrowhead). The cup is usually additionally secured with the screws (not show on the picture). latero-lateral (side) view-posterior part of the gluteus medius and vastus lateralis together with the external rotators are detached with the chisel on a thin flake of bone (f marked with double arrows). This is a modified direct lateral approach.

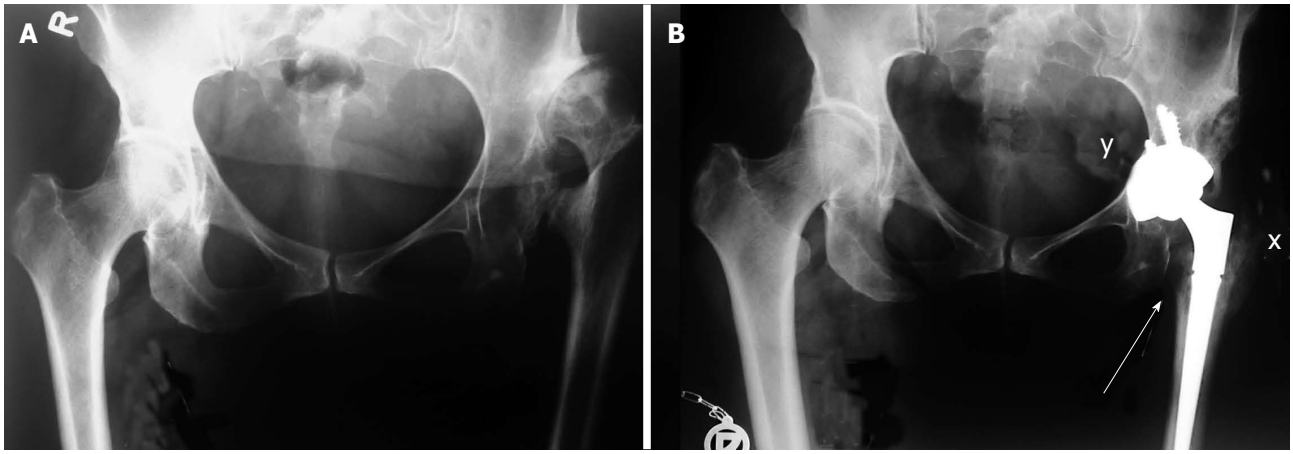


**Figure 6 X-rays of patient with Crowe type 4 dysplasia on the left side and normal hip on right side.** A: Preoperative X-ray with secondary osteoarthritis due to dysplasia, neoacetabulum formed superolaterally from original, true acetabulum and significant leg length discrepancy; B: Postoperative X-ray with implanted uncemented acetabular cup and femoral stem. Acetabular cup is protruding beyond the Kohler's line inside the pelvis (marked with y) and secured with 3 additional screws. Lesser trochanter is brought distally to the normal level so there is no leg length discrepancy postoperatively (marked with a single arrow). Modified direct lateral approach was used and posterior part of the gluteus medius and vastus lateralis together with the external rotators were detached with the chisel on a thin flake of bone, now they are completely attached and healed to greater trochanter (marked with x).

prosthesis was advanced distally and morcellized autologous bone-graft was applied to the osteotomy site. In that way, one of the most important complications after femoral shortening procedure: nonunion of the osteotomy site - was reduced to a minimun[69,72]. This method has all the characteristics of a simple, reliable and flexible surgical technique. Togrul *et al*[74] in 2010 presented a similar technique of femoral fixation that uses a transverse osteotomy for subtrochanteric shortening with the use of bone pegs prepared from the resected femoral segments which are then placed in the medullar canal around the stem thus providing femoral fixation. Authors reported 21 case with adequate union present in all cases, and early dislocation in only 2 cases.

Shortening procedures performed on femoral diaphysis were reported by Sener *et al*[71] in 2002, where proximal diaphyseal step-cut shortening osteotomy was performed after femoral reaming. Afterwards, step-cut was stabilised with two to three cerclage wires with the use of bone grafting. After fixation, intramedullary femoral reaming was continued until satisfactory cortical contact was achieved. Special attention was focused on the tight contact in distal fragment of the osteotomized femur (Figure 4H). Authors presented very good 5-year follow-up results. Results of very similar method with promising short-term to mid-term results for a Crowe's group IV DDH in adult patients were reported by Makita *et al*[75] in 2007. Later on, Neumann reported the results of very similar technique, but did not use any of the bone grafting techniques at the osteotomy sites[76].

Koulouvaris *et al*[77] reported in 2008 an interesting combined procedure where distal femoral shortening procedure was performed as an addition to THR of dysplastic and difficult-to-reduce hips. Authors used newer technologies such as the use of customized femoral implants and the use of 3D CT scan as an important tool in preoperative planning[77]. First, total hip arthroplasty with placement of acetabulum in anatomic position was performed. Then, femoral shortening procedure was performed on distal femur in the way that the first screw of the plate would be more than 2 cm separated from the femoral stem. The fixation of the femoral osteotomy was achieved with LC-DCP titanium femoral plate (Figure 4I). One of the major advantages of this technique is the possibility of conjoined correction of the ipsilateral knee valgus deformity, which can be performed simply by changing the shape of osteotomized fragment. In that case, regular fixation for valgus osteotomy of the knee was performed. Twenty-four patients were reported in the study, with follow-up period of 4.5 years. Authors reported excellent results: only 1 delayed union was observed, which resulted in malunion after 9 mo.

As shown above, large number of the femoral shortening procedures is described in literature. However, we have to emphasize that anatomical deformities on the femoral sides of dysplastic hip often require combined correction procedures that are frequently very challenging. According to our and other author's opinion, such procedures often require detailed preoperative planning combined with experienced surgeon's skills[78].

## CONCLUSION

For severe dysplastic hips, Crowe type Ⅲ and Ⅳ, we perform THA through modified direct lateral approach[7] and then we clean and prepare the acetabulum at the level of the ideal centre of rotation. Even though advantages of the modified approach are numerous one has to take into account that this approach cannot be extended proximally more than 3-4 cm above the tip of greater trochanter and there are some patients that develop pain over greater trochanter. Since there is always lack of bone mass at the level of the ideal acetabular roof, we perform cotyloplasty leaving only paper-thin medial wall, which we break during acetabular cup impacting (Figure 3I and Figure 5). In this way our acetabular dome is always protruding beyond Kohler's line in the pelvis but with solid primary stability, which we additionally improve by placing 2-3 screws in the superior direction. One has to be aware, as mentioned before, that it is difficult to control the amount of the medial wall fracture and complication such as fracture-dislocation of the cup inside the pelvis can occur. Superolateral area of the acetabulum is left uncovered as much as needed, even more than 30%. Then we proceed with femoral shortening according to Delimar *et al*[7]. First we peel of all rotators and posterior part of gluteus medius and vastus lateralis from greater trochanter on the very thin flake of bone. Then we shorten proximal femoral stump as much as it is necessary. After femoral broaching and trial reposition we can additionally resect proximal femur. When final components are placed, abductors are sutured (anterior and posterior part one to another but not to the greater trochanter) and leg is lengthened. Postoperative X-rays are taken (Figure 6). Rehabilitation starts on the second day with the same rehabilitation protocol as for any standard THA (when elongation of more than 5 cm is performed than for the first few days extension is not forced). After 4 to 6 wk full weight bearing is allowed but muscle strengthening is continued for additional 6 mo.

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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (5): Knee

# Positioning patients for spine surgery: Avoiding uncommon position-related complications

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## Abstract

Positioning patients for spine surgery is pivotal for optimal operating conditions and operative-site exposure. During spine surgery, patients are placed in positions that are not physiologic and may lead to complications. Perioperative peripheral nerve injury (PPNI) and postoperative visual loss (POVL) are rare complications related to patient positioning during spine surgery that result in significant patient disability and functional loss. PPNI is usually due to stretch or compression of the peripheral nerve. PPNI may present as a brachial plexus injury or as an isolated injury of single nerve, most commonly the ulnar nerve. Understanding the etiology, mechanism and pattern of injury with each type of nerve injury is important for the prevention of PPNI. Intraoperative neuromonitoring has been used to detect peripheral nerve conduction abnormalities indicating peripheral nerve stress under general anesthesia and to guide modification of the upper extremity position to prevent PPNI. POVL usually results in permanent visual loss. Most cases are associated with prolonged spine procedures in the prone position under general anesthesia. The most common causes of POVL after spine surgery are ischemic optic neuropathy and central retinal artery occlusion. Posterior ischemic optic neuropathy is the most common cause of POVL after spine surgery. It is important for spine surgeons to be aware of POVL and to participate in safe, collaborative perioperative care of spine patients. Proper education of perioperative staff, combined with clear communication and collaboration while positioning patients in the operating room is the best and safest approach. The prevention of uncommon complications of spine surgery depends primarily on identifying high-risk patients, proper positioning and optimal intraoperative management of physiological parameters. Modification of risk factors extrinsic to the patient may help reduce the incidence of PPNI and POVL.

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**Key words:** Spine surgery; Complication; Position; Nerve injury; Visual loss

**Core tip:** Perioperative peripheral nerve injury (PPNI) and postoperative visual loss (POVL) are rare complications related to patient positioning during spine surgery. It is important for spine surgeons to be aware of PPNI and POVL to participate in safe, collaborative perioperative care of spine patients. Proper education of perioperative staff, combined with clear communication and collaboration while positioning patients in the operating room is the best and safest approach. The prevention of uncommon complications of spine surgery depends primarily on identifying high-risk patients, proper positioning and optimal intraoperative management of physiological parameters.

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## INTRODUCTION

Surgical procedures involving the spine are one of the commonly performed procedures worldwide. The number of spine fusion surgeries performed in the United States has increased steadily over the past two decades[1-4]. Positioning patients for spine surgery is pivotal for optimal operating conditions and operative-site exposure. During spine surgery, patients are placed in positions that are not physiologic, would not be tolerated for prolonged periods by the patient in the awake state, and may lead to complications. Although the incidence of complications associated with positioning patients for spine surgery is relatively low, position-related complications can be devastating and life changing to patients and their families. Understanding these uncommon complications and their etiology is pivotal to prevention, and necessary if one is to obtain a truly informed consent from the patient. In this review article we discuss two of the uncommon, less recognized complications related to patient positioning during spine surgery; perioperative peripheral nerve injury and postoperative visual loss (POVL).

## PERIOPERATIVE NERVE INJURY

Perioperative peripheral nerve injury (PPNI) is a rare but important perioperative complication resulting in significant patient disability, functional loss and the potential for litigation[5,6]. The reported incidence of PPNI is 0.03%-0.1%[7,8]. The mechanism of perioperative peripheral nerve injury is not well understood[9]. In the American society of anesthesiologists (ASA) closed claims study, there is no apparent mechanism of injury in the majority of the nerve injury claims[6]. Neurosurgical and orthopedic surgical procedures have a significant association with perioperative peripheral nerve injury[7].

The normal reaction to increased loading of the peripheral nervous system (PNS) elements is progressively increasing muscle activity; this acts as a nociceptive mediated reflex to prevent further harmful elongation. But the use of muscle relaxants and inhaled anesthetics during general anesthesia may suppress this protective mechanism subjecting the PNS to greater elongation than would be tolerated in the normal awake state[10].

In an attempt to raise awareness and reduce the occurrence of PPNI, ASA formed a task force on the prevention of perioperative peripheral neuropathies. The task force published a practice advisory for the prevention of perioperative neuropathies in 2000 and 2011[11].

### *Anatomy and physiology of peripheral nerves*

The PNS carries information to and from the central nervous system (CNS). The functional unit of the peripheral nerve system is the neuron. The neuron consists of a cell body, dendrites and a long axon. The cell body contains the cytoplasm and the nucleus. Dendrites are attached to the cell body and carry impulses to the cell. Axons are attached to the cell body and carry impulses away from the cell. Conduction of an impulse along a neuron progresses from the dendrite to the cell body to the axon. The axon of one neuron and the dendrite of the next neuron are connected through the synapse. The synapse is a gap where the dendrites of one neuron and the axon of the next neuron communicate *via* chemical transmitters. Portions of the cell body and the axon are covered by Schwan cells, which form myelin segments. Myelin is an insulating layer around the axons allowing quicker and more efficient impulse transmission.

The interior of all nerve cells is negatively charged with respect to the exterior of the cell. Once the action potential of the nerve cell reaches the threshold voltage, sodium channels in the region of the action potential open, allowing sodium to flow into the nerve cell and leading to complete depolarization of the membrane. The depolarization caused by sodium influx opens adjacent voltage-gated sodium channels in the membrane leading to depolarization. The repetition of this depolarization process creates a wave of depolarization along the nerve fiber known as the action potential.

The peripheral nerve is composed of multiple nerve fibers (axons) bundled together. The bundles of nerve fibers are bound together by connective tissue sheaths and form fascicles. The endoneurium is a connective tissue sheath containing blood capillaries (vasa nervorum) that supply nutrients and oxygen to the nerve tissues. The endoneurium secretes the endoneurial fluid which surrounds the axons. The fascicles are wrapped in a fibrous tissue, the perineurium. Epineurium is the fibrous sheath that covers the entire nerve (Figure 1). The extrinsic plexus of blood vessels present in the epineurium penetrate the perineurium to anastomose with the intrinsic circulation in the endoneurium.

Tissue perfusion in the peripheral nerve is dependent on perfusion pressure. Perfusion pressure is defined as the difference between the mean arterial blood pressure and the internal pressure within nerve. In experimental animal models, high blood flow in the sciatic nerve was observed between mean blood pressures of 80-110 mmHg[12]. Acute hypotension was associated with a decrease in blood flow in the peripheral nerve[13]. Peripheral nerves lack vascular autoregulation[12-14]. Autoregulation is the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure. At mean blood pressures below 85 mmHg, there was marked decrease in the peripheral nerve blood flow[12]. A significant reduction in the blood flow to the nerve is required to affect the conduction of impulse in the nerve because blood flow to the peripheral nerve exceeds the metabolic requirements of the peripheral nerve by a significant margin[15]. Acute nerve ischemia leads to focal and generalized impairment of impulse conduction across the nerve that can be detected within 10 min of ischemia[16].

### *Mechanism of perioperative nerve injury*

Direct trauma causing disruption and destruction of nerve fibers can lead to peripheral nerve dysfunction. Although direct trauma to peripheral nerves can be the

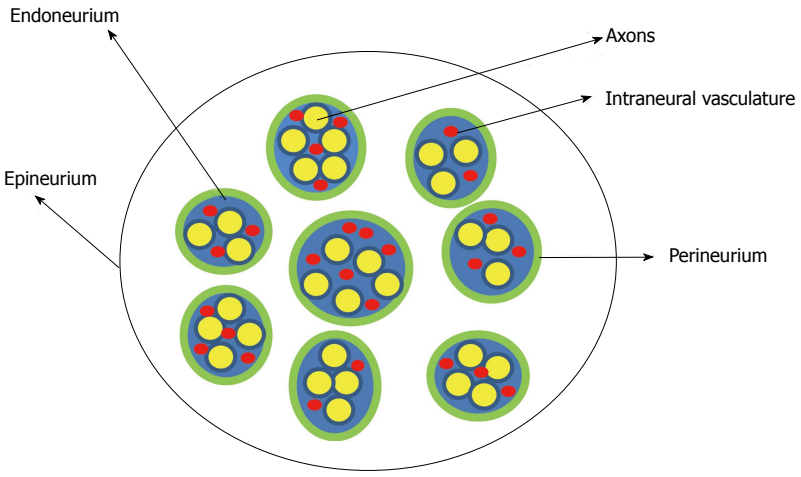


**Figure 1 Schematic representation of the cross section of the peripheral nerve.**

cause of PPNI, it is not the cause in the majority of cases.

One of the main and crucial mechanisms of PPNI is ischemia of nerve fibers[17,18]. Slowing of nerve conduction due to ischemia of the nerve fibers is the hallmark of peripheral nerve injury. Focal demyelination may occur if local ischemia is prolonged, leading to sustained axonal damage[19-21]. Peripheral nerve studies in experimental animal model demonstrated that reperfusion injury after prolonged ischemia (3-7 h) results in endoneurial edema, conduction block, blood-nerve barrier disruption, intramyelinic edema and demyelination[22-24]. Ischemia leads to demyelination in rat sciatic nerve[25]. Focal nerve ischemia is an important pathologic mechanism in hyperesthesia, Wallerian degeneration and axonal injury in animal models[17]. Persistence of ischemia can lead to permanent peripheral nerve injury. Ischemia may be the final pathway of perioperative neuropathy[26-30]. The interdependence between ischemic and mechanical factors (stretch and compression) as a cause to nerve injury is well established, although incompletely understood.

Stretch of the peripheral nerve is one of the main mechanisms of peripheral nerve injury in perioperative patients[31]. During spine surgery, under general anesthesia, patients are frequently placed in positions that may stretch nerve fibers beyond their resting length. Overstretch of the nerve can lead to direct nerve damage *via* disruption of axons and vasa nervosum. Peripheral nerve injury occurs if nerves are stretched beyond 5%-15% of their resting length[32-34]. Stretch of the peripheral nerve leads to an increase in the intraneural pressure and compression of the intraneural capillaries and venules leading to a reduction in the perfusion pressure of the nerve fibers and ischemia[34,35]. Stretch may lead to reduction in the intraneural blood flow, leading to ischemia and endoneurial edema[34,36,37]. Stretch of the peripheral nerves has been shown to suppress axonal transport leading to changes in conduction characteristics[32,33,38,39].

Peripheral nerve compression is another related mechanism of PPNI[31]. Compression of peripheral nerve leads to damage of nerve fibers. Compression may lead to an increase in intraneural and extraneural pressures leading to a reduction in perfusion pressure; a reduction in the perfusion pressure leads to ischemia and slowing of conduction in the nerve fibers. Many operative positions during spine surgery subject peripheral nerves to compression.

Recent evidence suggests an inflammatory mechanism leading to perioperative ulnar nerve injury. Patients with persistent postoperative neuropathy had evidence of inflammatory reaction in peripheral nerves. Nerve biopsy of these patients revealed diffuse generalized microneuritis. Immunotherapy treatment with high-dose steroids resulted in significant improvement of ulnar neuropathy in these patients[40].

### Risk factors for nerve injury

Certain drugs and chemicals may predispose patients to peripheral neuropathies[41]. Many conditions and medical diseases may render peripheral nerves more vulnerable to injury during the perioperative period[41]. Diseases affecting microvasculature, and anatomical differences, may contribute to nerve injury or render patients more susceptible to nerve injury. Hypertension, tobacco use, diabetes mellitus, general anesthesia, neurosurgical procedures and orthopedic surgery have been significantly associated with PPNI[7]. Advanced age has been linked to peripheral neuropathy after median sternotomy[42]. Hypovolemia, dehydration, hypotension, hypoxia, electrolyte disturbance and induced hypothermia have been associated with nerve injury[43]. The etiology of PPNI is multifactorial and involves patient predisposition, precipitating mechanical and physiologic factors.

### Ulnar neuropathy

Ulnar neuropathy is the most common site of PPNI[8]. Ulnar nerve injuries comprised 28% of all anesthesia-related nerve injury malpractice claims[6]. Perioperative ulnar neuropathy occurred in 0.5% of surgical patients; primarily men between 50-75 years of age[44]. Ulnar neuropathy can lead to significant morbidity and loss of function. Ulnar nerve injury results in the inability to oppose or abduct the fifth finger and loss of sensation of the fourth and fifth fingers. Permanent injury will lead to a claw-like hand deformity due to atrophy of the intrinsic muscle of the hands. In one study, 3 out of 7 patients

who developed perioperative ulnar neuropathy had permanent neuropathy with residual symptoms beyond 2 years[44]. Perioperative ulnar nerve injury has a delayed onset, most cases manifest within 2-7 d post-operatively (median 3 d)[5,19,44-49].

In a large retrospective review of ulnar neuropathy in anesthetized patients, the major complaints among patients with persistent ulnar neuropathy were their inability to grip tools and equipment due to loss of grip strength, discomfort and numbness. Perioperative ulnar neuropathy presented as sensory deficit in 47% of the cases while 53% of the deficits were mixed sensory and motor. Bilateral symptoms of ulnar neuropathy developed in 9% of the cases. Initial symptoms of were usually noted more than 24 h after the procedure, and appeared within 7 d in 90% of patients. Fewer than 10% of ulnar neuropathies were noted in the postoperative recovery unit. Fifty-three percent of patients with perioperative ulnar neuropathy who survived the first postoperative year regained complete sensory and motor functions and were asymptomatic. Six percent regained complete sensory and motor function but still complained of pain. At 1 year, 41% of patients had persistent deficits. Patients with sensory deficits had a better chance of complete recovery (80%) compared to patients with mixed motor and sensory deficits (35%)[19].

Patient related risk factors for perioperative ulnar nerve injury include male gender, older population, very thin and very obese patients, and prolonged postoperative immobilization[19]. The ulnar nerve may be susceptible to injury due to a pre-existing subclinical neuropathy. Pre-existing asymptomatic abnormal conduction in the contralateral ulnar nerve has been observed in patients who developed postoperative ulnar neuropathies[46]. Pre-existing subclinical neuropathy may manifest clinically in the perioperative period when patients are subject to certain predisposing factors[19,48,50]. Induced and prolonged hypotension has been associated with perioperative ulnar nerve injury[26,51,52]. Positioning during anesthesia has been related to ulnar neuropathy[52].

As stated above ulnar neuropathy occurs predominantly in men[5,19,47,53,54] with 70% of perioperative ulnar nerve injury cases occurring in males[19]. Anatomical differences may be responsible for this higher incidence of ulnar nerve injury. Studies of human male and female cadavers, showed that females have a significantly higher fat content (2-19 times) on the medial aspect of the elbow while men have a significantly larger tubercle of the coronoid process (1.5 times)[55]. Men have a thickened and more developed flexor retinaculum[8]. Men are more susceptible to direct pressure on unmyelinated ulnar nerve fibers than women[49].

The ulnar nerve has a superficial path along the medial epicondyle of the humerus[52]. The ulnar collateral artery and vein run in close proximity to the ulnar nerve and may be affected by external pressure leading to reduced perfusion, ischemia and nerve injury[30]. Compression of the ulnar nerve and its blood supply (the posterior ulnar collateral artery) at the area of the tubercle of the coronoid may lead to ischemia[55]. The ulnar nerve is relatively more sensitive to ischemia compared to median and radial nerves[27]. Experimental animal models demonstrated that the effects of compression on the ulnar nerve are potentiated by previous ischemia, even if the ischemia is of short duration[56]. The forearm position is a significant factor in determining pressure over the ulnar nerve at the elbow. Prielipp *et al*[30] investigated the relationship between forearm position and direct pressure on the elbow in awake normal volunteers, using a computerized pressure sensing mat. The study provided clear evidence that forearm supination significantly minimizes pressure over the ulnar nerve at the elbow (2 mmHg) compared with the neutral (69 mmHg) and prone (95 mmHg) forearm positions. Neutral forearm position resulted in significantly less pressure compared to the prone forearm position but more pressure compared to the supine forearm position. In the supine forearm position, the pressure over the ulnar nerve was low regardless of the degree of abduction of the arm at the shoulder. In the neutral forearm position, pressure over the ulnar nerve decreased as the arm was abducted between 30° and 90°. Pronation of the forearm produced the largest pressure over the ulnar nerve regardless of the abduction of the arm between 30° and 90°[30]. Extraneural pressures recorded along the path of the ulnar nerve in fresh cadaveric arms were significantly increased with elbow flexion beyond 90°. Concomitant shoulder abduction caused further increase in the pressure recorded at the post-condylar groove and the carpal tunnel[57].

Gelberman *et al*[58] investigated the relationship between the ulnar nerve and the cubital tunnel during flexion of the elbow in normal human cadavers. They observed a significant decrease in the cross-sectional area of the cubital tunnel coupled with an increase in the pressure within the cubital tunnel and ulnar nerve. Intraneural pressure of the ulnar increased significantly with the elbow flexed 70° or more. Extraneural pressure increased significantly when the elbow was flexed to 100° or more. The intraneural pressure was significantly increased at lesser degrees of flexion compared to the extraneural pressure. The authors conclude that the increase in the intraneural pressure of the ulnar nerve is not entirely due to extraneural compression. Dynamic changes in the cubital tunnel and the cross-section of the ulnar nerve contribute to the increased intraneural pressure with flexion. Compared with full extension, the mean area of the cubital tunnel in the subaponeurotic region decreased by 18% and 39% and the ulnar nerve mean area decreased by 24% and 50% with elbow flexed 90 and 135 degrees respectively. Intraneural and extraneural pressures within the cubital tunnel are lowest at approximately 45° of flexion[58]. Flexion of the elbow to 135° resulted in an 18% elongation of the ulnar nerve[59]. Elongation of peripheral nerve beyond 5%-15% of resting length can cause ischemia and nerve injury[32-34]. Stretch of the ulnar nerve by elevation of the shoulder, flexion of the elbow and dorsiflexion of the wrist caused a marked increase in the intraneural pressure[60].

Patel *et al*[61] assessed the morphologic changes in the ulnar nerve and cubital tunnel with elbow motion in fresh

human cadavers using magnetic resonance imaging. During full extension the ulnar nerve appeared round in serial cross-sectional images and was surrounded by fat except at the inferior aspect of the medial epicondyle where the nerve was directly adjacent to bone. On flexion the nerve displaced the fat posteriorly and was relocated to a more anterior position in the cubital tunnel. On flexion the cross-section of the nerve progressively flattened from a round to an elliptical shape. With progressive flexion the course of the nerve changed from tortuous to more direct. With progressive elbow flexion the proximal cubital tunnel takes a wider and flatter appearance with the largest diameter changing from anteroposterior to mediolateral. The diameter of cubital tunnel in the subaponeurotic region decreased with progressive elbow flexion[61].

Although the proportion of nerve damage claims has not changed between the 2 ASA closed claims studies performed almost a decade apart, the pattern of nerve injury has changed. Compared to the ASA closed claims report published in 1990, the report published in 1999 showed a relative decrease in the incidence of ulnar nerve injury claims as a proportion of total nerve injury claims and a relative increase in spinal cord injury claims. However, the actual incidence and trend of nerve injury cannot be determined based on the closed claims data since it lacks a denominator. The closed claims project examines anesthesia-related malpractice claims; it does not present the nerve injury in population. In the ASA closed claims study, the mechanism of ulnar neuropathy was explicitly stated in only 9% of the claims[6].

Perioperative ulnar neuropathy is not confined to surgical patients. A prospective study of ulnar neuropathy in patients admitted to internal medicine services for nonsurgical conditions revealed that 0.2% of the patients developed new onset ulnar neuropathy while in hospital. Patients commonly rest in a supine position, flexing their elbows and resting their arms on their chest and abdomen. Elbow flexion may increase pressure on the ulnar nerve in the postcondyler groove of the humerus due to stretching of the cubital tunnel retinaculum. Forearm pronation may lead to external compression of the ulnar nerve[45]. It is therefore prudent to instruct patients to avoid prolonged flexion of the upper extremity on the abdomen and chest in the supine position.

### Brachial plexus injury

Brachial plexus is the second most common site of PPNI accounting for 20% of all anesthesia-related nerve injury malpractice claims[6]. The reported incidence of brachial plexus injury in non-cardiac surgery is 0.02%[62]. The main mechanisms of brachial plexus injury are compression and stretch. The brachial plexus has a long course between the vertebra and the axillary fascia. Brachial plexus injury usually involves the upper nerve roots. Lower brachial nerve injuries are commonly associated with median sternotomy[43].

In the ASA closed claims project, patient positioning was responsible for 10% of brachial plexus malpractice claims. The use of shoulder braces and head-down position, arm malpositioning and prolonged neck extension were commonly identified mechanisms for brachial plexus injury[6]. The use of shoulder braces in Trendelenburg position may lead to compression of the brachial plexus between the clavicle and the first rib[8,63].

Brachial plexus injury is commonly due to overstretch of the brachial plexus[43]. Shoulder abduction greater than 90°, external rotation of the arm and posterior shoulder displacement can stretch the brachial plexus[43,64]. Downward tilting of the head and hyperabduction of the independent arm in the lateral position may stretch the brachial plexus and lead to brachial plexus injury[65]. Extension and lateral flexion of the head in the supine position may contribute to stretch of the brachial plexus on the contralateral side[43].

In the supine position, submaximal joint positions may stretch the brachial plexus to the extent it may affect physiologic processes in the peripheral nerve. Contralateral flexion of the cervical spine, lateral rotation of the shoulder combined with shoulder abduction and wrist extension may stress the brachial plexus. Elbow extension can cause substantial stress to the PNS. Simultaneous application of the different aforementioned components has a cumulative stressful impact on the brachial plexus. Individuals react differently to elongation of the peripheral nerve and individual variability increases as more components leading to stretch of the brachial plexus are added[10].

### Median neuropathy

Median nerve injury is relatively rare and responsible for only 4% of all anesthesia-related nerve injury malpractice claims[6]. The median nerve may be injured during the insertion of an intravenous catheter in the antecubital fossa. However, stretch is the main mechanism of median nerve injury due to operative positioning.

Median neuropathy usually presents as a motor neuropathy with loss of the ability to oppose the first and fifth digits and decreased sensation over the palmar surface of the lateral three and half fingers. Median neuropathies do not resolve easily with most patient having sustained symptoms of motor dysfunction. Extension of the elbow may overstretch the median nerve leading to injury[11]. Muscular patients and patients with limited elbow extension range may be at risk for median nerve injury if the arm is fully extended under general anesthesia. The reduced range of extension in these patients may lead to similar contraction of median nerve making it more prone to overstretch[66]. Overextension of the elbow in the supine position to a point that is uncomfortable to the patient in the awake state should be avoided[11]. Wrist hyperextension for arterial line placement may lead to transient but significant impairment of the median nerve function. Prolonged hyperextension of the wrist may lead to slowing of nerve conduction and median nerve injury[67].

### Radial neuropathy

Radial nerve injury is rare and accounts for just 3% of

all anesthesia-related nerve injury malpractice claims[6]. The most common mechanism of radial nerve injury is direct compression at the spiral grove of the humerus. It may occur in the lateral position with abduction of the independent arm beyond 90° and suspension of the arm from a vertical screen support[68]. Direct compression by the overhead arm board at the mid-humerus may occur in the lateral position. Injury to the radial nerve results in wrist drop, inability to extend the metacarpophalangeal joint and inability to abduct the thumb with loss of sensation from the lateral and posterior arm, posterior forearm and a portion of the dorsal hand.

### *Intraoperative neuromonitoring*

Intraoperative neuromonitoring is available in most institutions in the United States and is frequently used during spine surgery[69]. Commonly used intraoperative neuromonitoring modalities are somatosensory evoked potential (SSEP) and motor evoked potential. Neuromonitoring is primarily used to monitor the integrity of the spinal cord during spine surgery. However, SSEP monitoring has been used to detect peripheral nerve conduction abnormalities indicating peripheral nerve stress and impending injury during surgery under general anesthesia in variable intraoperative positions[70-86]. Conduction changes detected by SSEP may indicate position-related impending peripheral nerve injury. In a retrospective study of 1000 consecutive spine cases, position modification of the upper extremity lead to resolution of 92% of upper extremity SSEP changes[86]. Position modification strategies used in the review included correcting extreme elbow flexion and extension, decreasing shoulder abduction, releasing shoulder traction on tucked arms (caused by taping down the shoulder) and moving the upper extremity into the original position if the position had been modified. After position modification of the upper extremity and resolution of SSEP change, patients experienced no post-operative upper extremity peripheral nerve injury[86]. Significant SSEP change indicating impending upper extremity nerve injury is usually defined as reduction in amplitude of 50% or more and/or increase in latency of 10% or more[73,86]. Usually changes in both amplitude and latency are monitored and evaluated. Compared to latency, amplitude changes may be a more sensitive and valid measure of changes in nerve conduction[87,88]. Most SSEP components are mediated by large myelinated fibers. Some secondary peaks may be transmitted by smaller fibers. Potentials recorded from Erb's point may be the most sensitive to ischemia[28].

Significant SSEP changes indicate abnormal conduction and impending nerve injury. If the changes persist for a prolonged period of time, permanent nerve injury may occur[30]. The use of SSEP to monitor extremity nerve function and guide position modification of the upper extremity into a more favorable position for the peripheral nerve may protect peripheral nerves from injury under general anesthesia. The incidence of position related significant upper extremity SSEP changes during spine surgery ranges from 1.8% to 15% depending on the operative position, patient group and type of spine surgery[79,83,86].

## POSTOPERATIVE VISUAL LOSS

POVL is a rare but traumatic and devastating complication of spine surgery and general anesthesia. The reported prevalence rate of POVL after spine surgery is 0.0028%-0.2%[89-92]. The incidence of POVL associated with spine surgery in the prone position under general anesthesia has increased over the past several decades[93]. POVL usually results in permanent unilateral or bilateral visual loss. Most cases are associated with prolonged spine procedures in the prone position under general anesthesia. Posterior lumbar fusion and surgery for correction of scoliosis were associated with the highest rate of POVL[92]. POVL has been associated with instrumented spine surgery in the prone position[94]. The most common causes of POVL after spine surgery are ischemic optic neuropathy (ION) and central retinal artery (CRA) occlusion. ION is further classified into anterior ION (AION) and posterior ION (PION). PION is the most common cause of POVL after spine surgery. In 1999, the ASA committee on professional liability established the ASA POVL registry to identify predisposing factors and intraoperative risk factors. It is important for spine surgeons to be aware of POVL and to participate in safe, collaborative perioperative care of spine patients positioned in the prone position.

### *Anatomy and physiology of the optic nerve*

The eye is a sphere that gathers and converts light information into neuronal signals. The wall of the globe has 3 layers; the outermost sclera (white of the eye), the middle uveal tract (contains the choroid) and the innermost layer (the retina). There are no blood vessels in the retina; the choroid layer, located posterior to the retina contains blood vessels and provides the retina with oxygen and nutrients. Retinal ganglion cells (RGC) in the retina are highly specialized neurons that produce neural signals when stimulated by light. Neural signals are transmitted to the brain along axons of RGC in the optic nerve (cranial nerve Ⅱ).

The optic nerve is composed of about 1.2 million individual RGC axons and support cells. Axons of the RGC travel across the retina and converge near the center forming the optic nerve. This convergence of the RGC axons creates the blind spot of the eye, an area where no photoreceptors exist, only nerve fibers.

The optic nerve has a structure similar to the CNS tracts and is considered part of the CNS. In contrast to the ability of the mammalian PNS to regenerate axons after injury, mammalian CNS structural and functional regeneration after injury is minimal. Injury to the RGC usually results in lifelong visual loss due to the limited ability of RGC to regenerate their axons after optic nerve injury[95].

The blood supply of the eye comes from the ophthalmic artery, a branch of internal carotid artery. The CRA

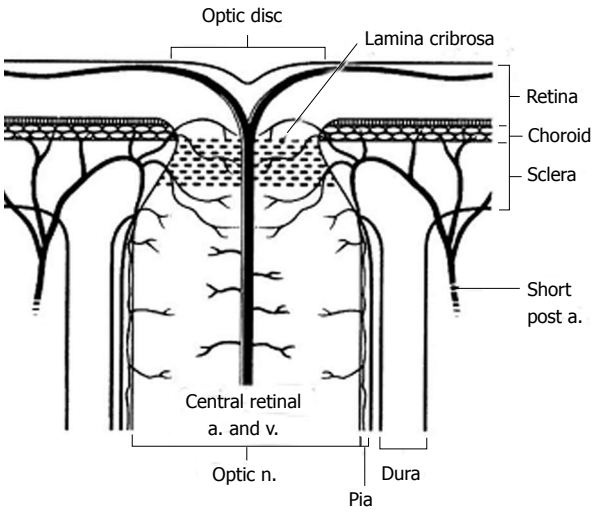


**Figure 2 Diagram of the anterior optic nerve showing the arterial and small vessel supply to the choroid and optic nerve as it passes through the lamina cribrosa.** Short post a: Short posterior ciliary artery; a: Artery; v: Vein; n: Nerve (Reprinted from Williams *et al*[140] with permission).

is a branch of the ophthalmic artery. The CRA penetrates the optic nerve superiorly and continues its course in the optic nerve to supply the retina. The ophthalmic artery gives rise to 1-5 posterior ciliary arteries. The posterior ciliary arteries give rise to short and long posterior ciliary arteries. The posterior ciliary arteries are end-arteries that provide blood supply to the head of the optic nerve and the retina.

The optic nerve can be divided into anterior and posterior portions based on differences in anatomy and blood supply[96]. The anterior portion (intraocular) of the optic nerve is that part of the optic nerve that lies anterior to the lamina cribrosa. The posterior (retrolaminar or intraorbital) portion of the optic nerve is the part of the optic nerve posterior to the lamina cribrosa. Lamina cribrosa is an elastic multilayered network of collagen fibers that insert into the scleral canal wall. The nerve fibers forming the optic nerve exit the eye posteriorly through the lamina cribrosa. The CRA and the central retinal vein pass through the lamina cribrosa to enter the optic disc.

The predominant cells in the anterior optic nerve are astrocytes, while microglial cells and oligodendrites are relatively more common in the posterior optic nerve. Unlike peripheral nerves, the posterior (retrolaminar) optic nerve is covered by all three meningeal layers; dura, arachnoid and pia matter.

The blood supply of the anterior optic nerve is derived from retinal arterioles, centripetal branches from the peripapillary choroid and short posterior ciliary arteries (Figure 2). The anterior optic nerve may receive blood from the intrascleral circle of Zinn and Haller when present.

The blood supply of the posterior (retrolaminar) optic nerve is derived from two vascular systems; the centripetal (peripheral) system and centrifugal system (axial). The centripetal vasculature is the main and most consistent system supplying the posterior optic nerve. It is formed primarily of recurrent branches of the peripapillary choroid, and the circle of Zinn and Haller, with additional pial branches from the CRA and other orbital arteries. The centrifugal blood vascular system consists of a few branches of the CRA The centrifugal system is not always present and the number of branches is inconstant. To summarize, the main blood supply of the anterior optic nerve is derived from the short posterior ciliary arteries and the peripapillary choroid. The main blood supply to the posterior optic nerve is derived from recurrent branches of the peripapillary choroid and pial branches of the CRA.

It is important to realize there is not one universal pattern of blood supply for the optic nerve. There are many anatomic variations in vascular supply, which can lead to variable patterns of ischemia among individuals[97-100]. In most individuals, there are 2 to 3 posterior ciliary arteries; however in some the number may range from 1 to 5. It is also important to note that posterior ciliary arteries are end-arteries, and thus watershed zones exist between them[100]. Watershed areas, by definition, are areas that are at risk for decreased blood supply. Blood flow to the posterior optic nerve may be particularly vulnerable to ischemia because most of the arteries supplying the posterior optic nerve are end-arteries[98].

### Blood flow to the optic nerve

The blood flow to the optic nerve head is dependent on perfusion pressure. Ocular perfusion pressure is the difference between mean arterial blood pressure and intraocular pressure (IOP) or venous pressure (whichever is higher)[101]. It is important to note that the mean arterial pressure determining optic nerve blood flow refers to that of the optic nerve vasculature and not the pressure in the brachial or radial arteries. Local arteriolar vasoconstriction may reduce perfusion to the optic nerve leading to ischemia despite a normal brachial blood pressure measurement. Thus three main factors determine optic nerve perfusion; vascular tone, arterial blood pressure and IOP.

### Autoregulation

There is evidence that the optic nerve head autoregulates blood flow[102-105]. Autoregulation is achieved through alterations in resistance of the terminal arterioles. There are limitations to the degree to which arteriolar resistance can be altered to maintain perfusion. Autoregulation works within a range of mean arterial pressure, below or above which the local perfusion is dependent entirely on the difference between mean arterial blood pressure and intraocular or venous pressure. Factors leading to the breakdown of autoregulation of blood flow to the optic nerve include age, hypertension, uncontrolled blood pressure, diabetes mellitus, atherosclerosis, hypercholesterolemia, and vascular endothelial disorders[106-109]. A study of the blood flow to the optic nerve head using laser Doppler flowmetry in healthy volunteers demonstrated that blood flow was constant between ocular perfusion pressures of 56 to 80 mmHg. Not all patients have autoregu-

lation of the blood flow to the optic nerve[105]. A study of autoregulation of the optic nerve in humans showed that 2 out 10 healthy young volunteers did not demonstrate autoregulation[104].

### Arterial blood pressure

Arterial blood pressure is one of the main determinants of blood flow to the anterior and posterior optic nerve. There is a progressive fall in the blood pressure from the internal carotid artery, to the ophthalmic artery, to the posterior ciliary artery and then to the small branches supplying the optic nerve. The blood pressure in optic nerve may be half or less than that measured in the brachial artery[109]. Vascular changes such as atherosclerosis, vasospasm and vasculitis may lead to further decreases in blood flow to optic nerve. Critical drops in blood pressure below the lower limit of autoregulation will lead to a reduction in optic nerve blood flow. Hypotension resulting from antihypertensive medications or shock may lead to ischemia of the optic nerve and anterior ischemic optic neuropathy[110-113]. Nocturnal hypotension has been associated with glaucomatous visual loss[110,113,114]. Nocturnal arterial hypotension may be a key factor in the development of non-arteritic AION as more than 75% of these patients discover visual loss upon awakening in the morning[115]. Arterial hypertension can decrease blood flow to the optic nerve if it is outside the upper limit of autoregulation or there is an absence of autoregulation. In this setting a decrease in the blood flow is due to arteriolar vasoconstriction[109].

### IOP

IOP is defined as the pressure exerted by the contents of the eye on its containing wall. Intraocular components like blood and aqueous humor can undergo significant volume changes that significantly alter IOP. External pressure on the eye globe can increase IOP by direct and indirect effects through volume changes of intraocular components. The normal IOP ranges from 10-20 mmHg with a diurnal variation of 2-3 mmHg. IOP decreases at night. IOP is a key determinant of blood flow to the optic nerve head. The blood flow to the optic nerve head is inversely proportionate to the IOP outside the range of autoregulation or if autoregulation is absent or defective. This effect may be intensified when coupled with hypotension or local vasospasm[116]. IOP may affect the blood flow to the anterior (intraocular) optic nerve. The effect IOP has on blood flow to the posterior (retrobulbar) optic nerve is unclear and probably of lesser significance.

Changes in arterial $PCO_2$ tension can affect intraocular blood volume and IOP independent of hemodynamic changes[117-121]. The vascular resistance of the choroidal vessels varies directly with inhaled $CO_2$[122]. High levels of $PCO_2$ lead to intraocular vasodilation increasing intraocular blood volume and IOP.

The choroid is a vascular structure that contains the majority of the intraocular blood volume. Congestion of the choroid leads to an increase in the intraocular blood volume and IOP. The choroid is characterized by very high blood flow[123]. Most of the blood volume of the choroid is in the venules of the choroid. Venular filling of choroid depends on the pressure in the orbital veins[117]. Pressure in the orbital veins can be affected by body position[117,124,125]. Increases in orbital venous pressure may lead to an increase in IOP though choroid congestion. Trendelenburg position increases central venous pressure and may lead to an increase in IOP through congestion of the choroid. The choice of the operating room table and frame (Jackson table or Wilson frame) has no significant role in IOP increase caused by the prone position[126].

The majority of the aqueous humor outflow is passively drained into the episcleral veins[127,128]. This passive outflow process depends on the gradient between IOP and episcleral vein pressure (EVP). High IOP may reduce aqueous humor drainage while having minimal effect on production leading to an increase of the total aqueous humor volume[126]. The episcleral veins are valveless veins connected to the central venous circulation. Cephalad shift of blood and increase in central venous pressure (CVP) will increase the EVP[124,129]. A positive correlation exists between episcleral venous pressure and IOP.

Elevation in central venous pressure may reduce venous return from the eye leading to an increase in IOP. There is close correlation between CVP and IOP[117,118,130]. A parallel and instantaneous decrease in CVP and IOP was noticed with a change from Head-down (Trendelendburg) position to head-up (reverse Trendelenburg) position[117]. Factors that cause significant increase in CVP may lead to an increase in IOP. These include increased intrathoracic pressure, extreme neck flexion, dependent position of head relative to the heart and abdominal compression. The venous pressure may increase beyond IOP, and in such cases it becomes a key determinant of ocular perfusion pressure and blood flow to the optic nerve.

### Effects of general anesthesia and surgical position

General anesthesia decreases IOP in the supine position[116,130,131]. IOP pressure has been shown to increase in anesthetized patients in the supine head-down (Trendelenburg) position[130,132]. Peak airway pressure, mean arterial blood pressure, duration of surgery and end-tidal $CO_2$ are significant predictors of IOP in the anesthetized patient placed in the supine head-down position[132]. The prone position has been shown to increase IOP under general anesthesia in adult and pediatric patients[131,133]. IOP has been shown to increase in awake vertically inverted volunteers[134]. IOP has been shown to increase with elevated arterial carbon dioxide tension in anesthetized patients without eye disease[117]. Hyperventilation caused a rapid fall of IOP. IOP changes due to arterial carbon dioxide tension in anesthetized patients are presumably vascular in nature and are related to changes in the choroidal blood volume[117]. Intraoperative fluid balance may affect IOP. Acute oral water loading has been shown to significantly, though transiently, elevate IOP[135] while dehydration has been associated with significant

reduction in IOP[136]. In the prone position, general anesthesia may lead to an increase in the intraocular blood volume by impairing autoregulation in the choroid circulation[137]. The IOP may become a critical factor in the perfusion of the anterior optic nerve in the presence of decreased hematocrit and mean arterial blood pressure[126]. Ozcan *et al*[126], showed that an increase in the IOP caused by the prone position in awake volunteers was ameliorated but not normalized by a 10° head-up (reverse Trendelenburg) position[126].

### ION

ION is the most common reported cause of POVL after spine surgery[138-140]. Perioperative ischemic neuropathy is a multifactorial disease that is not well understood. ION presents as acute loss of vision or visual field defect. More than 50% of the cases present in ASA POVL registry had bilateral ION[141]. ION is divided into AION and PION. AION involves ischemia and infarction of the anterior optic nerve, while PION involves ischemia and infarction of the posterior optic nerve. It is uncommon for AION and PION to be present simultaneously. Usually ION presents as selective AION or PION, presumably due to different predisposing factors and differences in the blood supply to those portions of the nerve[141]. Hypertension, diabetes, obesity, hypotension, anemia, prone position, smoking, vascular disease, increased blood viscosity and abnormal anatomy have been associated with ION and perioperative visual loss[139,140,142-147]. Anemia, hypotension, peripheral vascular disease and blood transfusion were associated with ION after spine surgery[90,92]. ION has been associated with adverse effects of hypertensive medications and with sildenafil[110,148]. ION is more common in males[139,149]. The protective effect of estrogen in experimental animal models of cerebral ischemia has been established and may contribute to the lower incidence of ION in females[150]. Obesity, the use of the Wilson spinal frame, longer anesthetic duration and lower colloid use during intraoperative fluid administration have been associated with ION and POVL[149]. Most cases of ION occurred in relatively healthy individuals, further confirming the role interindividual anatomic and physiologic variations may play in the development of ION.

The association between hypotension, anemia and ION is unclear. Anemia and hypotension has been associated with ION[90,92]. However ION has been diagnosed in patients with a hematocrit nadir of 40% during spine surgery. In a retrospective case-control study by Myers *et al*[94], there was no difference in the lowest blood pressure between patients who developed POVL and those who did not. ION may occur in the absence of hypotension[139]. Although deliberate hypotension for spine cases has not been associated with POVL in previous studies, the studies lack power to detect a complication with a significantly low incidence like POVL[151,152]. ION may be due to a "compartment syndrome of the optic nerve", a hypothesis related to increased venous pressure and interstitial fluid accumulation within the lamina cribrosa of the optic nerve (semi-rigid) or the bony optic canal[139].

Awake volunteers positioned in the prone position demonstrated a significant increase (20 mmHg) in the IOP after 8 min compared to the supine position (14.1 mmHg)[153]. Cheng *et al*[131] investigated the effect of prone positioning on IOP in 20 anesthetized patients having spine surgery. Patients with preexisting eye disease or previous eye surgery were not included. Patients were positioned in the prone position with their heads in pinned head-holder in a neutral position with neck flexion limited to less than 15° from horizontal. Mean arterial pressure was kept within 20% of awake values and end–tidal carbon dioxide level was maintained at 30-35 mmHg. IOP was measured at baseline and 5 times throughout the procedure. Two measurements of the IOP were made in the prone position; before incision and after the conclusion of the surgery. The IOP in the prone position before incision was significantly higher (27 mmHg) than both supine anesthetized and awake (baseline). The IOP was significantly higher (40 mmHg) in the prone position after the conclusion of surgery compared to all previous measurements. The mean duration in the prone position before the second measurement was 320 min. The authors concluded that IOP increased significantly in the anesthetized patient in the prone position and the magnitude of this increase is related to the amount of time spent in that position. Increases in IOPmay lead to reductions in ocular perfusion pressure despite normal systemic blood pressure[131].

Lee *et al*[139] analyzed 93 spine cases with POVL from the ASA POVL registry. Ischemic optic neuropathy was the cause of visual loss in 89% of cases. PION was the most common cause of optic neuropathy occurring in 56 of 83 ION cases. Nineteen patients were diagnosed with AION and 8 patients had unspecified ION. Compared to cases of CRAO, ION cases occurred more often in males (72%) undergoing elective surgery (96%). Most patients were relatively healthy with no preoperative history of glaucoma. Most cases of ION occurred with spine fusion and instrumentation involving more than one vertebral level in the thoracic, lumbar or sacral spine. All but 2 patients were positioned prone. The mean anesthetic duration was 9.8 h with 84% of cases lasting 6 h or longer. The mean prone duration was 7.7 h. Eighty-two percent of cases had an EBL of 1 liter or more. Only one patient in 83 showed signs of periocular trauma. Bilateral ION was documented in 66% of ION cases with a median onset time for reporting symptoms of 15 h. ION can occur without compression of the globe as 16 patients who developed ION were placed in Mayfield pins. Key findings of the review were the higher incidence of ION in males, the association of ION with an EBL of 1000 mL or greater, and a duration of surgery of 6 h or longer. The authors recommend discussing the risk of POVL with patients undergoing lengthy spine surgery in the prone position[139].

Shen *et al*[89] investigated the prevalence of POVL in the United States over a 10-year period from 1996 to 2005 using The Nationwide Inpatient Sample. The preva-

lence rate for POVL was 0.03% after spinal fusion and 0.0086% after laminectomy without fusion. Age, male gender, anemia, and posterior approach for surgery were associated with significantly higher odds of developing POVL. Patients younger than 18 years had the highest prevalence rate (0.35%). The prevalence rate of POVL was 0.05% in the posterior approach compared to 0.006% in the anterior approach. Men had 1.3 time higher odds ratio of visual loss, and twice the odds ratio for developing ION compared to women. Contrary to POVL after cardiac surgery, existing co-morbidities were not associated with greater odds for developing POVL and ION with spine fusion surgery[89].

Holy *et al*[138] performed a retrospective matched case-control study to determine the incidence and risk factors of ION in a single institution. The reported incidence of documented ION after spine surgery was 0.36%. The majority of cases (75%) of ION patients after spine surgery had PION. The majority (94%) of the patients with ION in all surgical procedures (including spine surgery) were men. The authors found no difference in hematocrit levels or blood pressure values or the use vasopressor between cases and controls[138].

Grant *et al*[147] investigated the effect of prolonged prone positioning on ocular parameters in 10 volunteers. The authors demonstrated a progressive increase in the IOP, choroid layer thickness and retrobulbar diameter of the optic nerve in the prone position compared to supine position over 5 h. The peak increase for most parameters was at 5 h in the prone position. Compared to the prone horizontal position, a 4° reverse Trendelendburg prone position had minimal effect on these changes. With elevation of the head of the stretcher 30° in the supine position, all parameters retuned to baseline after 30 min. In the prone position, the optic nerve diameter showed a significant increase in diameter without significant difference between horizontal and 4° Trendelenburg. Choroid layer thickness showed mild improvement (reduction) with 4° Trendelenburg position. The authors related the increase in the prone diameter of retrobulbar optic nerve to a dependent increase in subarachnoid fluid or venous congestion rather than intrinsic swelling[147].

### AION

AION is associated with spine surgery and is the most common cause of ION associated with open heart surgery[138]. AION results from ischemia of the anterior (intraocular) optic nerve presumably due to occlusion of the posterior ciliary circulation[154]. AION is painless and usually irreversible[141]. High cholesterol, smoking, high fibrinogen levels[154], diabetes[155], nocturnal arterial hypotension[110] and lack of autoregulation[104] have been associated with occurrence of non-arteritic spontaneous AION. Interindividual variation in the blood supply to the anterior optic nerve may predispose patients to ischemia in watershed zones leading to AION[99]. Variability in the severity of the visual loss associated with AION may be due to variation in the blood supply resulting in various ischemic effects[140,156]. An increase in IOP may play a role in reduced perfusion to the anterior (intraocular) optic nerve. AION has been associated with increased blood viscosity. An increase in blood viscosity may reduce perfusion pressure leading to ischemia of the anterior portion of the optic nerve. Sickle cell disease and polycythemia may be associated with AION presumably due to increased blood viscosity and decreased perfusion of the optic nerve in certain individuals[141,157]. AION may occur due to reduced oxygen carrying capacity and transport, as in the case anemia and hemorrhage[158,159]. Patients with a small optic disc are at higher risk of developing AION[160,161].

In AION the optic disc is initially swollen. Early swelling of the optic disc is a key differentiating point from PION. Over months the swelling gradually evolves into optic atrophy[138,141,156,162-164]. Splinter hemorrhages around the optic disc may be present[165]. Visual defects most commonly occur in the inferior half of the visual field[145,166,167].

### PION

PION is the most common type of ION after spine surgery and is the most common cause of POVL associated with spine surgery[139,141,162]. PION occurs due to ischemia of the retrobulbar (intraorbital) optic nerve. Reported risk factors associated with PION include; prone position, prolonged spine surgery, systemic hypertension, intraoperative hypotension, anemia, diabetes, smoking and coronary artery disease[142].

In contrast to anterior ION, optic nerve swelling is absent on ophthalmoscopic examination. Later in the course of PION, the atrophy of the posterior optic nerve fibers will involve the anterior optic nerve head resulting in a pale and atrophic optic disc. The etiology of PION is multifactorial[140,141]. Severe anemia and hypotension in predisposed individuals placed in the prone position for prolonged periods of time are reported to be more likely causes of PION rather than occlusive vascular disease[141]. Interindividual variability and inconsistency in the blood supply to the posterior (retrobulbar) optic nerve plays a role in the development of postoperative PION[140,168]. PION have been associated with surgery, trauma and gastrointestinal bleeding in which severe anemia and hypotension occurred[91,94,140,169,170]. Prognosis is usually poorer with PION compared to AION[171].

Arterial infarction of the retrobulbar optic nerve due to ischemia is primarily due to decreased oxygen delivery. Decreased oxygen delivery may be due to a decrease in arterial perfusion pressure, increased resistance to blood flow or a reduction in oxygen carrying capacity[147]. The prone position may contribute to increased orbital venous pressure or venous congestion which may contribute to a decrease in arterial perfusion pressure and venous infarct respectively. One of the postulated mechanisms for PION is venous infarct. Venous infarct is a venoarteriolar response caused by secondary constriction in small arterioles in response to venous congestion[172,173].

Gill *et al*[141] reviewed 7 studies representing 102 cases of POVL associated with spine surgery. PION was the

most common cause of POVL. Patients who developed POVL after spine surgery had an age range of 46 to 53 years and at least one co-morbidity. Median operative time ranged from 385 to 410 min while the average blood loss ranged from 3.5 to 4.3 L. There was no visual improvement in the majority of cases. The authors concluded that an acute anemic state may have additive or synergistic effects in predisposed patient with certain comorbidities leading to the visual loss associated with spine surgery[141].

Enlargement of the superior ophthalmic veins with bilateral PION after prolonged spine surgery has been reported in a 55 years old male. Magnetic resonance imaging revealed significant enlargement of the superior ophthalmic veins 19 h after the surgery that resolved 5 mo after the surgery. Enlargement of the superior ophthalmic veins indicate the role of orbital venous pressure in the development of PION associated with surgery in the prone position[174]. Prolonged prone positioning has been shown to increase the diameter of the retrobulbar optic nerve possibly due venous congestion[147].

### Central retinal artery occlusion

Central retinal artery occlusion (CRAO) may be caused by direct pressure on the globe, emboli or low retinal perfusion pressure[141]. Pressure on the eye globe increases IOP and has been associated with POVL [91,175,176]. The use of a horseshoe headrest for spine surgery in the prone position has been associated with CRAO and POVL[176,177]. Analysis of the spine cases with POVL showed that CRAO was present in 10 of the 93 cases[139]. The mean age for patients with CRAO was 46 years. Horseshoe headrests were used in 3 cases. Mayfield pins were not used in any of the cases with CRAO. Median estimated blood loss and mean anesthetic duration were significantly less in CRAO cases compared to patients with ION. All cases of CRAO were unilateral. Periocular trauma was documented in 7 of the 10 cases of CRAO. Risk factors for CRAO differ considerably from those of ION. Cases of CRAO after spine surgery have not been associated with degree of blood loss, anemia, bilateral loss of vision, or duration of the prone position, indicating a different etiology than ION[139]. Ophthalmologic examination shows pale, edematous retina, fibrin or cholesterol emboli and cherry-red spot on the fovea. Optic atrophy occurs in half the patient with CRAO[140].

## POSITIONING PATIENTS FOR SPINE SURGERY

Awareness of the potential rare complications of patient positioning during spine surgery is essential for improved care and reducing the likelihood of occurrence of such complications. Complete prevention of PPNI and POVL is unrealistic because of the multifactorial etiology of the complications and lack of clear, definitive knowledge regarding etiology. Proper education of perioperative staff, combined with clear communication and collaboration while positioning patients in the operating room is the best and safest approach. The prevention of uncommon complications of spine surgery depends primarily on identifying high-risk patients, proper positioning and optimal intraoperative management of physiological parameters. Modification of risk factors extrinsic to the patient may help reduce the incidence of perioperative peripheral nerve injury and POVL.

### Identifying high risk patients

High-risk patients for PPNI are usually middle aged males, with extreme body habitus. Prolonged hospitalization is a risk factor for the development of perioperative ulnar neuropathy. Certain operative positions used during spine surgery may create risks for loss of nerve function of the upper extremity. The prone position has been linked to claims of nerve injury[5]. Patients placed in the prone surrender (superman) position and lateral decubitus position had a significantly higher incidence of position-related impending upper extremity nerve injury compared to patients positioned in the supine arms tucked, supine arms out, and prone arms tucked positions[86]. Patients with a previous history of upper extremity peripheral nerve injury should be considered at increased risk of developing PPNI.

High-risk patients for POVL are those expected to undergo prolonged procedures on multiple vertebral levels in the prone position with a significant anticipated blood loss. The ASA task force for the prevention of POVL considers a surgery prolonged when it exceeds 6.5 h and significant blood loss when the patient's blood loss exceeds 44.7% of estimated blood volume[178]. It is advisable to discuss POVL with these patients when obtaining informed consent. It is also important to inform patients about the multifactorial etiology of POVL, the lack of clear understanding of the etiology, anatomical differences between individuals and the very low incidence of this rare, but devastating complication. Consideration should be given to staging surgery in high-risk patients, as this may reduce the risk of POVL[178]. However, the decision to stage spine surgery for high-risk patient should be individualized and weighed against other perioperative risks.

### Proper positioning

**The prone surrender position:** In the prone surrender (superman) position, injury can occur along the entire length of the brachial plexus. Patients placed in the prone surrender(superman) position had a significantly higher incidence of position-related impending upper extremity nerve injury detected by SSEP compared to patients positioned in the supine arms tucked, supine arms out and prone arms tucked positions[86]. Stretch is the main mechanism of injury. If the head is directed away from the arm this can stretch the brachial plexus, therefore lateral neck rotation should be avoided. Although patients may comfortably tolerate arm abduction greater than 90° in the prone surrender position[11], it is advisable to limit the shoulder abducted to less than 90° to avoid overstretch

**Figure 3 Positioning patient in the prone surrender (superman) position.** The head should be in neutral position on foam supporting head frame (*e.g.*, proneview®) to avoid any direct pressure to the eye. The shoulders should be abducted less than 90°, lateral rotation of the upper arm and extreme elbow flexion should be avoided. The forearm should be positioned in the neutral position to minimize direct pressure on the ulnar nerve in the elbow. Soft foam padding should be placed under the elbows and between the inner upper around the gel rolls (or supporting frame) supporting the body. The level of the forearm should be at or below the mattress surface.

of the brachial plexus. Depression of the shoulder girdle should be avoided. The longitudinal axis of the forearm should be parallel to the longitudinal axis of patient to avoid outward rotation of the arm. Extreme elbow flexion should be avoided. However, in the prone position the range of motion for the elbow extension and flexion is limited. The forearm should be placed in a neutral position to minimize the direct pressure on the ulnar nerve at the elbow (Figure 3). The forearm should be at or below the table mattress surface. The elbow and the inner aspect of the upper arm should be padded with foam to avoid direct pressure on the nerves. Prolonged overextension of wrist over the wrist board placed for arterial lines should be avoided as it may stretch the median nerve. The head of the humerus may compress the neurovascular bundle in the axilla leading to nerve damage[179]. In a steep, prone Trendelenburg position the brachial plexus may be compressed between the clavicle and the first rib especially with use of shoulder braces. Vigilance and frequent checking of patient positioning is important. The use of SSEP helps to detect impending upper extremity peripheral nerve injury and guide position modification of the upper extremity.

The prone position is a known risk factor for POVL[139]. When patients are placed in the prone position, direct pressure on the eye must be avoided as it may cause CRAO[178]. The horseshoe head rest has been associated with CVAO and POVL in the prone position and therefore should be avoided if possible. Head positioning in Mayfield pins avoids direct pressure on the eye globe (Figure 4). Another choice is using foam positioning devices for the head, like the proneview®. The proneview® consists of a foam cushion in a plastic frame that supports the face without applying pressure on the eyes, nose or mouth and a mirror that allows frequent examination of the eye and facial structures (Figure 5). The use of the Wilson spinal frame has been associated with ION and POVL[149]. High-risk patients should be positioned with the head above the heart when possible. This will help reduce venous congestion in the eye and orbit and hopefully avoid an increase in the IOP and intraorbital pressure. The head should be in a neutral forward position when possible avoiding significant neck flexion, extension, lateral flexion or rotation[178].

**The lateral decubitus position**: The lateral decubitus position is used less frequently than the prone position for spine surgery. Patients placed in the lateral decubitus position had a significantly higher incidence of position-related impending upper extremity nerve injury detected by SSEP compared to patients positioned in the supine arms tucked, supine arms out and prone arms tucked positions[86]. In the lateral decubitus position compression is the main mechanism of peripheral nerve injury of the dependent brachial plexus. The brachial plexus may be compressed between the thorax and the humeral head[43]. The use of chest roll (also known as axillary roll) may help reduce the brachial plexus injury at this compression point. It is important to apply the chest roll under the chest and not in the axilla (Figure 6). Placing the roll in the axilla will increase the pressure on the brachial plexus in the axilla predisposing the patient to nerve injury. In the lateral decubitus position, there is increased pressure under the dependent shoulder. The average pressure under the dependent shoulder in the lateral position is 66 mmHg (and can exceed 100 mmHg). The pressure under the dependent shoulder decreased to 20 mmHg when the chest wall was elevated using an inflatable chest roll. The pressure further decreased to 12 mmHg when the head was supported by a second inflatable pillow to allow straightening of the cervical spine avoiding lateral angulation of the cervical spine. Patients placed in the lateral decubitus position had an average lateral angulation of neck of 14 degrees. After applying an inflatable chest roll, the average lateral angulation of the neck significantly increased to 20°. When the neck was brought into alignment by inflating a second pillow under the head, the lateral neck angulation decreased significantly to 4°. Using inflatable pillows beneath the dependent chest was associated with significantly less pressure beneath the

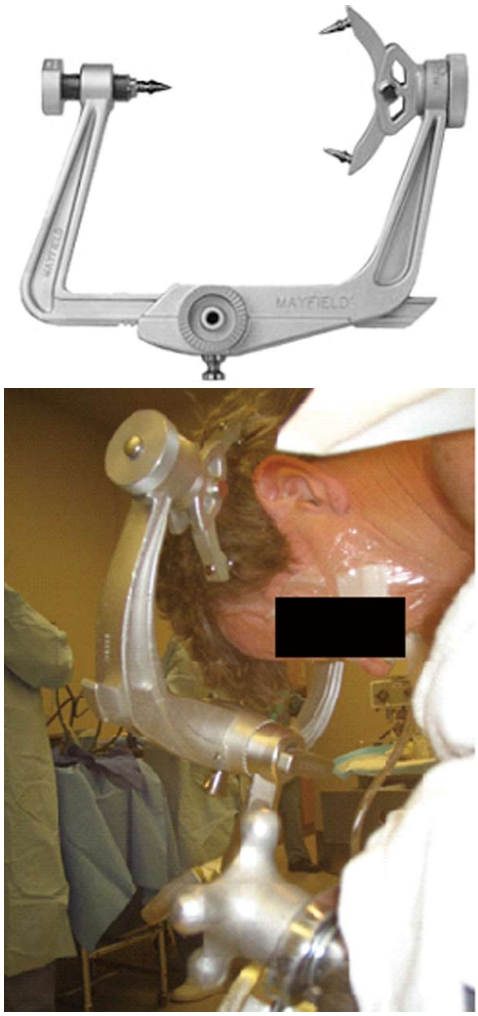

**Figure 4 Mayfield (pinned) head holder.**

**Figure 5 The proneview® allows prone positioning without any pressure on the facial structures.** The mirror provided allows frequent checking of facial structures in the prone position.

dependent shoulder and chest compared to a 1000 mL intravenous fluid bag or gel-pads. Prolonged lateralization of the cervical spine can stretch the brachial plexus on the nondependent side[180]. Pronation of the forearm, shoulder abduction more than 90°, extreme elbow flexion and extension should be avoided in the nondependent arm. The nondependent arm rest should be positioned in a way that maintain the arm horizontal and at the same level of shoulder joint (Figure 7). Excessive elevation of the nondependent arm at a level higher than the shoulder joint can overstretch the brachial plexus and predispose the patient to radial nerve injury in the nondependent arm.

POVL has been associated with spine surgery in the lateral decubitus position[139]. Asymmetric bilateral PION with significant involvement of the dependent eye has been reported after spine surgery in the lateral decubitus position[181]. Compression of the dependent eye should be avoided. Neutral forward position of the neck should be maintained to optimize venous drainage from the eye and the orbit. High-risk patients should be positioned with the head above the heart when possible[178].

**Supine and prone arms tucked positions:** Patients are placed in the supine arms tucked and prone arms tucked position for anterior and posterior cervical spine fusion surgeries respectively. The incidence of impending position-related upper extremity nerve injury detected by SSEP changes are 1.8% and 2.1% for the supine arms tucked and prone arms tucked positions respectively[86]. In both positions, it is important to position the forearm in a neutral position while padding the elbow with foam pad. The neck should be maintained in the neutral forward position whenever possible. In the prone arms tucked position, the use of a horseshoe head rest should be avoided. The use of the Mayfield pinned head holder is preferable to avoid direct external pressure on the eye. High-risk patients should be positioned with the head above the heart when possible[178].

### *Intraoperative management of physiological parameters*

Ischemic times and thresholds that may lead to clinical perioperative injury of the peripheral nerve and the optic nerve are not documented in humans. With the lack of

**Figure 6 Proper placement of chest roll under the dependent chest in the lateral decubitus position.** The chest roll should not be placed under the dependent axilla.

**Figure 7 Positioning the upper extremity in the lateral decubitus position. The shoulder abduction more than 90°, extreme elbow flexion and forearm pronation should be avoided in the nondependent arm.** The nondependent and dependent elbows should be padded with foam. Placing foam or blankets under the dependent hand and foreram to avoid full extension may reduce the likelihood of median nerve injury. Head and neck should be in neutral forward position avoiding neck flexion extension, lateral rotation and lateral flexion.

this knowledge, it is advisable to optimize physiologic parameters by maintaining them close to patient's baseline values, especially in high-risk cases. Physiologic parameters determining oxygen delivery to the peripheral nerve and the optic nerve may have additive or synergistic effect in predisposed patients placed in challenging operative positions for prolonged periods. Maintaining physiologic mean arterial blood pressure parameters, avoiding severe anemia and venous congestion are important aspects of intraoperative management that may improve oxygen delivery to areas at risk.

Although patient predisposition and intraoperative positioning are usually the risk factors associated with peripheral nerve injury, hypotension and anemia can affect oxygen delivery to the peripheral nerve especially in the presence of stretch or compression. Mean arterial blood pressure has been identified as an independent predictor of upper extremity neurapraxia detected by SSEP in the prone surrender position[182]. The extent and duration of hypotension, and anemia that may cause PPNI in predisposed individuals is not documented.

The ASA task force on the prevention of POVL believes that the use of deliberate hypotension during spine surgery has not been shown to be associated with the development of perioperative visual loss; however, it is advisable to avoid deliberate hypotension in high-risk patients (*e.g.*, with preoperative chronic hypertension). If deliberate hypotension will be used in patients without preoperative hypertension, the blood pressure should be maintained on average within 24% of baseline MAP or with a minimum systolic BP of 84 mmHg. Central venous pressure monitoring should be considered in high-risk cases. Colloids should be used with crystalloids in patients with substantial blood loss. Hemoglobin should be monitored periodically in high-risk cases with significant blood loss. There is no documented lower level of hemoglobin that would eliminate the risk of POVL[178].

Until we have a better understanding of the effects of hypotension and anemia on PPNI and POVL it is advisable to maintain intraoperative mean arterial blood pressure and hemoglobin levels close to preoperative levels in patients at high-risk for PPNI and POVL.

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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (5): Knee

# Enhanced microfracture techniques in cartilage knee surgery: Fact or fiction?

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## Abstract

The limited intrinsic healing potential of human articular cartilage is a well-known problem in orthopedic surgery. Thus a variety of surgical techniques have been developed to reduce joint pain, improve joint function and delay the onset of osteoarthritis. Microfractures as a bone marrow stimulation technique present the most common applied articular cartilage repair procedure today. Unfortunately the deficiencies of fibrocartilaginous repair tissue inevitably lead to breakdown under normal joint loading and clinical results deteriorate with time. To overcome the shortcomings of microfracture, an enhanced microfracture technique was developed with an additional collagen Ⅰ/Ⅲ membrane (Autologous, Matrix-Induced Chondrogenesis, AMIC®). This article reviews the pre-clinical rationale of microfractures and AMIC®, presents clinical studies and shows the advantages and disadvantages of these widely used techniques. PubMed and the Cochrane database were searched to identify relevant studies. We used a comprehensive search strategy with no date or language restrictions to locate studies that examined the AMIC® technique and microfracture. Search keywords included cartilage, microfracture, AMIC®, knee, Chondro-Gide®. Besides this, we included our own experiences and study authors were contacted if more and non published data were needed. Both cartilage repair techniques represent an effective and safe method of treating full-thickness chondral defects of the knee in selected cases. While results after microfracture deteriorate with time, mid-term results after AMIC® seem to be enduring. Randomized studies with long-term follow-up are needed whether the grafted area will maintain functional improvement and structural integrity over time.

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**Key words:** Cartilage; Microfracture; Autologous, Matrix-Induced Chondrogenesis; Knee; Chondro-Gide®

**Core tip:** Articular cartilage has a limited healing potential which presents a well-known circumstance in orthopedic surgery. This fact has led to a variety of surgical techniques for treating articular defects and currently the microfracturing presents the most commonly used procedure. The aim of this article is to give an overview about actual studies regarding microfracture and the AMIC® technique in cartilage knee surgery and to show recent developments.

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## INTRODUCTION

Articular cartilage has a limited healing potential which presents a well-known circumstance in orthopedic surgery[1]. The affected patients suffer from pain, stiffness and loss of quality of life. This fact has led to a variety of surgical techniques for treating articular defects and currently the microfracturing presents the most commonly used procedure[2]. Pridie recognized the potential of mesenchymal stem cell (MSCs) stimulation for the aim of cartilage repair in the 1950s while Steadman *et al*[3] described further developments of penetrating the subchondral bone for the recruitment of MSCs in the 1990s. In microfracture (MFx) the MSCs migrate in the fibrin network of the blood clot and this clot is transformed into repair tissue by the contained bone marrow components. In this context the blood clot is not mechanically stable to withstand tangential forces[4,5]. Therefore Benthien *et al*[6] developed the Autologous, Matrix-Induced Chondrogenesis (AMIC®) technique. This procedure uses a natural collagen Ⅰ/Ⅲ scaffold (Chondro-Gide®, Geistlich Pharma AG, Switzerland) which covers the microfractured area and stabilizes the formed blood clot. Several clinical results of AMIC® have already been published[6-9].

The aim of this article is to give an overview about actual studies regarding microfracture and the AMIC® technique in cartilage knee surgery and to show recent developments.

## PRE-CLINICAL RATIONALE

The potential of mesenchymal stem cell (MSCs) stimulation for the aim of cartilage repair was first described by Pridie[10]. Steadman developed out of this the microfracture technique[3]. Both techniques have similarities including focal penetration of the subchondral plate to expose cartilage defects to the benefits of cellular and growth factors influx, as well as improving anchorange of the new tissue to the underlying subchondral bone and to some extent surrounding cartilage. However, while functional outcomes have been reported, there is a paucity of data on the histological, biochemical and molecular changes in human patients[3,11].

Regarding the application of a collagen membrane in cartilage defects like used in AMIC®, Kramer *et al*[12] showed in an in-vitro work that a membrane consisting of collagen can retain cartilage building cells, like, *e.g.*, mesenchymal stem cells from bone marrow after microfracturing. In conclusion MSCs, found in the membrane, were successfully differentiated into adipogenetic, osteogenetic and chondrogenetic lineage. Dickhut *et al*[13,14] demonstrated in another in-vitro study that a biphasic carrier made of collagen type I/III, like for, *e.g.*, Chondro-Gide® (Geistlich Pharma AG, Switzerland) used for AMIC®, supports chondrogenesis of MSCs and further that in comparison to collagen-free-membrane the form stability of the repair tissue was enhanced.

Gille *et al*[15] tested in a sheep study with a follow-up period of 12 mo the addition of a collagen membrane to microfractured areas. The authors confirmed that the average thickness of the repair tissue was greater when a collagen Ⅰ/Ⅲ scaffold was used compared to microfracture alone.

## CLINICAL STUDIES

### *Microfractures*

While clinical efficacy of the MFx technique for articular cartilage repair in the knee has recently been subjected to an evidence-based systematic analysis (28 studies describe 3122 patients), the published data about AMIC is in comparison still limited[16].

In general diverse factors are known to influence the clinical outcome after microfractures: size and location of the defect, sex and age of the patient, surgical technique and postoperative rehabilitation program[17,18].

Regarding the size of the defect Gudas *et al*[19] showed in a prospective randomized clinical study that the International Knee Documentation Committee (IKDC) score in young athletes showed significant worse outcome in the microfractured group if the lesion was greater as 2 $cm^2$ and concluded that the lesion size affects the outcome of microfracture.

According to this, Knutsen *et al*[20] presented in another prospective randomized clinical study comparing autologous chondrocyte implantation with microfracture significant higher short form 36 (SF-36) scores in MFx group associated with lesions under 4 $cm^2$ and also concluded that the lesion size is associated with MFx outcome.

De Windt *et al*[21] analyzed in a prospective cohort study the prognostic value of the defect location (medial *vs* lateral) on clinical outcome 3 years after cartilage therapy for a focal cartilage lesion in autologous chondrocyte implantation (ACI) and MFx. The authors found a significant better Knee and Osteoarthritis Outcome Score (KOOS) for medial than for lateral lesions and therefore concluded that the defect location is related to clinical outcome of ACI and MFx. Another prospective cohort study by Kreuz *et al*[22] confirmed the effect of defect location for clinical outcome after microfracture procedure. IKDC and Cincinnati score as well as MRI findings showed significant better outcome when MFx was performed in femorale condyle versus tibia, trochlea and retropatellar regions.

In a prospective study by Mithoefer *et al*[23] a lower body mass index (BMI) correlated with higher scores for the activities of daily living and SF-36 after microfracture in 48 symptomatic patients with isolated full-thickness articular defects in the knee joint. Worst results were seen in patients with a BMI > 30 $kg/m^2$.

Highlighting the patients age, de Windt *et al*[21] showed in a prospective study treating 55 patients with MFx and ACI that the KOOS improvement was significantly better for patients under 30 years compared with older patients[21]. Data of a randomized controlled trial with 80 human subjects treated with ACI or MFx by Knutsen, are

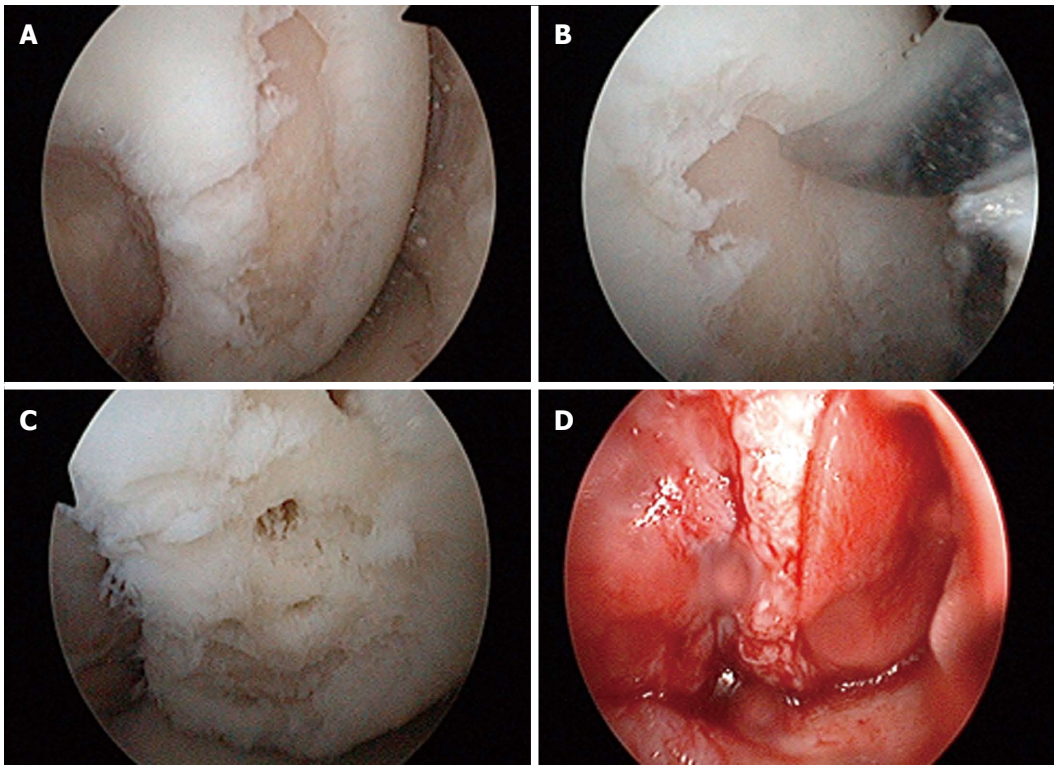


**Figure 1 Twenty years old female with a chondral defect on the lateral condyl after trauma.** The AMIC® technique was done arthroscopic assisted: after debridement of the chondral defect (A), numerous perforations of the subchondral lamina were performed (B, C). The implantation of the matrix was performed under dry, arthroscopic conditions, as published before (D)[27].

in accordance with findings from de Windt *et al*[21]. Both authors concluded that the patient age influences the clinical outcome of ACI as of MFx. In contrast we could not show a significant impact of age on the results after AMIC®[24].

### *Autologous, matrix-induced chondrogenesis*

To overcome the shortcomings of the microfracture technique, an enhanced procedure was first described in 2005 by Behrens *et al*[25] and first initial results were presented by our study group. Figure 1 shows step-by-step an arthroscopically AMIC® procedure. In a prospective series, we investigated 27 patients with a follow-up-period up to 62 mo and a mean of 37 mo. The mean age of the patients was 39 years (range 16-50 years) and the mean defect size was 4.2 $cm^2$ (range 1.3-8.8 $cm^2$). 87% of the patients were subjectively highly satisfied and the outcome scores applied [Lysholm, International Cartilage Repair Society (ICRS), Meyer, Tegner, Cincinnati] showed significant increase up to 24 mo. Patients with lesions larger 8 $cm^2$ had greatly reduced scores. In this series, a potential gender-specific dimorphism was obvious; males had significantly higher values in the ICRS score compared with their female counterparts[24]. We couldn't approve these findings in a recent study evaluating 57 patients treated with AMIC[8]. In this study a significant decrease of pain in the visual analogue scale (VAS) from a mean of 7.0 preoperatively to 2.7 at 1 year and 2.0 at 2 years postoperatively was found (Figure 2). Improvement of the Lysholm score also showed significant results with a mean score of 50.1 preoperatively, 79.9 at 1 year and 85.2 at 2 years postoperatively (Figure 2). Younger patients with no ligamentous instability, meniscal deficiency or patellofemoral malalignement had the best outcome[8].

Kusano *et al*[26] presented clinical and radiographic results in a retrospective study with a mean follow-up of 29 mo of patients treated with AMIC for full-thickness cartilage defects of the knee. They found significant improvements in the IKDC, Lysholm, Tegner and VAS pain score. Moreover, the patients were satisfied while the MRI findings showed generally incomplete or inhomogeneous tissue filling.

A current randomized, controlled trial by Anders *et al*[7] compared the AMIC technique with microfracture during 1- and 2-year follow-up. The authors included 38 patients with a mean defect size of 3.4 $cm^2$ and mean age of 37 years. The clinical follow-up was performed with the modified Cincinnati and the IKDC score. MRI findings revealed a homogenous defect filling in the majority of patients (Figure 3). No significant statistical differences could be found between the groups but improvements in both scores were seen at 1- and 2-years postoperatively. It is open to debate if a significant difference of both groups has to be expected within the first 2 years of follow-up.

Modifications to the original AMIC technique may have a promising future. An arthroscopic approach of the AMIC® technique was published by Piontek *et al*[27]. Compared to open surgery, the described arthroscopic technique may offer advantages including minimal soft

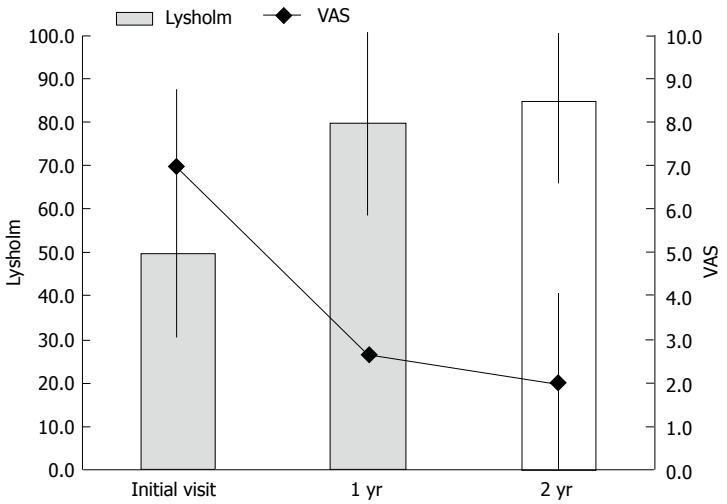


**Figure 2 Significant improvements of the mean Lysholm and visual analogue scale score after 1 year and further increased values up to 2 years postoperatively in patients with cartilage knee defects treated with AMIC®[32].** VAS: Visual analogue scale.

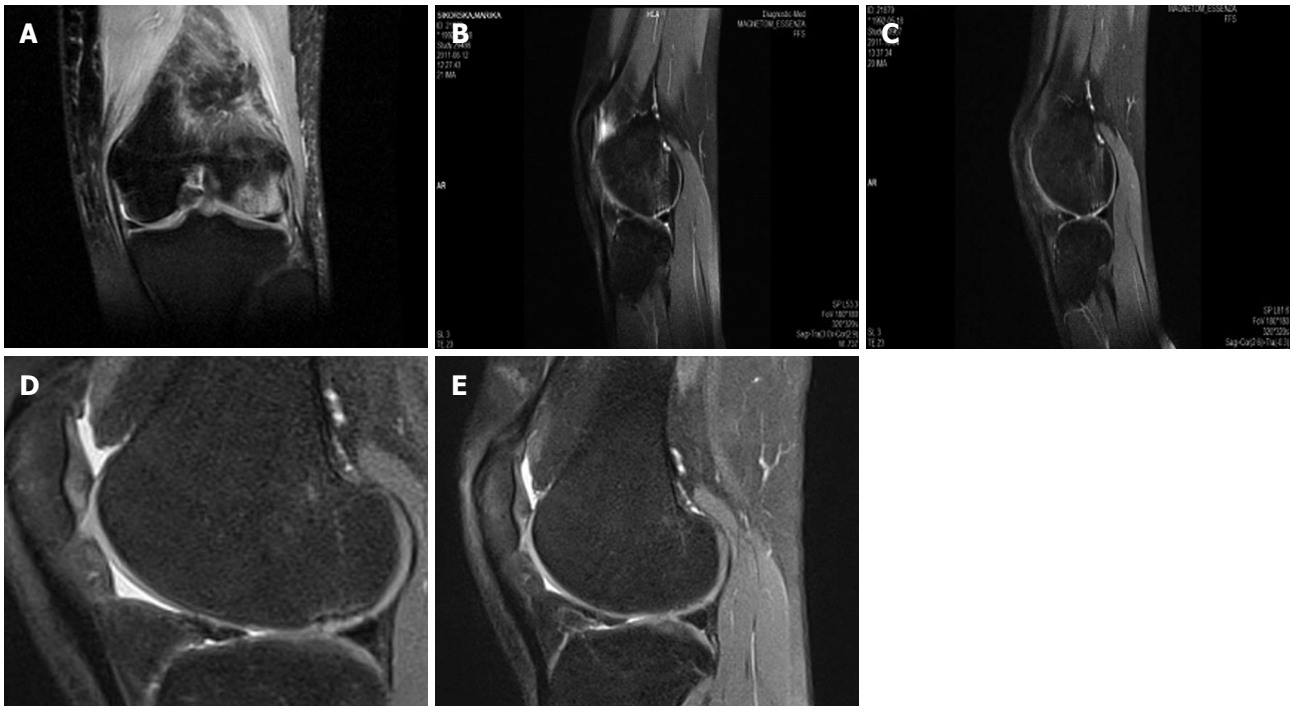


**Figure 3 The same patient showing enhanced defect filling demonstrated by follow-up magnetic resonance imaging before surgery (A) and 3 (B), 6 (C), 12 (D) and 24 mo (E) after the index procedure.**

tissue trauma and minimal blood loss. Dhollander *et al*[28] *e.g.*, performed a modified so called AMIC plus technique (AMIC plus platelet-rich-plasma gel) and were able to show clinical improvements. Emerging techniques, *e.g.*, the addition of concentrated bone marrow from the iliac crest or platelet rich plasma gel may be beneficial, but the impact needs to be proven in further studies[29]. Benthien *et al*[30] and Chen *et al*[31] presented in a recent study first results with a so called nanofracture®.

## CONCLUSION

In conclusion both techniques (microfracture and AMIC®) present an effective and safe method of treating full-thickness chondral defects of the knee. While results after microfractures deteriorate with time, clinical outcome after AMIC® seems to be more enduring. By now, only one randomized trial has been published comparing microfractures and AMIC®. This limitation involves the extent to which the findings can be generalized beyond the cases studied. The number of cases is too small for broad generalizations. However, these limitations should be seen as fruitful avenues for future research along the same lines.

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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (5): Knee

# Principles of postoperative anterior cruciate ligament rehabilitation

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## Abstract

It is known that anterior cruciate ligament (ACL) reconstruction needs to be combined with detailed postoperative rehabilitation in order for patients to return to their pre-injury activity levels, and that the rehabilitation process is as important as the reconstruction surgery. Literature studies focus on how early in the postoperative ACL rehabilitation period rehabilitation modalities can be initiated. Despite the sheer number of studies on this topic, postoperative ACL rehabilitation protocols have not been standardized yet. Could common, "ossified" knowledge or modalities really prove themselves in the literature? Could questions such as "is postoperative brace use really necessary?", "what are the benefits of early restoration of the range of motion (ROM)?", "to what extent is neuromuscular electrical stimulation (NMES) effective in the protection from muscular atrophy?", "how early can proprioception training and open chain exercises begin?", "should strengthening training start in the immediate postoperative period?" be answered for sure? My aim is to review postoperative brace use, early ROM restoration, NMES, proprioception, open/closed chain exercises and early strengthening, which are common modalities in the very comprehensive theme of postoperative ACL rehabilitation, on the basis of several studies (Level of Evidence 1 and 2) and to present the commonly accepted ways they are presently used. Moreover, I have presented the objectives of postoperative ACL rehabilitation in tables and recent miscellaneous studies in the last chapter of the paper.

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**Key words:** Anterior cruciate ligament rehabilitation; Eccentric exercise; Proprioception; Strengthening; Postoperative; Anterior cruciate ligament

**Core tip:** In this topic highlight, I will review the answers given by some literature studies to questions in the literature about anterior cruciate ligament rehabilitation such as "could common ossified knowledge or modalities really prove themselves?", "is postoperative brace use really necessary?", "what are the benefits of early restoration of the range of motion?", "to what extent is neuromuscular electrical stimulation effective in protecting from muscular atrophy?", "how early can proprioception training and open chain exercises begin?", "should strengthening training start in the immediate postoperative period?"

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## INTRODUCTION

Anterior cruciate ligament (ACL) reconstructions have to be combined with detailed postoperative rehabilitation in order for patients to return to their pre-injury activity levels. ACL reconstruction ensures structural ligament repair, whereas rehabilitation protects and maintains the lig-

**Table 1 Goals of 0-1 mo (acute phase)**

| |
|---|
| Education of patient |
| Pain control |
| Decrease effusion |
| Increase range of motion |
| Be able to do straight leg raise (1–2 d[1]) |
| Be able to lift the leg in all directions without assistance (1–7 d) |
| Flexibility (hamstrings, calves) |
| Strengthening (quadriceps, hamstrings, hip, calf, core, upper body, non-injured leg) |
| Patellar mobilization |
| Proprioceptive/balance training (start walking with crutches) |
| Start cardiovascular fitness (arm ergometer) |
| Achieve and maintain near or full ROM in knee flexion and extension (full extension 1–5 d[1], full flexion 2-3 wk[1]) |
| Achieve and maintain weight bearing gait (2 crutches 0-1 wk[1], 1 crutch 0-1 wk[1], no crutches 0-2 wk[1]) |
| No apprehension when walking without a crutch |
| Home training program (2-3 h/d[1], therabands, ROM exercises, *etc.*) |
| Start bicycling (90°-100° in active flexion[1]) |
| Start pool exercises (after suture removal, when wound is closed[1]) |
| Start to fight with fear of re-injury physically and psychologically |
| Return to work (3-4 wk[1] if office work) |
| MD visit 1/wk |

[1]Author's approach.

ament repair and the physical and psychological state and performance capabilities of the athlete. The above paragraph is maybe the summary of the one point on which there is consensus about ACL reconstruction. Different rehabilitation protocols post-ACL reconstruction exist in our country and all over the world at sports medicine departments of universities and sports medicine clinics, as indicated on their websites. This lack of consensus led to uncertainties, which resulted in aggressive and non-aggressive approaches. Studies in the literature tried to determine the earliest optimal time to start rehabilitation and how long it should take, considering all parameters of the rehabilitation process. Although there are many studies on this topic, there is a lack of consensus in the literature even about commonly accepted modalities. Today, specialists decide on the type of exercises that need to be prescribed, and when in the ACL rehabilitation process to start them on the basis of their experience and interpretation of the condition. Different interpretations lead to more questions, which in turn lead to more original articles. New trial outcomes modify and develop current protocols. Thus, it would not suffice to say that the required exercises or modalities should be performed in a specific period of time. The ACL rehabilitation objectives that I summarize in Table 1, Table 2, Table 3 and Table 4 do not indicate a precise time; the times may overlap and modifications have to be made on the basis of the criteria associated with the time schedule.

Protocols and interpretations may differ in ACL rehabilitation approaches, but what remains the same is the outcome that every sports medicine specialist tries to achieve. The overall objectives before a return to sports activities are control of pain and swelling, a full range of motion and flexibility, elimination of muscle atrophy, a normal gait, a return to work for non-athletes, a return to pre-injury muscular strength and endurance levels, maintenance of cardiovascular fitness, restoration of proprioception, a return of self-confidence and overcoming kinesiophobia. When all these objectives are achieved the athlete can return to sports activities.

**Table 2 Goals of 1-4 mo (maintenance and acceleration phase)**

| |
|---|
| Decrease and disappearance of effusion |
| Full and pain-free knee range of motion |
| Continue flexibility exercises |
| Continue strengthening exercises (add isokinetic hamstring exercises) |
| Swimming |
| Bicycling (indoor) |
| Core training progression |
| Proprioceptive progression (focus on weak positions) |
| Maintain cardiovascular fitness |
| Determine and manage hamstring, quadriceps strength deficits |
| Prepare physically and psychologically for jogging |
| Deep water running |
| MD visit 2/mo |

My aim is a review of the most common modalities in ACL rehabilitation, such as postoperative bracing, early range of motion (ROM), neuromuscular electrical stimulation (NMES), proprioception, open/closed chain exercises and early strengthening; I preferred not to approach the subject from the basic definitions and historical perspective, and present in the last chapter recent miscellenous studies.

## POSTOPERATIVE BRACE USE

The objectives of postoperative brace use are restriction and development of the ROM of the knee, resistance of the knee to medial and lateral stressors, knee stability, and protection from knee injuries, however its role in ACL rehabilitation is controversial.

McDevitt *et al*[1] reported in 2002 that there was no definite evidence of improvements in outcomes or protection from re-injuries associated with the use of a brace in postoperative ACL reconstruction.

Swirtun *et al*[2] stated that use of a brace in non-operated ACL-injured patients reduced the feeling of instability, but increased complaints during day-to-day activities. They also underlined in their trial that the positive effects were not supported by objective outcomes.

Wright *et al*[3] indicated in a systematic review in 2007 that wearing of a knee brace had no additional treatment value after ACL reconstruction. This conclusion was supported in 2009 by Andersson *et al*[4].

Birmingham *et al*[5] conducted a randomized controlled trial in 2008 to compare the outcomes of a rigid knee brace and a neoprene sleeve in 150 patients post-ACL reconstruction during exercise and all physical activities. The authors stated in the conclusion of their trial that the use of a rigid knee brace postoperatively was not superior to the use of a neoprene sleeve on the measured outcomes. Nevertheless, they stressed that the subjective

**Table 3 Goals of 4-6 mo (sports-specific phase)**

| |
|---|
| No effusion |
| Pain free jogging and running (no effusion) |
| Pain free landing (from double to single leg) |
| Pain free hopping (from double to single leg) |
| Functional strengthening (plyometrics, agility drills, *etc.*) |
| Sports specific proprioception training |
| Sport specific cardiovascular fitness |
| Training in the sports field |
| Adequate neuromuscular control |
| Continue fighting against fear of re-injury |
| Success in functional tests |
| MD visit 1/mo |

**Table 4 Month 4-6 (return to sports phase)**

| |
|---|
| Flawless running |
| Good psychology |
| Maintain good results of functional tests |
| Adequate sports specific aerobic/anaerobic measures |
| Quadriceps and hamstring strength at least 85% of the normal leg |
| No swelling |
| No laxity |
| No fear |

confidence rating of patients that used the rigid knee brace was higher than in the neoprene sleeve group[5].

Can the use of a brace attenuate pain, which is a significant problem in the postoperative period? Hiemstra *et al*[6] tried to answer this question in their randomized controlled trial from 2009. They carried out a comparative study of pain, use of analgesics, effusion and ROM parameters in 88 patients who were immobilized and non-immobilized post-ACL reconstruction. For immobilization, a soft, unhinged knee brace was used. They found no differences in pain or any of the secondary outcomes between immobilized and non-immobilized patients at any point during the first 14 d after ACL reconstruction[6].

Mayr *et al*[7] randomized 73 patients to compare the clinical outcomes of postoperative ACL rehabilitation using a water-filled soft brace to those using a hard brace. Braces were applied for 6 wk after the surgery. The soft brace group had significantly higher postoperative International knee documentation committee (IKDC) subjective ratings, Tegner activity scores and Lysholm knee scores and significantly less effusion. The hard brace group had significantly more extension deficits and no significant difference was reported between the groups on knee ROM, knee laxity and thigh atrophy parameters. The authors stated that the water-filled soft brace was easy-to-use and safe and might be an efficacious alternative to the hard brace[7].

In a recent study, Stanley *et al*[8] reported that the use of a knee extension constraint brace reduced the peak posterior ground reaction force when walking, but this effect was not observed when descending stairs and jogging. They concluded that the knee extension brace modified the lower extremity movement pattern which made re-injuries less possible and this is why it could be used for postoperative ACL rehabilitation[8].

Kruse *et al*[9] investigated the outcome of 11 studies in their systematic review and concluded that the postoperative use of a brace did not provide any additional benefits. Lobb *et al*[10] found in their systematic review strong evidence of no added benefit of the use of a brace for 6 wk postoperatively compared with standard treatment in the short term. Meuffels *et al*[11] reported in their study, which referred to the recommendations of the Dutch Orthopaedic Association, that a brace can be used in patients with instability symptoms who do not qualify or who do not want to qualify for operative treatment.

In our clinical approach, we do not use postoperative braces in many of our patients. We prefer using braces for only 1-2 wk in patients who find it difficult to regain their confidence or are temperamentally conservative and anxious. In our clinical experience, the most common complaints associated with postoperative brace use are too much restriction during motion and the desire to be able to move independently sooner. The question "is the use of a brace required?" is mainly answered with "No, it is not" by the literature. Nevertheless, as indicated in the introduction, optimistic specialists based on their clinical experience and referring to trials that find the use of braces beneficial continue using them in the postoperative period. I think that force vectors of the knee joints during movement need to be investigated and compared in future research studies in order to clarify this point.

## EARLY RESTORATION OF ROM

Many investigators underline that the priority goal of postoperative ACL rehabilitation should be restoration of the full ROM[12-15].

Rubinstein *et al*[12] reported that full knee extension in the immediate postoperative period in 194 patients that underwent autogenous bone-patellar-tendon ACL reconstruction did not damage the graft or joint stability. Protection of the graft is important for both the patient and the orthopedist who performed the surgical procedure. Orthopedists refer their patients to those sports medicine clinics they are convinced will perform a rehabilitation modality that will not adversely affect the graft recovery process. It is obvious that patient compliance with the rehabilitation protocol will improve when patients trust the orthopedist who performed the surgical procedure, and orthopedists trust physicians responsible for the rehabilitation program.

An early start to quadriceps exercises in the postoperative period has been reported to improve early ROM development[13]. Another study found that restoration of symmetrical ROM in the early period of ACL rehabilitation was quite valuable for long-term ROM maintenance of the patients[14]. Early restoration of strength and ROM will accelerate early mobilization of the patient and more effective participation of the patient in the following rehabilitation phases. This in turn will allow for different training activities to be performed on the knee joints and long-

term ROM maintenance will be ensured. Previous studies have shown that patients who maintain normal ROM according to IKDC criteria have better outcomes after ACL reconstruction[16,17]. In their study of the long-term outcomes of postoperative ACL reconstruction, Shelbourne and Gray reported that the most important reason for low subjectivity scores of the patients was the absence of normal knee extension and normal knee flexion[17].

The reason for early ROM restoration brings to the fore the question of whether rehabilitation should be accelerated or non-accelerated. There is no consensus on this subject in the literature. Beynnon *et al*[18] reported that in postoperative ACL rehabilitation, accelerated programs were not significantly different from non-accelerated programs on knee laxity, clinical assessment, proprioception, functional performance and thigh muscle strength parameters. Shelbourne followed the recommendations regarding immediate full extension and maintenance and stated that, after ACL reconstruction graft remodeling, continued loss of ROM could be associated with long-term osteoarthritis modifications in radiography[15].

In a recent study, Christensen *et al*[19] found no differences between early aggressive and nonaggressive rehabilitation after ACL reconstruction on the primary outcomes of knee laxity and subjective IKDC score. In addition, they observed no differences in secondary outcomes between groups for differences in ROM and peak isometric force values. Kruse *et al*[9] stressed in the conclusion of their systematic review that further investigations were needed to clarify the effect of accelerated, aggressive rehabilitation on quick return to sports.

In the light of the above studies we can say that the importance of early ROM recovery in postoperative ACL rehabilitation is obvious. However it is still uncertain when to start ROM exercises in the early postoperative period. Early ROM of extension and flexion is known to reduce the risk of arthrofibrosis[20]. We target a full ROM in the first 2-3 wk in our patients. This can be accepted as the accelerated approach in the literature. In our experience, ROM recovery in the first 2-3 wk should be encouraged unless there is a problem with compliance of the patient with the treatment.

## NEUROMUSCULAR ELECTRICAL STIMULATION

In the early phase, normal gait should be restored by controlling and synchronizing the quadriceps with the antagonist hamstring. Improvement of gait varies from person to person. Sensitivity to pain, anxiety and other factors can prolong this period. In this phase, in nearly all cases atrophy of the quadriceps caused by a knee effusisson that inhibits the quadriceps muscle is observed. Many studies have proven that electrical stimulation (ES) protects from muscle atrophy[21-23].

Sisk *et al*[24] examined the effect of prolonged daily ES on quadriceps strength in casted 22 patients during the 6 wk following anterior cruciate reconstruction. They found no difference in quadriceps strength between the two groups during the 7th, 8th, and 9th week postoperatively. The length of time (how much time per day and how many weeks) for the use of ES in the ACL rehabilitation process is not known yet.

Wigerstad-Lossing *et al*[21] in a 1988 study found that the effect of ES plus voluntary muscle contraction increased the isometric muscle strength more than control group. In the conclusion of their study they stated that ES combined with voluntary muscle contraction was significantly protecting from atrophy of the muscles. In a study in 1988 Delitto *et al*[22] compared the isometric torque values of an ES co-contraction group and voluntary isometric co-contraction group in postoperative ACL reconstruction. They found that isometric torque was significantly increased in the extensors and flexors in the ES group.

In a study in 1991, Snyder-Mackler *et al*[23] evaluated 10 patients who were randomized to ES with voluntary contraction *vs* only voluntary contraction. They found a significantly positive difference in the ES group on the values for cadence, walking velocity, stance time of the involved limb, and flexion-excursion of the knee during stance *vs* the voluntary exercise group. They emphasized that the ES group had stronger quadriceps muscles and more normal gait patterns than those in the voluntary exercise group[23].

In a study in 1995 Snyder-Mackler *et al*[25] investigated 110 patients in 4 groups, a high-intensity NMES group, a high-level volitional exercise group, a low-intensity NMES group, and a combined high- and low-intensity NMES group. They found that high intensity ES either alone or in combination with low intensity ES increased recovery of the opposite limb quadriceps strength.

Although most of the above-mentioned studies stressed the benefit of ES, Wright *et al*[26] reported in a systematic review in 2008 that the quality of these studies varied; many did not address randomization or were not blinded and their results were not evaluated by independent observers. In the light of these findings, they underlined that NMES helped the development of the quadriceps, but one could not conclude that NMES was certainly required for successful ACL rehabilitation[26].

In a study in 2011, Hasegawa *et al*[27] administered NMES from postoperative day 2 following ACL reconstruction until the 4th month. They reported that early NMES helped the recovery of knee extension strength measured at 3 mo postoperatively. Moreover, there was a significant increase in the vastus lateralis and calf thickness at 4 wk postoperatively in the NMES group *vs* the control group[27].

In an interesting recent study, NMES was found to modify gene expression in mice post-ACL surgery and delay atrophy of the muscles. NMES was reported to decrease atrogene and myostatin accumulation in the quadriceps muscle and protect from early atrophy on postoperative day 3 but did not affect atrophy on the 7th and 15th day[28]. Future human gene studies may be the key in answering the question of how long NMES and

other modalities should be applied postoperative.

Most of the above-mentioned studies report that NMES contributes to atrophy prevention in postoperative ACL rehabilitation[21-23,25,27], whereas some publications report no such effects[24,26]. When using NMES as part of our treatment we ask the patient to do voluntary muscle contraction each time. Even if we assume that NMES is not efficacious, we think that it could contribute to atrophy prevention when combined with voluntary muscle contraction.

## PROPRIOCEPTION

Balance and proprioception training have a positive effect on joint position sense, muscle strength, experienced knee function, outcome of functional capacity, and return to full activity[29-32]. Hewett *et al*[33] stated that balance exercises on the balance board could start early in the postoperative period. Proprioceptive exercises actually begin when the patient steps on the ground early in the postoperative period. Early start of locomotion at a level tolerated by the patient will ensure early restoration of proprioception and facilitate progress in proprioceptive exercising.

Friden *et al*[34] reported in a review published in 2001 that despite the existence of many proprioception tests there were no standardized reference tests. They also underlined that the link between the conscious and non-conscious proprioceptive system and their specific roles was unknown. Additionally, they stated that information regarding how proprioceptive training restored sensorial defects was limited. Nevertheless, they reported that during rehabilitation each patient must create muscle strength, alertness, and stiffness in harmony with the disturbed mechanics of the knee, which were present both after nonoperative treatment of the ACL and after a reconstruction of the ACL[34].

In a systematic review published in 2003, Thacker *et al*[35] stated that neuromuscular and proprioceptive training was an important factor in protection from knee injuries. At the same time, they wrote that the studies reviewed were inadequate due to methodological mistakes, and more studies were needed to shed light on this topic in the future[35].

A study in 2005 investigated the effect of early proprioceptive coordination training on neuromuscular performance values post-ACL surgery. The authors stated they found a highly statistically significant correlation between the single leg stance, one leg hop, Lysholm, and Tegner tests at 6 wk, and 4, 6, 9 and 12 mo in the postoperative period[36].

In a randomized controlled study, Cooper *et al*[37] compared the effects of proprioceptive and balance exercises and the strengthening program in the early period post-ACL reconstruction. The investigators reported that the strengthening exercise group had better Cincinnati and patient specific functional scale scores than the proprioceptive group, and early postoperative strengthening training could be more beneficial than proprioceptive training[37]. It is difficult to clearly draw the line between muscle strengthening training and proprioceptive training. Each strength training has proprioceptive properties and most proprioceptive exercises have strength-associated properties.

Angoules *et al*[38] compared knee proprioception post-ACL reconstruction with hamstring *vs* patellar tendon autografts. They reported that there was no statistically significant difference in the joint position sense and threshold to detection of passive motion values between graft groups during any time period, and the knee proprioception returned to normal in postoperative month 6[38].

In a systematic review in 2011, Howells *et al*[39] tried to answer the question whether postural control could be restored postoperative ACL reconstruction. The authors stated that the results were not conclusive due to the limited number of studies on this topic and different methodologies applied in them. They stressed that deficits in dynamic tasks may be more relevant to people intending to return to sport following surgery due to the inherently dynamic nature of sport and should perhaps be the focus of future research[39].

In a recent study, athletes who underwent postoperative ACL reconstruction proved able to start balance training on the Biodex platform 4 wk earlier than with the use of the conventional approach. The authors concluded that the combination of classical rehabilitative techniques with balance training, Speed Court training, and training on the alpine ski simulator made it possible to begin special alpine ski training on the snow 2 mo earlier than with the use of conventional methods[40].

There is no clearly defined starting time for proprioceptive training. Regain of confidence, absence of pain and willingness to exercise are factors contributing to the start of balance training.

## OPEN/CLOSED CHAIN EXERCISES AND EARLY STRENGTHENING

Closed chain exercises can be introduced in early rehabilitation due to their benefits, *e.g.*, reduction of shear and acceleration forces on the joints, development of dynamic early joint stability and stimulation of proprioceptors. The question is which open chain exercises can be used safely at which stage in the rehabilitation process. According to Fitzgerald, closed chain exercises are considered safer and more functional compared to open chain exercises[41]. Notwithstanding, Seto *et al*[42] stated that the open and closed chain exercises could co-exist in enabling rehabilitation and strengthening objectives. In their prospective randomized trial, Bynum *et al*[43] reported that closed kinetic chain (CKC) exercises were recommended to provide improved arthrokinematics in comparison with open kinetic chain (OKC) exercises for rehabilitation of ACL injury. Kvist *et al*[44] stated that CKC exercises produced a smaller magnitude of anterior tibial translation (ATT) than OKC activities.

Some studies[45,46] have reported that the kinematic ef-

fects, resulting from hamstring co-activation and increase in the joint compression force during CKC exercises, are not sufficient to reduce ATT significantly. There are also reports of larger ATTs and similar ACL strain during CKC compared with OKC exercises[45,47]. In the early phase of rehabilitation, closed-chain exercise therapy is likely to give fewer patello-femoral complaints and less laxity than open-chain exercises[4,26,31]. Heijne *et al*[48] aimed to evaluate physical outcome after ACL reconstruction with early *vs* late initiation of OKC exercises for the quadriceps in patients operated on either patellar tendon or hamstring grafts. They reported an exercise program with early OKC exercises (postoperative week 4) would lead to more laxity with hamstring grafts than late OKC exercises (postoperative week 12)[48].

Glass *et al*[49] published a systematic review about the effects of open *vs* closed kinetic chain exercises on patients with ACL-deficient or -reconstructed knees in 2010. In their conclusion, they wrote that CKC and OKC exercises seem to have similar outcomes on knee laxity, knee pain, and function and therefore could both be used during the rehabilitation of a patient with ACL deficiency or post-ACL reconstruction[49]. They stated that one article found positive significant effects with inclusion of OKC exercises in the rehabilitation program[50] and another found significant benefits with a combination of OKC and CKC exercises[51]. CKC exercises alone were not found by any studies to be superior to OKC exercises. Mikkelsen *et al*[51] found that using CKC and OKC exercises together led to greater quadriceps torque return and a quicker return to sport than CKC alone. Tagesson *et al*[50] reported that OKC exercises for quadriceps led to better gains in quadriceps strength than when using CKC exercises. In their systematic review, Glass *et al*[49] concluded that OKC exercises should be initiated after the 6$^{th}$ week of the postoperative period. Meuffels *et al*[11] stated that only the use of closed-chain exercises was recommended in early rehabilitation.

A recent study measured the amount of ATT of ACL-deficient knees during selective OKC and CKC exercises. The authors found no significant differences between the ATTs of the ACL-deficient and intact knees at all flexion angles during forward lunge and unloaded open kinetic knee extension. Nevertheless, they recommended that weight-bearing CKC exercise should be preferred over OKC knee extension exercises in ACL-deficient knees[52].

Fridén *et al*[53] stated that there were no clinical trials that evaluated outcomes of OKC exercises in a restricted ROM for pain, function, muscle strength, and anterior knee laxity at 1 year after surgery. The goal in their randomized controlled clinical trial was to determine if an early start of OKC exercises for quadriceps strength in a restricted ROM would promote a clinical improvement without causing increased anterior knee laxity in patients after ACL reconstruction. They concluded that an early start of OKC exercises for quadriceps strengthening in a restricted ROM did not differ from a late start in terms of anterior knee laxity.

In a study in 2005, Shaw *et al*[13] started isometric quadriceps exercises and straight led raises in a group immediately postoperative and compared the result with the non-exercise control group. In postoperative week 2, both groups were enrolled in the same rehabilitation system. They concluded that there was no significant difference in the 6$^{th}$ month postoperatively regarding knee laxity, hop tests, Cincinnati score and isokinetic quadriceps force measurements[13].

Gerber *et al*[54-56] compared the effects of progressive eccentric exercises started in 3$^{rd}$ and 12$^{th}$ week after ACL reconstruction. In their first study, eccentric exercises were performed in knees with full ROM at 20°-60° knee flexion. They reported no statistically significant difference between both groups on pain, effusion and anterior laxity parameters in the 14$^{th}$ week postoperatively[55]. In another study in 2009, they extended the follow-up period to 1 year and detected a statistically significant increase in the cross-sectional areas and volumes of the quadriceps and gluteus maximus muscles and in the quadriceps muscle strength in the group that started eccentric exercises early *vs* late[56].

Sekir *et al*[57] compared the outcomes of isokinetic hamstring strengthening exercises initiated in 3$^{rd}$ and 9$^{th}$ wk post-ACL reconstruction with patellar tendon autograft. The group that started early hamstring strengthening had a better quality of life, activities of daily living in the 1$^{st}$ month, and isokinetic hamstring strength performed at 60°/s angular velocity. Sekir *et al*[57] reported that early hamstring strengthening was not harmful at any point in time during the ACL rehabilitation process.

In a systematic review in 2012, Kruse *et al*[9] reported that immediate postoperative weight-bearing, knee ROM from 0° to 90° of flexion, and strengthening with closed-chain exercises were likely safe, and starting eccentric quadriceps strengthening and isokinetic hamstring strengthening at week 3 after ACL surgery might improve or accelerate strength gains.

In the literature, CKC exercises were proved to benefit the patient in the early postoperative period and new studies focus on the safest point in time to start OKC exercises in early ACL rehabilitation. This remains uncertain. We want to underline that in our clinical approach we are cautious when it comes to the initiation of early postoperative OKC exercises.

## RECENT MISCELLANEOUS STUDIES

In this part, I have reviewed the outcomes of some recent interesting studies.

In a study published in 2013 patients that underwent ACL surgery were divided into 2 groups, smokers and non-smokers. The stability and functional scores of the smokers were found to be worse (less satisfactory) than those of the non-smokers. The Achilles tendon-bone allograft of the smokers group rendered the worst result *vs* the other autografts, and the bone-patellar tendon-bone autograft was reported to be more appropriate for ACL reconstruction in smokers[58].

A 15-year prospective, randomized, controlled trial published in 2013 compared the failure rate, knee injury osteoarthritis outcome score (KOOS) (pain, symptoms, Sport/Rec, quality of life, daily living function), Tegner activity scale, anterior knee pain-score, Lysholm score, Rolimeter laxity, extension deficit, single hop and crossover hop for distance outcomes of an iliotibial band autograft and bone-patellar-bone autograft. The authors concluded that the use of an iliotibial band graft could be a safe alternative[59].

In a recent study, Månsson *et al*[60] aimed to identify preoperative factors that had a positive affect on postoperative health-related quality of life. The study concluded that preoperative pivot shift, knee function, ROM and Tegner activity levels were significant factors for postoperative health-related quality of life[60].

A systematic review published in 2013 investigated the psychological predictors of postoperative ACL reconstruction. Self-confidence, optimism, and self-motivation factors were reported to have a predictive value for outcomes. They stated that postoperative emergence of knee symptoms and compliance with rehabilitation were adversely affected by preoperative stress and positively affected by social support[61].

In a randomized, controlled trial published in 2013, Frobell *et al*[62] followed-up 121 patients for 5 years who were part of the same rehabilitation program after ACL reconstruction. The trial concluded that early or late ACL reconstruction did not differ significantly in absolute KOOS4 score, all 5 KOOS subscale scores, SF-36, Tegner activity scale, meniscal surgery, and radiographic osteoarthritis parameters[62].

A retrospective comparative study published in 2013 investigated the return to sport rates after ACL reconstruction; 46% of 135 patients returned to their preinjury levels while 56% did not (non-returners). Half of the reasons why non-returners did not return to sport were related to fear of reinjury[63].

Fridén *et al*[64] reported that the impact of fear on self-report of function and performance following ACL reconstruction was less clear. The findings of this study lend further support to the theoretical application of the fear-avoidance model in knee rehabilitation, and identified fear of movement/reinjury as a potential target for ACL reconstruction rehabilitation guidelines.

Nyland *et al*[65] drew attention to the importance of kinesiophobia. They believed that increased self-efficacy and confidence and decreased kinesiophobia suggested a greater patient willingness to use the involved lower extremity. Ardern *et al*[66] stated that the single limb hop for distance and the crossover hop test scores served as indicators of an athlete's likelihood to return to sport.

On the other hand, in their systematic review, Narducci *et al*[67] underlined that although functional performance testing was valuable for the assessment of ACL injured patients, they did not identify any clinical test or battery of tests that predicted the athletes' ability to return to play sports.

In a cohort study in 2012, Logerstedt *et al*[68] stated that the outcomes of the single-legged hop tests conducted in the 6$^{th}$ mo after ACL reconstruction were valuable in predicting outcomes in the 1$^{st}$ postoperative year, whereas preoperative single-legged hop tests did not have a predictive value for the postoperative outcome. Moreover, they indicated the presence of minimal side to side differences in the crossover hop tests conducted in the 6$^{th}$ mo postoperatively could improve knee functions in the 1$^{st}$ year postoperative period if patients continued with the training program[68].

Two separate studies reported that the coordinated coactivation of the hamstrings and quadriceps might play a role in mitigating primary injury risk by reducing ligament strain[69] and promoting normal landing mechanics[70]. In a cross-sectional study in 2012, Begalle *et al*[71] reported that the most balanced quadriceps-hamstring coactivation ratios were identified in the single-limb deadlift, lateral-hop, transverse-hop, and lateral band-walk exercises which could be safely used in post-injury rehabilitation programs. They stressed that balanced agonist and antagonist coactivation might also protect the reconstructed knee against second ACL injury risk *via* similar protective mechanisms[71].

## CONCLUSION

The basic approach in ACL rehabilitation is to ensure a return to sports activities at the 6$^{th}$ mo postoperatively. However, many studies have been and will be conducted with the purpose of shortening this period for all rehabilitation modalities. The objective is to find the optimal strengthening and maximal safe loading times and type of loading for all rehabilitation modalities without creating ACL re-injury. Although there are many studies in the literature on ACL rehabilitation that have not been mentioned in this review, they did not result in the setting of definite and clear criteria and standards, and the reason could be that these have touched upon the mere surface of the topic. As new studies are underway with the advancement of technology we hope to find out how modalities used in ACL rehabilitation affect genetic and biochemical pathways. Today postoperative ACL rehabilitation guidelines are time-focused. This approach makes implementation of the program easier, but does not cover all cases. Rehabilitation varies and should vary from person to person, so it would not be wrong to assume that future ACL rehabilitation guidelines will focus on rehabilitation techniques instead of time. I believe that, with the emergence of criteria-based guidelines, standardization will come.

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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (5): Knee

# Common controversies in total knee replacement surgery: Current evidence

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## Abstract

Total knee replacement (TKR) is a widely used operation that has radically improved the quality of life of millions of people during the last few decades. However, some technical details, concerning the surgical procedure and the rehabilitation following total knee arthroplasty, are still a matter of a strong debate. In this review of the literature, we have included the best evidence available of the last decade, in an effort to shed light on some of the most controversial subjects related to TKR surgery. Posterior-stabilized or cruciate-retaining prosthesis? To use a tourniquet during operation or not? Do patients need continuous passive motion for their post-surgery rehabilitation? To resurface patella or not? These are some of the most controversial topics that until now have been persistent dilemmas for the orthopedic surgeon. Results of this systematic review of the literature are highly controversial. These conflicting results are an indication that larger and more well conducted high quality trials are needed in order to gain more secure answers. At the same time, it is becoming apparent that a meticulous operative technique, respecting the soft tissue envelope and knowing the principles of alignment and soft tissue balancing, are some of the parameters that might contribute more to achieving the optimal results for the patients.

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**Key words:** Total knee replacement; Controversy; Literature review; Patella resurfacing; Patella eversion; Posterior stabilized; Cruciate retaining; Tourniquet; Continuous passive motion

**Core tip:** A literature review has been conducted in an effort to present the best available evidence of the last decade and to shed light on some of the most controversial subjects related to total knee replacement surgery. Patella resurfacing or not? Posterior cruciate retaining or sacrificing? Continuous passive motion or not? Tourniquet or not? These are some of the most debatable topics that until now have been persistent dilemmas for the orthopedic surgeon. Results of this systematic review of the literature are highly controversial. These conflicting results are an indication that larger and better conducted high quality trials are needed in order to gain more secure answers.

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## INTRODUCTION

Knee osteoarthritis (OA) is a very common condition with prevalence increasing with age. Recent studies estimated that the global burden of radiologically confirmed, symptomatic knee OA in 2010 was estimated to be 3.8%. This is a huge number, considering the world population, and it is expected to increase as the population ages[1].

Total knee arthroplasty (TKA) is a widely used operation that has radically improved the quality of life of millions of people suffering from symptomatic knee OA during the last decades[2]. Studies have shown that TKA is one of the most common procedures performed during hospital stay, and according to the national registries, there is a continuously increasing number of operations performed worldwide each year[3]. It has been estimated that, by 2030, the demand for primary TKA is projected to increase to 3.4 million surgeries performed annually in the United States alone[4].

Indeed, studies have shown that TKA is one of the most rewarding surgical procedures both for patients and surgeons[2]. However, other studies have shown that there is still a percentage of patients that remains dissatisfied with their clinical outcome[5-7]. As a result, there is an ever increasing effort in research and development in the field of knee arthroplasty aiming to improve patient safety and outcomes.

Several techniques have been described according to the patient's particular characteristics, and each of them has its own pros and cons, indications and contraindications. More specifically, some technical details, concerning the surgical procedure and the rehabilitation following TKA, are still a matter of a strong debate, despite the extensive investigations in the literature about their use. For example, the use of a posterior-stabilized or cruciate-retaining prosthesis, the necessity for a tourniquet and for continuous passive motion (CPM), the necessity for patella resurfacing or eversion during surgery, are some of the most controversial topics that until now have been persistent dilemmas for the orthopedic surgeon.

Thus, we tried to shed some light into these controversies, by extracting from the literature high quality papers that have as an object the answer to the previously reported questions.

An extensive search was conducted in MEDLINE (PubMed), Web of Science, and the Cochrane database for high quality. Prospective. randomized trials and meta-analyses. In order to be up-to-date and present the most recent findings, we preferred to include in our study only the papers published in the last decade. Initially, one reviewer conducted the literature search and retrieved the references for evaluation. A second reviewer independently selected the trials to be included in the review and also screened the reference lists of the selected articles in order to identify studies that were missed in the initial search.

## POSTERIOR STABILIZED *VS* CRUCIATE RETAINING TKA

Retaining the posterior cruciate ligament (PCL) or not still remains a matter of a strong controversy among the orthopedic surgeons. Numerous studies have yielded conflicting results. In this review, we were able to identify 8 relevant studies (6 prospective randomized trials and 2 meta-analyses).

The high quality papers that we collected began with the review of Jacobs *et al*[8] in 2005, who concluded that sacrificing the PCL leads to superior results concerning the range of knee motion, although they mention that the methodological quality of the studies that were included was highly variable and the results should be interpreted with caution. In 2008, Harato *et al*[9] performed a prospective randomized trial, with a minimum follow-up of 5 years, which confirmed the superiority of sacrificing the PCL (prosthesis Genesis Ⅱ), for postoperative knee motion, but no significant difference was reported in knee function, postoperative complications and patient satisfaction. The randomized controlled trial by Chaudhary *et al*[10] also in 2008, is another study that finished with the conclusion that posterior-stabilized TKA does not have different outcomes with the posterior-retained one regarding pain, knee function, and quality of life scores. Furthermore, in contrast with the previously reported trials, the authors found that the range of knee motion 2 years after surgery was similar for the 2 kinds of TKA[10]. Kim *et al*[11] in 2009, in a prospective randomized study (minimum follow-up of 2 years), compared high-flexion posterior-retained with high-flexion posterior-stabilized prosthesis and also did not notice a difference in range of knee motion, clinical and radiographic results. However, in 2011, Seon *et al*[12] published another prospective randomized study which also compared high-flexion posterior-stabilized TKA with high-flexion posterior-retained TKA and disagreed: the former prosthesis proved superior to the latter in weight-bearing maximum flexion and posterior femoral roll-back, although no difference was noted in clinical outcomes. Yagishita *et al*[13] performed a prospective randomized study in 2012, with a minimum follow-up of 5 years, which indicated that posterior-stabilized prosthesis showed better results in postoperative knee motion, posterior knee pain at passive flexion and patient satisfaction, but no significant difference was found between the 2 types of TKA regarding Knee Society Score. On the other side, in 2012, Li *et al*[14] in a meta-analysis of randomized controlled trials, compared the 2 types of knee prosthesis and reported similar outcomes in postoperative knee pain, function, complications and prosthesis survivorship. Finally, the meta-analysis of randomized and quasi-randomized controlled trials by Verra *et al*[15] in 2013, confirmed that there was no difference between posterior-stabilized and posterior-retained TKA regarding pain, and clinical and radiological outcomes, despite the fact that the range of motion and Knee Society Score were found higher with the former type.

Thus, we can conclude that, generally, in the literature, neither the one nor the other prosthesis has been proved to offer clear clinical advantages. Nevertheless, we cannot neglect the fact that the studies that reported differences between the 2 types of TKA found superiority of posterior-stabilized knee prosthesis mainly with regard to range of motion (Table 1).

### *Is it necessary to use a tourniquet?*

A strong debate is found in the literature about the

**Table 1 Studies comparing posterior cruciate retaining *vs* posterior cruciate sacrificing total knee replacement methods**

| Ref. | Type of study | Outcome |
|---|---|---|
| Verra *et al*[15] | Meta-analysis of randomized and quasi-randomized controlled trials, comparing retention with sacrifice of the PCL in primary TKR | No clinically relevant differences found. Range of motion was 2.4° higher in the PCL sacrificing group |
| Li *et al*[14] | Meta-analysis of randomized controlled trials comparing posterior cruciate-retaining with posterior stabilized TKA | No differences between the 2 designs |
| Yagishita *et al*[13] | Prospective, randomized study comparing high-flexion CR design implanted in one knee and high-flexion PS design implanted in the other knee in simultaneous bilateral TKA | PS prosthesis better in postoperative knee motion, posterior knee pain at passive flexion and patient satisfaction |
| Seon *et al*[12] | Prospective randomized trial, comparing *in vivo* kinematics, range of motion, and functional outcomes in patients who received either a high-flexion cruciate retaining or a high-flexion cruciate substituting TKR | No differences in clinical outcomes. PS TKR superior to CR TKR in weight-bearing maximum flexion and posterior femoral roll-back |
| Kim *et al*[11] | Prospective randomized trial, comparing ROM and functional outcome in knees receiving either a high-flexion posterior cruciate-retaining or a high-flexion posterior cruciate-substituting TKR | No differences among groups |
| Chaudhary *et al*[10] | Prospective randomized study comparing range of motion of posterior CR *vs* posterior cruciate-substituting (PS) (TKA) | No differences among groups |
| Harato *et al*[9] | Prospective, randomized clinical trial comparing midterm outcomes of posterior CR *vs* posterior cruciate-substituting (PS) procedures using the Genesis Ⅱ (TKA) | No significant difference in knee function, postoperative complications and patient satisfaction. Superior ROM in the PS group |
| Jacobs *et al*[8] | Systematic review and meta-analysis of prospective randomized trials | Range of motion 8° higher in the posterior-stabilized group compared to the PCL retention group |

TKR: Total knee replacement; TKA: Total knee arthroplasty; PCL: Posterior cruciate ligament; PS: Posterior stabilized; CR: Cruciate retaining; ROM: Range of motion.

usefulness of the tourniquet in TKA. We were able to identify 11 studies (4 meta-analyses and 7 prospective randomized trials) which aimed to answer this question.

The high-quality papers that we found in the last decade began with the prospective randomized study by Ishii *et al*[16] in 2005 about the optimal time of tourniquet deflation in cementless TKA. The authors concluded that tourniquet release before wound closure caused a significant increase in total blood loss. Consequently, they recommended that the tourniquet should be released after wound closure and that a compressive dressing should be applied[16]. Moreover, on the same subject, a meta-analysis of randomized controlled trials by Rama *et al*[17] in 2007, indicated that early tourniquet release for hemostasis increases blood loss, but also decreases the risk of regional postoperative complications (wound complications, symptomatic deep venous thrombosis and knee stiffness requiring manipulation) and the risk of reoperation. The first high-quality study that we noted in the last decade concerning the dilemma about the use of a tourniquet or not is the prospective randomized trial of Li *et al*[18] in 2009. A tourniquet was not recommended because it caused significantly increased blood loss, lower free hemoglobin levels, more extensive postoperative swelling, and ecchymosis. Also, straight leg raising and knee flexion in the early period after surgery were negatively influenced by the use of a tourniquet, which, therefore, was clearly discouraged by the authors[18]. To strengthen this point of view, Smith *et al*[19] in 2010, with their meta-analysis and systematic review, concluded that the use of a tourniquet was combined with significantly greater incidence of pulmonary embolism, blisters, deep vein thrombosis, superficial wound healing disorders, hematoma, peroneal nerve palsy, and greater intraoperative blood loss, but no significant difference in total blood loss. On the other hand, in 2012, we noted a randomized controlled trial by Tai *et al*[20], which supported the use of a tourniquet. It was proved that it significantly reduced total blood loss, excessive postoperative inflammation, and muscle damage, but caused slightly more postoperative pain, which, nevertheless, did not affect postoperative recovery. Alcelik *et al*[21], in a meta-analysis of randomized controlled trials in the same year, agreed that the use of a tourniquet restricted total blood loss, but was accompanied by a significantly higher rate of minor complications and did not affect the time of surgery and the incidence of thromboembolism. However, Ledin *et al*[22] in their randomized study, also in 2012, were not in favor of the use of a tourniquet, claiming that it did not improve the fixation of the components of TKA (as was indicated by the measurement of their migration with radiostereometric analysis), increased postoperative pain, and reduced the range of knee motion (the follow-up was up to 2 years after surgery). Additionally, in 2012, Mittal *et al*[23] performed a randomized controlled trial to investigate the possible advantages of tourniquet application only during cement fixation: the authors noted a significantly higher risk of transfusion and no functional benefit up to 1 year after surgery and, therefore, did not present restricted application of a tourniquet around the cement fixation as the optimal solution. Another interesting randomized controlled trial in 2012, by Olivecrona *et al*[24], demonstrated that measuring the limb-occlusion pressure before surgery reduced cuff pressure during surgery without influencing the quality of the bloodless field. Furthermore, the authors did not note differences in the parameters of postoperative pain, knee motion, and wound-related complications between the groups and came to an important secondary finding: in patients with a cuff pressure less than 225 mmHg, there were no postoperative infections and a lower rate

**Table 2 Studies investigating the usefulness of tourniquet use in total knee replacement**

| Ref. | Type of study | Outcome |
|---|---|---|
| Molt *et al*[27] | Prospective randomized controlled trial. To use a tourniquet or not. To evaluate the early migration, measured by RSA, of cemented knee prosthesis | No differences between the groups regarding the translation or rotation of the components as measured by RSA |
| Tarwala *et al*[26] | Randomized trial. To use a tourniquet only during cementation or up to wound closure | No differences in surgical time, pain scores, pain medicine requirements, range of motion, hemoglobin change, or total blood loss |
| Li *et al*[25] | Meta-analysis of randomized controlled trials. To use a tourniquet or not | Tourniquet effective for reducing intraoperative blood loss but not for reducing the postoperative blood loss and total blood loss |
| Olivecrona *et al*[24] | Randomized controlled trial. Tourniquet cuff pressure based on the patient's systolic blood pressure or based on the measurement of the limb occlusion pressure | No differences between the groups regarding postoperative pain or complications. Tourniquet cuff pressure based on measurement of the limb occlusion pressure had less wound complications |
| Mittal *et al*[23] | Double-blind, randomized controlled trial. Tourniquet application only during cement fixation or continually | Higher risk of transfusion in the short tourniquet use group. No difference in the Oxford knee score or rate of recovery |
| Ledin *et al*[22] | Randomized trial of cemented TKR. To use a tourniquet or not | Tourniquet increased postoperative pain and reduced the range of knee motion. Tourniquet group had less overt bleeding |
| Alcelik *et al*[21] | Systematic review and meta-analysis of selected randomized controlled trials. To use a tourniquet or not | Tourniquet restricted total blood loss, but was accompanied with significantly higher rate of minor complications |
| Tai *et al*[20] | Prospective randomized trial. To use a tourniquet or not | Tourniquet effectively reduced blood and avoided excessive postoperative inflammation and muscle damage. Tourniquet group had slightly more post-op pain |
| Smith *et al*[19] | Meta-analysis of randomized and non-randomized trials. Tourniquet use or not | No advantage to using a tourniquet in knee replacement surgery for reduction of transfusion requirements |
| Rama *et al*[17] | Meta-analysis of randomized trials. Tourniquet release either before or after wound closure | Tourniquet release before wound closure increases the blood loss. However, tourniquet release after wound closure can increase the risk of early postoperative complications requiring another operation |
| Ishii *et al*[16] | Randomized trial in patients who had undergone cementless TKA. Tourniquet release either before or after wound closure | Tourniquet release before wound closure caused a significant increase in total blood loss |

RSA: Radiostereometric analysis.

of wound complications[24].

In 2013, Li *et al*[25] performed a meta-analysis of randomized controlled trials and concluded that the use of a tourniquet significantly decreased the intraoperative blood loss but did not influence total blood loss. Besides, patients with a tourniquet did not have neither a higher risk of thromboembolic complications nor significant difference in the time of surgery compared with patients without a tourniquet[25]. Also, in 2013, Tarwala *et al*[26] in a randomized trial, examined the outcomes of the use of a tourniquet only during cementation and found that it offered bloodless bone for fixation, and did not influence the surgical time, pain, range of knee motion and total blood loss. Consequently, they recommended this method, claiming that it may restrict the possible risks related to prolonged tourniquet use[26]. Finally, the prospective randomized study by Molt *et al*[27] in 2013, underlined that tourniquet use did not affect the stability of the tibial tray of cemented TKA in a 2-year follow-up, as was demonstrated by a radiostereometric analysis.

In conclusion, we can see that the answer to the complicated dilemma "tourniquet or not?" is still difficult despite the extensive research on this subject. It is evident that several questions emerge about tourniquet use, related, for example, to the optimal timing of its release, the ideal cuff pressure, and the stages of surgery in which it should be inflated. Thus, further research is required to clarify these ambiguous aspects of tourniquet use and to construct definite guidelines. Table 2 summarizes the findings of the previous studies.

## CPM: TO USE OR NOT TO USE?

We were able to identify 11 studies (3 meta-analyses and 7 prospective randomized trials) investigating the usefulness of CPM post TKR surgery.

The meta-analysis of Brosseau *et al*[28] in 2004 is the first high quality study that we noted in the last decade, concerning the question about the use of CPM. The authors concluded that there was a significant improvement in active knee flexion and analgesic use up to 2 wk postoperatively, while the average hospital stay was decreased, as was the need for knee manipulations under anesthesia[28]. However, the authors also highlighted the need for further research about the use of CPM, because of its inconvenience and expense, and put the question about the determination of protocols concerning the duration and intensity of CPM application[28]. Following this study, Leach *et al*[29] in 2006 published a prospective randomized trial, with a 1-year follow-up, in which they concluded that CPM does not offer significant benefits in range of knee motion and pain, after the application of a specific CPM protocol. This publication initiated a series of high-quality studies, which, since then, have contested the use of CPM after TKA. More specifically, in 2007, Postel *et al*[30] in their review of level I and II studies, noted that CPM offered short-term benefits concerning postoperative pain, swelling and knee motion, but claimed that long-term benefits were not established, and underlined the necessity for investigation of different CPM modalities and comparison with alternative intermittent mobiliza-

**Table 3 Studies investigating the usefulness of continuous passive motion after total knee replacement**

| Ref. | Type of study | Outcome |
|---|---|---|
| Maniar *et al*[35] | Prospective randomized trial. To use or not to use continuous passive motion post TKR | No benefit from CPM use in immediate functional recovery post-TKR and postoperative ROM. The postoperative knee swelling persisted longer in the CPM group |
| He *et al*[34] | Meta-analysis of randomized trials (Cochrane). CPM or not against VTE | No evidence that CPM reduces VTE after TKR |
| Harvey *et al*[33] | Meta-analysis of randomized trials (Cohrane). CPM use or not | CPM increases passive knee flexion ROM by mean 2 degrees and active knee flexion ROM by mean 3 degrees. This effect is too small to clinically justify the use of CPM. Weak evidence that CPM reduces the need for manipulation under anesthesia |
| Alkire *et al*[32] | Prospective randomized study. CPM use or not for computer-assisted TKA | No statistically significant difference in flexion, edema or drainage, function, or pain between groups 3 mo post-surgery |
| Lensenn *et al*[31] | Randomised controlled trial. Effectiveness of prolonged CPM use *vs* in hospital only use of CPM | No long term difference in ROM or any of the outcome assessments |
| Leach *et al*[29] | Prospective randomized trial investigating the effect of CPM on range of knee flexion, lack of extension, pain levels and analgesic use after TKR | No differences among studied groups |
| Brosseau *et al*[28] | Meta-analysis of studies examining the effectiveness of CPM | Significant improvement in active knee flexion and analgesic use 2 wk postoperatively with the use of CPM and PT compared with PT alone |

CPM: Continuous passive motion; VTE: Venous thromboembolism; PT: Physiotherapy; TKR: Total Knee replacement; ROM: Range of motion.

tion techniques for safer conclusions. Moreover, in 2008, Lensenn *et al*[31] in a randomized controlled trial, came to agree that CPM improved short-term range of knee motion but they did not recommend its prolonged use as an adjunct to physiotherapy, because their long-term results did not confirm their initial conclusion. To the previously mentioned papers, which were about conventional TKA, Alkire *et al*[32] added a prospective randomized trial in 2010 which examined the effectiveness of the use of CPM in computer-assisted TKA: they concluded that CPM did not offer any significant benefit concerning the range of knee motion, pain, swelling, and knee function[32]. Additionally, the use of CPM was discouraged by the review of randomized controlled trials by Harvey *et al*[33] also in 2010, who supported that, in the patients who participated, range of knee motion, pain, swelling, quadriceps strength, length of hospital stay, and incidence of manipulation under anesthesia, did not show significant improvement after the use of CPM[33]. Another interesting parameter of the possible effectiveness of CPM was investigated by He *et al*[34] with their review of randomized controlled trials concerning the possible prevention of venous thromboembolism. They claimed that CPM did not significantly reduce this risk. Finally, Maniar *et al*[35] in a prospective randomized trial in 2012, further discouraged the use of CPM after TKA, supporting that it not only did not significantly improve immediate functional recovery, but also had a negative impact on postoperative swelling.

From the previously reported data, we can conclude that there is no recent high-quality published study that is in favor of the use of CPM during rehabilitation after TKA and, therefore, remaining extensive use of routine CPM should probably be reconsidered (Table 3).

## PATELLA RESURFACING OR NOT?

Patellar resurfacing during TKA is another subject about which orthopedic surgeons express different points of view and is a matter of long-standing debate. We were able to identify 10 studies (5 prospective randomized trials and 5 meta-analyses), aiming to answer the question of resurfacing the patella or not.

In 2007, Burnett *et al*[36] performed a prospective randomized trial with a minimum follow-up of 10 years and noted similar results for patellar resurfacing and nonresurfacing regarding the patient's pain, satisfaction, knee motion, and revision rate. A few years later, Burnett *et al*[37] in 2009, published the updated data from the previous randomized trial. Results confirmed the previously reported findings for the same parameters. A well conducted systematic review of the literature, which reported significant advantages of patellar resurfacing, was published by Calvisi *et al*[38] and merits mention. The authors concluded that this procedure reduced the risk of anterior knee pain, pain during stair climbing, and the patella-related reoperation rate, while increasing patient satisfaction and did not significantly influence knee motion[38]. However, they were not clearly in favor of the method of patellar resurfacing[38]. More recently, in 2011, Breeman *et al*[39] in a randomized controlled trial with a 5-year follow-up, found that this method did not have a significant impact on functional outcomes, reoperation rate, and total healthcare cost. Also in 2011, Pavlou *et al*[40] expressed the same opinion by performing a meta-analysis which indicated that patellar resurfacing did not significantly affect anterior knee pain and functional outcomes. The authors noted more reoperations in the non-resurfacing group, but they considered this result as possibly artificial, because secondary patellar resurfacing offers a surgical option for the therapy of anterior knee pain[40]. Furthermore, Fu *et al*[41] in 2011 published a meta-analysis in which they did not support patellar resurfacing as a matter of routine, as they did not notice a marked advantage, although they did note that this method reduced the

**Table 4 Patella resurfacing *vs* non-resurfacing in primary total knee replacement**

| Ref. | Type of study | Outcome |
|---|---|---|
| Chen *et al*[48] | Meta-analysis of randomized controlled trials Patellar resurfacing *vs* nonresurfacing in primary TKR | Patellar resurfacing reduces the risk of reoperation after TKR. No difference between the 2 groups in terms of anterior knee pain, knee pain score, Knee Society score and knee function score |
| Pilling *et al*[44] | Meta-analysis of randomized controlled trials. Patellar resurfacing *vs* nonresurfacing in primary TKR | The reoperation rate due to anterior knee pain, and the patella-femoral complication rate was significantly higher in the resurfacing group. The knee component of the Knee Society Score was higher in the resurfacing group. No significant difference was observed for the function component of the Knee Society Score or for any other reported knee score |
| Beaupre *et al*[43] | Randomized controlled trial. Patellar retention *vs* patellar resurfacing in primary TKR | No differences among the studied groups |
| Liu *et al*[46] | Randomized prospective trial. Patellar reshaping *vs* resurfacing in TKR | No significant differences between the 2 groups in terms of total Knee Society score, Knee Society pain score, Knee Society function score and anterior knee pain rate |
| Fu *et al*[24] | Meta-analysis of randomized controlled trials. Patellar resurfacing *vs* nonresurfacing | Patellar resurfacing reduce the risk of reoperation after TKR. No difference in anterior knee pain |
| Breeman *et al*[39] | Multicenter, randomized controlled trial. Patellar resurfacing or not | No significant difference between the 2 groups regarding functional outcome, reoperation rate, and total health care cost at 5 yr post TKR |
| Pavlou *et al*[40] | Meta-analysis of Level-I randomized controlled trials. Patellar resurfacing or not | No significant differences between groups with regard to the incidence of anterior knee pain. Higher rate of reoperations was observed in the non-resurfacing group |
| He *et al*[34] | Meta-analysis of randomized trials. Patellar resurfacing or not | Reoperation for patella-femoral problems significantly more likely in the nonresurfacing group. No difference between the 2 groups in terms of anterior knee pain rate, knee pain score, knee society score and knee function score |
| Burnett *et al*[37] | Prospective randomized trial. Patella resurfacing *vs* nonresurfacing in patients undergoing bilateral TKA | No differences regarding the studied parameters |
| Burnett *et al*[36] | Prospective randomized trial. Patella resurfacing *vs* nonresurfacing in patients undergoing bilateral TKA | No differences with regard to range of motion, Knee Score, satisfaction, revision rates, or anterior knee pain |

TKR: Total knee replacement; TKA: Total knee arthroplasty.

risk of reoperation. Additionally, Li *et al*[42] also in 2011, in a meta-analysis of randomized controlled trials, reported that, despite the fact that the risk for reoperation due to patella-femoral problems was significantly reduced by patellar resurfacing, there was no difference in pain and knee function. Beaupre *et al*[43] in 2012, performed a randomized controlled trial, with a follow-up of 5-10 years, in which they agreed that patellar resurfacing showed no difference with non-resurfacing regarding knee specific outcomes, like pain, stiffness, and function. Also in 2012, Pilling *et al*[44] in a meta-analysis of randomized controlled trials, highlighted the advantages of this method in the field of preventing additional surgical procedures and patella-femoral complications, but, nevertheless, reported no difference in operative time, infection rate, radiographic appearance, patient satisfaction, and anterior knee pain.

Of note, Altay *et al*[45] in 2012, investigated the subject of patellar denervation only, without patellar resurfacing: their prospective randomized study demonstrated that patellar denervation could significantly restrict anterior knee pain with satisfactory clinical and radiological outcomes, without patellar resurfacing[45]. Another alternative solution was presented by Liu *et al*[46] in a prospective randomized trial in the same year, compared patellar resurfacing with patellar reshaping, *i.e.*, removing the partial lateral aspect of the patella and the surrounding osteophytes and trimming the patella to match the trochlea of the femoral component. In a minimum follow-up of 7 years, the authors did not find a difference between the 2 methods regarding pain, radiographic findings, and functional knee scores, but recommended patellar reshaping, because it retained sufficient patellar bone stock and could easily be converted to patellar replacement in the case of recurrent anterior knee pain[46].

In 2013, the randomized controlled trial by Pulavarti *et al*[47] shed more light on the subject of patellar denervation without resurfacing: the method appeared safe, and improved patient satisfaction and range of knee flexion but did not ameliorate validated knee scores in a follow-up of 2 years[45]. Finally, Chen *et al*[48] also in 2013, published a meta-analysis of randomized controlled trials which supported the point of view that patellar resurfacing reduced the risk of reoperation and, moreover, gave better results in Knee Society Score in a follow-up of 5 years or more, but the overall benefits of the method were not sufficient to convince the authors to prefer this method over patellar non-resurfacing[48].

In conclusion, it is clear that patellar resurfacing as a common practice is not supported enough by the high-quality trials of the last decade, although some benefits have been adequately documented. More specifically, current evidence tends to suggest that patellar resurfacing may reduce the reoperation rate due to patello-femoral problems. Several alternative methods have been recommended with promising results, but future research will further clarify whether the advantages of patellar resurfacing are strong enough to encourage its use among the

**Table 5 Patellar eversion *vs* subluxation**

| Ref. | Type of study | Outcome |
|---|---|---|
| Umrani *et al*[52] | Prospective randomized trial. Patellar eversion or not (mid-vastus approach) | No statistical differences between 2 groups throughout the follow-up periods in recovery of quadriceps force or power and clinical data |
| Arnout *et al*[51] | Prospective randomized study. Medial parapatellar arthrotomy with patellar eversion *vs* same approach without eversion | Patellar dislocation without eversion improved range of motion at 1 yr postoperatively. All other studied parameters were not significantly different |
| Dalury *et al*[50] | Prospective randomized trial. Patellar eversion and anterior tibial translation *vs* patellar subluxation and no tibial translation | No significant differences between the treatment groups at 6 wk, 12 wk or 6 mo after surgery |
| Walter *et al*[49] | Prospective, randomized, blinded study. Mid-vastus split with or without patellar eversion *vs* median parapatellar arthrotomy or a mid-vastus split both without patellar eversion | Significantly earlier return of straight leg raise was noted when patellar eversion was avoided |
| Reid *et al*[53] | Prospective randomized double-blinded study. Patients undergoing TKA through a standard medial parapatellar approach assigned to either retraction or eversion of the patella groups | No significant clinical differences in the early to medium term. With patella retraction, there may be an increased risk of damage to the patellar tendon and increased risk in implant malpositioning |

orthopedic community (Table 4).

## PATELLAR EVERSION OR NOT?

Patellar eversion during TKR surgery has traditionally been used to facilitate exposure and component positioning. More recently, the theory that avoiding patella eversion results in better range of motion and earlier quadriceps recovery has gained popularity. However, controversy regarding this technique still exists. Few high-quality trials (more specifically, 5 prospective randomized studies) have been published in the literature during the last decade concerning the usefulness of patellar eversion in TKA. Initially, in 2007, Walter *et al*[49] performed a study which led them to the conclusion that avoiding patellar eversion led to earlier return of quadriceps function and a decrease in the length of patient stay in hospital. On the other hand, in 2009, Dalury *et al*[50] claimed that patellar eversion and anterior tibial translation showed no significant difference to patellar subluxation and avoiding tibial translation on range of knee motion, quadriceps strength and patient's knee preference, up to 6 mo after surgery. Furthermore, Arnout *et al*[51] in 2009, in a prospective randomized study, concluded that patellar dislocation without eversion improved the active and passive range of knee motion up to 1 year postoperatively and recommended this procedure as safe. Umrani *et al*[52] in 2013, found that patellar eversion did not significantly affect quadriceps recovery after TKA up to 1 year after surgery. In the most recent study, Reid *et al*[53] in 2014 found that patients who underwent TKR with patella eversion had similar clinical outcome 3 mo and 1 year postoperatively with patients who had TKR with patellar subluxation. They also noted that patellar subluxation may lead to an increased risk of damage to the patella tendon and increase in tibial component malpositioning.

As a conclusion, we could say that the available evidence is not strong enough to support either patellar eversion or subluxation, as a standard technique during TKR surgery. More high-quality trials need to be performed for stronger evidence. Table 5 summarizes the available evidence.

## CONCLUSION

Results of this review of the literature are highly controversial. We have tried to extract the best and most up-to-date evidence available regarding some of the most debatable aspects of TKR surgery regarding the everyday surgical technique of thousands of orthopedic surgeons around the world. These conflicting results indicate that larger and more well conducted high quality trials are needed in order to gain more secure evidence. At the same time, it is apparent that, irrespective of the variations in the operative techniques, certain parameters may contribute more to long-term successful results after TKR surgery. A meticulous operative technique, respecting the soft tissue envelope, and knowing the principles of alignment and soft tissue balancing are some of the parameters that may be of major relevance in achieving optimal results for TKA patients.

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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (5): Knee

# Neuromuscular interactions around the knee in children, adults and elderly

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## Abstract

Although injury and neuromuscular activation patterns may be common for all individuals, there are certain factors which differentiate neuromuscular activity responses between children, adults and elderly. The purpose of this study is to review recent evidence on age differences in neural activation and muscle balances around the knee when performing single joint movements. Particularly, current evidence indicates that there are some interesting similarities in the neuromuscular mechanisms by which children or the elderly differ compared with adults. Both children and elderly display a lower absolute muscle strength capacity than adults which cannot fully be explained by differences in muscle mass. Quadriceps activation failure is a common symptom of all knee injuries, irrespective of age but it is likely that its effect is more evident in children or adults. While one might expect that antagonist co-activation would differ between age categories, it appears that this is not the case. Although hamstring: quadriceps ratio levels are altered after knee injury, it is not clear whether this is an age specific response. Finally, evidence suggests that both children and the elderly display less stiffness of the quadriceps muscle-tendon unit than adults which affects their knee joint function.

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**Key words:** Knee stability; Knee joint; Stiffness; Electromyography; Strength imbalance; Aging, Co-activation; Age; Injuries

**Core tip:** Children and elderly display a lower absolute muscle strength capacity than young adults. This may be due to a higher quadriceps activation failure as well as a more compliant quadriceps muscle-tendon in children (probably due to maturation) and elderly (due to age effects on neuromuscular system) than adults which, in turn, leads to an altered strength capacity. In contrast, age differences in muscle co-activation are not age dependent. Current evidence precludes any conclusions on whether muscle strength balance ratios are age specific.

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## INTRODUCTION

The well documented benefits of physical activity and

exercise for health include an increase in physical competency and psychosocial interaction as well as decreased health risks[1,2]. However, physical activity also carries a risk of injury[3,4].

The knee joint is one of the most common injured joints[5]. Alteration of normal neuromuscular function around the knee is considered as a significant contributor to injuries. For this reason, restoration of neuromuscular function represents a fundamental aim of post-injury rehabilitation.

Although injury and neuromuscular activation patterns may be common for all individuals, there are certain factors which differentiate neuromuscular activity responses between children, adults and elderly. The effects of growth and maturation on neuromuscular function have not been thoroughly investigated but there is evidence that children display different neuromuscular profiles compared with adults. It is also known that aging has a significant impact on the force generation capacity of the muscular system which is accompanied by changes in neuromuscular activation patterns. The purpose of this study is to review current and recent evidence on neural activation and muscle strength balances around the knee in children, adults and aged individuals. The main research question was whether there are similarities in neuromuscular interaction during single joint tests across the life span.

There are numerous techniques to evaluate neuromuscular function depending on the scope of assessment and the applied methodology. Evaluation may help in the understanding of the causes of knee injury, and aid in the development of more effective training and rehabilitation programs[6,7]. After providing a brief introduction on knee injury epidemiology, age differences in four different areas of neuromuscular function will be examined. First, the ability of the central nervous system to provide the essentially stimuli for muscular activation are examined. This is translated into quantification of the extent the central nervous system is able to activate the entire motor pool. Second, muscle co-activation which is defined as the simultaneous activity of various muscles acting around the knee will be examined. This is achieved mainly by comparing electromyography (EMG) signals of the antagonistic muscle groups of the knee. Third, muscle strength imbalances around the knee will be examined, mainly refereeing to the hamstrings (H) to quadriceps (Q) moment ratio (H:Q ratio) during isometric or isokinetic tests. Forth, factors related to the properties of the muscle-tendon units of the knee joint and their role for knee joint function will be presented. This study will focus on experimental evidence from single joint movements rather than multi-joint activities.

## RESEARCH

A worldwide review of published work on neuromuscular interactions during single joint movements was conducted. Studies were selected for this review if they were written in English, they focused on neuro-muscular or musculo-tendinous strategies during knee joint tests. The literature search was performed from date of inception until end of November 2013 on the following electronic databases: Scopus (1995-2013), Web of Science (1970-2013), PubMed (1948-2013), Proquest, CINAHL, EBSCO, Embase, and Cochrane. The use of key words "knee", "age-related", "neuromuscular", "children" "knee flexors", "knee extensors", "activation level", "neural adaptation", "ageing", "muscle strength", "antagonist", "coactivation", "co-contraction", " tendon stiffness" "injury mechanisms". Studies excluded were non-English language papers, conference abstracts, research reports, personal correspondence. A total of 831 studies that met the inclusion criteria were assessed by two co-authors followed by blind assessment by a third co-author with respect to: (1) sample size; (2) reliability of measurement protocols; and (3) clear data presentation. Case studies or studies which did not report the reliability of their protocol or their data were not clearly presented were excluded from the analysis.

## KNEE INJURY EPIDEMIOLOGY: A SHORT OVERVIEW ON AGE DIFFERENCES

The current literature on knee injuries is extensive and it cannot be fully presented in this review. Nevertheless, it is worthwhile to provide a brief overview on potential similarities and differences in knee injury profiles across lifespan.

Knee injuries are frequently seen in the everyday clinical practice of orthopaedic surgeons and general practitioners. In the general population, the incidence is suggested to be 11 cases per 1000 person-years[8]. In a recent study, Gage *et al*[9] examined 6664324 knee injuries and they found that individuals aged 15 to 24 years displayed the highest injury rate while children younger than 5 years had the lowest rate which is confirmed by similar studies in this area[8,10,11].

The most common injury is a knee sprain without clearly identifiable internal derangement, and the most common diagnoses are anterior cruciate ligament (ACL) tear (20.3%), medial meniscus tear (10.8%) and chondral lesion (10.6%)[10]. Other frequent diagnoses include acute patellar dislocation (22%) and collateral ligament tear (9%)[12].

There are various factors which have been considered to increase the risk for knee joint injury. In general, a higher age increases the risk of disabling knee injuries[13]. However, it appears that risk factors act in combination with other factors rather than individually. For example, higher age, obesity, and poor physical conditioning are frequently suggested to be risk factors for musculoskeletal injuries as a whole[13-15]. In another example, a higher age combined with higher weight increase the risk for deeper chondral lesions[15] as well as knee injuries in general[12]. The number of chondral lesions increases with age[16].

Systematic participation in sports and gender are ad-

ditional factors which are also related to a higher injury risk. It is not surprising that current literature focuses primarily on young athletes[3,10,17-19]. For example, knee injuries are reported to account for 60% of high school sports-related surgeries[17,20]. Patellar dislocations typically occur in young adults during sports[21]. Risk factors for acute patellar dislocations are suggested to be higher height and weight[12,22]. Participation in sports, quadriceps muscle weakness, and female sex are associated with ACL tears[23-26] while all these factors acting in combination with older age increase the risk for meniscal tears[5,27]. Further, female athletes have been reported to be four to six times more likely to sustain a major knee injury[17,20].

Individuals 65 years and older sustained a higher proportion of injury due to stairs, ramps, landings, and floors (42.0%), compared to adults and children[9]. Furthermore, ageing is a well-defined risk factor for knee osteoarthritis, as the risk for osteoarthritis increases by 2 to 10 times in people between 30 and 60 years of age and even more for individuals above 60 years[28,29]. Knee arthritis is more common among men below the age of 50, while it is more frequent among women above this age[30]. Obesity and overweight are also known risk factors for knee osteoarthritis, due to mechanical overload of the knee joints[30-33]. Occupations requiring repetitive weight-lifting and squatting[34] as well as repetitive knee torsion[35] and knee bending have been associated with knee osteoarthritis.

To summarize, it appears that knee injury rates are higher in young adults than children and the elderly. Adults suffer mostly from ligamentous injuries chondral lesions and sprains, children display less serious injuries while arthritis represents a characteristic injury of older individuals. Knee injury risk factors, such as obesity, gender, body mass index and poor physical conditioning or systematic participation in sports contribute to injury, irrespective of age.

## COMMON NEUROMUSCULAR MECHANISMS AROUND THE KNEE

### *Arthrogenic muscle inhibition*

Knee injury or surgery or arthritis lead to weakness of the quadriceps muscle group[36-40]. One of the factors responsible for this atrophy is an on-going neural inhibition that prevents the quadriceps from being fully activated, a process known as arthrogenic muscle inhibition. This inhibition has been quantified using EMG or the interpolated twitch technique. In addition, activation failure can be induced by experimentally creating an effusion (*via* saline injection into the joint) which is typically seen after knee surgery[41].

Even early after injury, quadriceps weakness can be substantial, despite little time for atrophy[36]. Quadriceps EMG signal reduction ranges from 50% to 70% in the first few hours after meniscectomy; it then increases up to 80% for the next 3 d and it remains at high levels up to 15 d[42]. The reduction in the quadriceps EMG is somewhat lower after total knee arthroplasty reaching 30% in the first 4 wk after surgery[43]. Following ACL surgery, activation failure continues for approximately 6 mo[44,45] but it is gradually reduced to 6% deficit 18 mo after[46]. Similarly, total knee arthroplasty is followed by significant quadriceps inhibition up to 6 mo[47] and 24% decline 33 mo[47] after surgery.

The magnitude of quadriceps failure depends on the severity of joint damage, especially in individuals with ACL problems. For example, Urbach *et al*[48] found a lower central activation deficit in 30 patients with isolated rupture of the ACL compared with that displayed by patients with ACL rupture and accompanying joint damage. ACL rupture leads to a 3%-8% decline in quadriceps activation[36,49] while ACL rupture with simultaneous damage in other joint structures leads to a higher decline[48,50].

Central activation failure can also affect the uninvolved side[36,49-51]. Becker *et al*[51] showed that patients who underwent partial meniscectomy displayed a 20% failure in the injured side and 17% failure in the contralateral side. Similar results were reported for individuals who experienced an ACL injury[49] which led the authors to conclude that the difference between ACL injured patients and controls is due to a reduction in muscle size and activation failure. Chmielewski *et al*[36] also reported a decline in central muscle activation of 21% in both limbs post ACL-surgery[36]. Would this indicate a generalized activation failure and not solely a preferential one? The implication for testing and rehabilitation after knee surgery is that using strength measurements of the uninvolved limb as targets for rehabilitation of the involved limb may set lower strength targets than needed. In fact, Urbach *et al*[48] reported that due to contralateral deficits in central activation, the mean underestimation of the isometric muscle-force deficit ranged from 22% to 48%. Therefore, the validity of tests for the assessment of muscle function when using the uninjured side as reference was questioned. Others, however, did not find a quadriceps inhibition of the contralateral limb[52] proposing that rehabilitation protocols after knee joint injury should focus on ipsilateral and not bilateral neuromuscular and mechanical alterations that occur as a result of joint damage.

There are several factors which may contribute to activation failure such as swelling[53], pain[54], inflammation[55] and damage to joint receptors[56]. For example, activation failure may be due to swelling[53] and an associated increase in intraarticular pressure[57]. Since intraarticular pressure is higher towards knee extension, inhibition will be greater near extension rather than flexion[58]. For these reasons, in the acute stages after injury or surgery, isometric quadriceps exercises should be performed in 30 to 50° of knee flexion, where intraarticular pressure is the lowest[40].

The mechanisms responsible for arthrogenic inhibition vary and include both central and peripheral nervous system. In a recent review, Rice *et al*[40] identified three spinal pathways which may affect arthrogenic inhibition. First, inhibition of group I nonreciprocal interneurons

which receive inputs from tendon organs. Second, an enhanced flexion reflex that inhibits agonist activity and facilitates antagonist muscle activation[59]. Third, a deficit in the transmission of Ia input to the motoneuron pool, termed γ-loop dysfunction may be observed after ACL injury[60,61]. In addition, to the above spinal mechanisms, the role of corticomotor excitability as a contributor to activation failure was also examined. Interestingly, Heroux and Trenblay[62] reported a higher excitability of corticomotor projections targeting muscles in ACL deficient individuals. It has been proposed that this increase in corticospinal excitability may serve to counteract a-motoneuron inhibition by spinal reflex pathways[40].

In summary, athrogenic muscle inhibition represents a common symptom seen after many knee injuries. In many instances, clinicians consider reduced quadriceps strength as a result of muscle atrophy. However, the presence of inhibition after injury indicates that interventions employing only muscle strengthening exercises are not entirely appropriate to enhance neuro-muscular function. The use of techniques to increase quadriceps activation, such as electrical stimulation, has the potential to increase the effectiveness of rehabilitation programs.

### Muscle co-activation

Neuromuscular function is not only related to the ability to recruit the entire motor unit pool of a certain muscle but also to the ability to achieve an optimal activation of all muscles acting around the knee. Muscle co-activation has been examined by comparing the surface electromyographic (EMG) signal of the involved muscles expressed as percentages of reference EMG values[63-67] or by using the EMG signals to calculate a co-contraction index[68]. Numerous studies have examined antagonist co-activation levels during various activities[69-72]. Antagonist co-activation of the hamstrings in most movements ranges from 5% to 10% and increases in more demanding activities such chair up and down exercises[69].

Early evidence indicated that hamstrings co-activation represents a reflex response to ACL loading which is also accompanied by quadriceps inhibition[64]. The presence of mechanoreceptor input provided by the cruciate ligaments have been confirmed in healthy individuals[73] but it is absent following surgical ACL reconstruction[74]. This was supported by several studies showing a higher hamstring EMG in ACL deficient patients during the impact phase of the side-step cutting manoeuvre[75], walking[76,77] or landing[78] although such patterns have not always been confirmed[79,80]. In addition, some studies have reported an earlier onset of muscle activity during the late stance phase of walking after ACL injury[76,77,79]. The increased and earlier hamstring and gastrocnemius activation in ACL deficient individuals aims to maintain the knee joint stable by preventing anterior subluxation as the ground reaction forces increase upon heel contact[76-77]. In addition, increased level of antagonist co-activation increases joint active stiffness[69]. This is also related with proprioception deficits often observed in ACL deficient knees[81].

More recent evidence indicates that non-contact ACL injuries are more likely when total hamstring pre-activation is much less than the corresponding quadriceps pre-activity during side cutting[82]. Furthermore, a higher hamstring coactivation near terminal knee extension was observed in ACL deficient individuals compared with uninjured individuals[83]. The observation that co-activation is found in both uninjured and injured individuals led Alkjaer *et al*[83] to suggest that antagonist co-activation is not only a reflex response but it may be modulated by central motor programming. Some evidence seems to support this statement[84,85], although, clearly more concrete evidence is necessary.

Using mathematically or EMG-driven models, research studies have estimated the antagonist moment in healthy subjects[86,87] and in ACL deficient subjects[83-84] as well as its effect on joint forces[73,86,88,89]. Isolated contraction of the quadriceps increases shear force between the tibia and the femur at the last 20° of knee extension which is partly counteracted by hamstring activation[86,88,89]. This results also in a wider pressure distribution along the articular surfaces of the joint and prevents early tissue damage and osteoarthritis[73] while it may reduce ACL strain at angles near full extension[90]. This notion is supported by modeling data by Yangawa *et al*[91], which confirms that coactivation of the hamstring muscles during isolated dynamic (isokinetic) knee extension effectively reduces anterior tibial translation. Further evidence seems to confirm these findings as a higher hamstring coactivation and moment near terminal knee extension was observed in ACL deficient individuals compared with uninjured individuals[83]. The elevated antagonist hamstring moment observed in the ACL deficient subjects may reflect a compensatory neuromuscular adaptation to counteract the increased laxity of the knee joint[83]. However, others have not found any difference in antagonist hamstring moment between ACL deficient, ACL reconstruction, and uninjured individuals[84]. Methodological issues in EMG - moment data treatment may account for these variations[83] which guarantees further research in this area.

### Strength imbalances

Since neuromuscular activation is altered in knee pathological conditions, then changes in force generation capacity of the surrounding musculature may be observed. These are also accompanied by alterations in size of the muscle as a result of injury or subsequent immobilization. Muscular imbalances around the knee refer mainly to the relationship between absolute muscle strength developed by antagonistic muscle groups. The H:Q peak moment ratio takes into consideration the function of two opposing (agonist-antagonist) muscle groups and it represents the most frequent parameter used to estimate muscle strength balance[6,7,92].

The methods used to calculate the H:Q strength ratios vary. Early research studies have mainly examined the concentric H:Q ratios, frequently defined as "conventional" ratios[93,94]. A theoretical value of 0.6 of the ratio ob-

tained frequently under isometric or slow isokinetic concentric tests is often considered as "normal"[95]. However, conventional ratios have been gradually been replaced by the "functional" ratios which involve the calculation of eccentric H: concentric Q ($H_{ecc}$:$Q_{con}$) muscle strength ratio[6,7,92,93,96].

There has been a long debate on the usefulness of antagonist to agonist strength ratios as an injury predictor or as a target for restoring normal knee muscle function[97]. A methodological approach is to measure H:Q ratio in athletes in the pre-season period and follow this for the forthcoming seasons. It has been found that athletes with a Hcon:Qcon ratio closer to 1.0 may have a reduced risk of hamstrings strain[98]. Also, a Hcon : Qcon ratio closer to 1.0 in athletes with ACL injury has been suggested to reduce the risk of an anteriolateral subluxation of the tibia[99]. Croisier *et al*[100] identified a lower $H_{ecc}$:$Q_{con}$ ratio in players with a previous hamstring injury during the pre-season assessment and applied a rehabilitation program to restore the ratio into normal values. They then followed the players for 12 mo. Their results showed that none of the players experienced a re-injury. Further, epidemiological evidence in 462 players followed for one season showed a total of 35 hamstring injuries, most of which were experienced by players with lower Hcon:Qcon and Hecc:Qcon ratios[101]. Recently, Kim *et al*[95] found an association of lower than 0.6 of the $H_{con}$:$Q_{con}$ ratio at 60°/s and non-contact leg injuries in National College American Association athletes. In an almost parallel study, Fousekis *et al*[102] reported that professional soccer players with Hecc strength asymmetries were at greater risk of hamstring strain while players with Qecc strength and flexibility asymmetries were at greater risk of quadriceps strain.

Other studies have examined the ability of H:Q ratio to identify individuals with knee joint problems from uninjured ones. Early studies have identified[79,92] a significantly lower isokinetic Q moment in patients with ACL deficiency compared to healthy subjects while $H_{ecc}$ and $H_{con}$ moment deficits were not as significant. This is in line with later studies[103,104] who reported a higher H:Q ratio in subjects with ACL reconstruction[103,104] compared with uninjured individuals. Similar findings have been reported when comparing individuals with knee osteoarthritis with controls[105,106] which may indicate that compensation strategies with regards to antagonist to agonist muscle balances are more generic than solely ACL problems.

Knee related injuries may also be due to differences in strength between the two legs. Furthermore, strength levels of the unaffected limb frequently represent a reference value against which restoration of strength of the affected limb. Evidence on bilateral leg differences in soccer players is unclear as some studies have reported no differences[107] whereas others reported a 10% difference in both Q and H strength in favor of the non-dominant leg[108]. Others, however, have shown that bilateral leg differences exist only in the hamstrings but not in the quadriceps (players displayed weaker hamstrings in the dominant leg than the non-dominant one)[109,110]. The existence of muscle specific bilateral differences in strength led researchers to explore whether H:Q ratios differ between limbs. Again, there is some evidence that the non-dominant or non-preferred limb shows somewhat higher ratios than the dominant one but still this evidence is not always statistically significant[108,111] or differs between tested speeds[110]. However, a lower $H_{ecc}$ moment in the injured limb compared to the contralateral limb continues even after ACL reconstruction surgery[112]. It is not clear whether such deficits pre-existed or they were due to ACL injury or reconstruction.

Although functional ratios have been considered as better indicators of muscle balance, there is still not sufficient evidence supporting their use. A problem associated with the use of H:Q ratios is that they were assessed using peak force values during a maximum voluntary effort[113-115]. This raises two issues: (1) that injuries occur at a specific joint angle while the H:Q ratio is calculated using peak force values irrespective of joint angle. The value of calculating the H:Q ratio at a specific joint angle, the one which is closer to the injury mechanism of the specific knee structure would be higher[116] (Figure 1). Particularly, peak moment H/Q ratio ranges from 0.5 and 0.6[96,117] and increases near full knee extension exceeding values of 1.0[117,118]. This increase was attributed to a relative dominance of the H near full extension[118] in order to stabilize the knee joint when the strain on the ACL is the greatest[90]. The shift of $H_{ecc}$/$Q_{con}$ ratio at angles of knee extension was also attributed to a limitation in knee extensor motor unit recruitment at joint angles of greatest ACL strain[118]. Nevertheless, whether H:Q ratio at a specific joint angle can discriminate knee injured individuals from uninjured ones or to predict injury is still unclear; (2) during explosive movements, such as soccer match play situations, the time available to stabilize the knee joint is frequently very short (< 50 milliseconds)[119]. However, during a standard isometric test the peak force occurs within 400-500 ms from onset of contraction. This suggests that in most explosive movements there is no time available for maximum force generation. Thus, the relevance of using Hcon:Qcon and $H_{ecc}$:$Q_{con}$ based on peak values has been questioned[120]. In one of the first studies, Aagaard *et al*[115] proposed that rate of force development (RFD), defined as the rate of rise in force at the onset of contraction, may be a better index of neuromuscular activity around the knee. Based on these aspects, Zebis *et al*[120] have recently assessed the H:Q ratio using the RFD values obtained during maximum isometric contraction in twenty three soccer players. They reported that two female players who sustained an ACL injury had a normal H:Q peak force ratio but a low RFD H:Q ratio.

### Gender differences

Male and female relative H:Q ratio profiles differ significantly during and following puberty[121]. Isokinetic dynamometer measurements show that male athletes demonstrate significantly greater hamstrings peak torques with

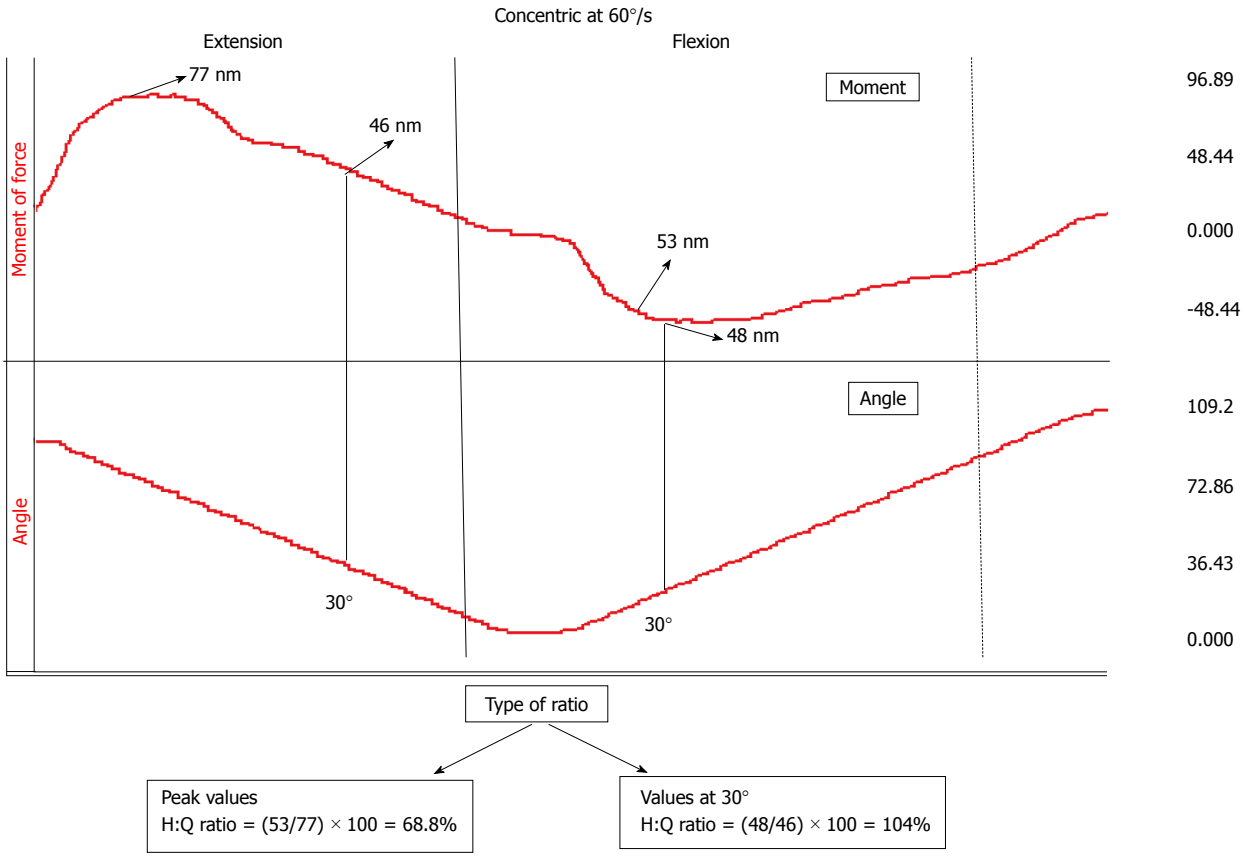


**Figure 1 An example of different methods to calculate the hamstrings:quadriceps ratio.** The raw data from moment of force (upper line) and angular position (lower line) as recorded from an isokinetic concentric knee extension-flexion trial. Using peak moment values results to a different ratio value compared with that obtained using values at a knee flexion angle of 30°. H: Hamstrings; Q: Quadriceps.

increasing maturity, while peak hamstrings torque remains stable with increasing maturational stage in female athletes[121]. Thus, it appears that lower hamstrings strength and H:Q ratios of female athletes relative to males may be related to the development of neuromuscular imbalances associated with the onset on maturation. These neuromuscular imbalances may increase injury risk in pubertal and post pubertal female athletes[121,122]. In a thorough review, Hewett *et al*[123] analysed 23 research studies and reported that isokinetic H:Q ratios do not differ between genders at slow velocities. As angular velocity increases, males display higher H:Q ratio than females. The authors commented that this difference may be related to females' decreased ability to dynamically control the knee joint during sports activities. However, more recent studies have reported an increase in both conventional and functional ratios in female athletes with increasing angular velocity[124,125], which is not in line with the above conclusion. This might be due to differences in the characteristics of the samples examined, as both these studies referred to trained female athletes whilst data examined by Hewett *et al*[123] included mainly sedentary or untrained individuals.

Gender differences in knee injury occurrence are also related to more global neuromuscular differences that lead to injury than solely H:Q ratios. Muscle co-activation can decrease the dynamic valgus motion of the knee, which potentially places the knee at increased risk of injury[123,126]. Individuals with chronic ACL deficiency showed lower internal/external rotation strength ratios than controls and acute ACL deficient subjects, indicating a compensatory mechanism developed by the patients to unload the ACL[103]. In contrast, ACL reconstruction patients showed fewer deficiencies compared with controls[103].

Gender differences in hamstring and quadriceps muscle co-activation have also been examined. Palmieri *et al*[127] reported that females displayed lower co-activation than males and that medial co-activation had a linear relationship with external knee abduction moment in females only. A higher knee abduction moment is considered as a risk factor for ACL injury[128]. Therefore, it appears that females display a greater risk for ACL injury than males. Similar results were reported by Rozzi *et al*[129] upon landing from a jump. There is no single explanation on why females display deficits only on lateral muscles and not on the medial part. There are suggestions that lateral muscles may co-activate more than the medial ones to resist internal rotation moments which may increase ACL loading[130]. However, more evidence is necessary.

## NEUROMUSCULAR INTERACTIONS AROUND THE KNEE IN CHILDREN

Muscle strength increases during maturation, in terms

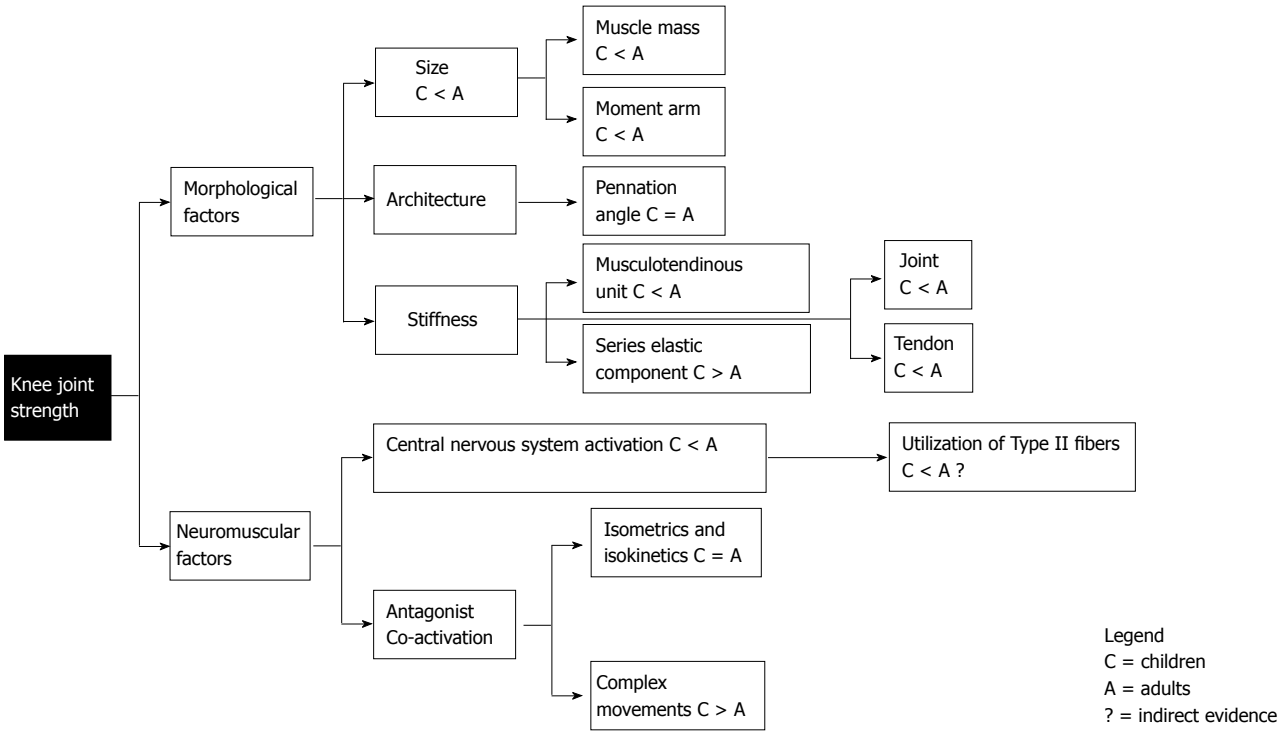


**Figure 2 Schematic summary of comparison between children (C) and adults (A) regarding factors influencing knee joint strength.**

of joint moment. This development is primary a consequence of hormonal changes which result in muscle mass augmentation (hypertrophy)[131], and in limb size increase (moment arm)[132]. However, differences in strength between children and adults cannot be fully explained by these parameters[133]. This designates the possible contribution of neuromuscular factors that could play a role in force deficit observed in children compared to adults. There are two main issues to mention regarding the neuromuscular aspect: Firstly, the level of central activation, *i.e.*, to what extent the central nervous system is able to activate the entire motor pool, and secondly, the level of antagonist co-activation, which reduces the net amount of moment produced around the joint. Hence, strength gain observed during developmental ages could be partly attributed to neural adaptations. In addition to this, differences between children and adults in muscle tendon unit (MTU) architecture and stiffness might also play a role on the force development around the knee joint (Figure 2).

Earlier studies have shown that the isokinetic strength normalized to cross sectional area (CSA) and thigh length is lower in 6-9 years old children compared to young adults[131]. The fact that this difference was more profound when the angular velocity was increasing reveals that muscle and limb size could not be the only factor affecting force production. This could be explained by findings supporting that children might have lower proportion of type-Ⅱ muscle fibers[134], which have fast contractile properties. However, several studies revealed no significant differences in muscle-fiber composition between children and adults[135,136].

This raises the question whether children and adults possess similar proportion of muscle fibers types, but the former are not capable of fully recruit the fast ones. It has been shown that especially in large muscle groups, such as the quadriceps, children are incapable to fully recruit their motor units[137]. More recent studies using the twitch interpolation technique with magnetic or electric stimulation demonstrated that children activate their motor units in lesser extent than adults during knee extension[138], and this is particularly evident in girls when compared to women[139]. This finding observed in children could at least partially account for their force deficit compared to adults. Furthermore, assuming that the size principle is valid for children too (*i.e.*, the higher the level of activation, the larger in size -and thus faster- motor units are recruited), it would be expected that children utilize in lesser extent type-Ⅱ (fast) motor units compared to adults. This assumption is supported by experimental findings for the knee extensors, revealing that children have lower rate of torque development under isometric[140] and dynamic conditions[141].

Despite the simplicity of using the anatomical CSA for the estimation of muscle size of children and adults, the most appropriate measure is the physiological CSA, which accounts for the pennation angle and is calculated as the ratio of muscle volume to fascicle length[138]. However, no difference between 8-10 years old children and adults is observed in the pennation angle of all quadriceps heads[138]. To our knowledge, no respective data exist in the current literature, regarding the pennation angle for the hamstring muscles in children and adults. This piece of information could have important implications, since

the pennation angle influences the shortening velocity of a muscle (and the force capacity of a muscle), and might affect the torque H:Q ratio at different contraction velocities.

Decreased torque H:Q ratio is an indicator for potential increased probability of lower extremity injury[142]. More particularly, it has been shown that collegiate athletes with isokinetic at 180 deg/s peak torque H:Q ratio less than 0.75 have higher incidence of injury[143]. According to cross-sectional studies, the isokinetic torque H:Q ratio at 60 deg/s remains unchanged from the age of 7 to 18 years, although the CSA H:Q ratio increases gradually after the age of 10 years[144]. On the other hand, post-pubescent athletes demonstrate a close correlation between the hamstrings and quadriceps CSA and the flexion and extension torque, respectively[145]. Furthermore, during puberty strength improvement of the knee flexors is diverged from the extensors, particularly for the females[121]. Although in males the hamstrings and quadriceps isokinetic peak torque increases proportionally during growth[107,121], in females the peak torque of hamstrings does not follow the improvement achieved in quadriceps[121]. This deficit in knee flexion torque observed in females results in a decreased torque H:Q ratio. Further gender specific imbalances are observed on the level of knee anterior/posterior and medial/lateral muscle activation[146] during dynamic multijoint tasks. Females activate their quadriceps more compared to males[147-150] and this could contribute to the decreased H:Q ratio in torque output. Furthermore, decreased medial to lateral quadriceps[151] and hamstrings[129] activation ratio observed in females, could increase valgus, and varus laxity. These observations regarding the imbalances in activation level and torque output of the thigh muscles could increase the risk for ACL injury because hamstrings function synergistically with the ACL, especially at knee joint angles less than 45 degrees[64].

A factor that could modify the torque H:Q ratio is the level of antagonist co-activation. However, no significant differences between children and adults have been observed[152,153]. Furthermore, in isometric contractions, the antagonist co-activation is even lower and still not significant between age groups[139,154]. On the other hand, co-activation is higher in children compared to adults when performing tasks involving multiple joints such as gait[155] and jumps[156,157]. This implies that movement coordination and learning factors might be an issue during developmental ages[133], considering that the process of maturation of the corticospinal tract in terms of conduction velocity is not complete until the age of 11 years[158] and that the pyramidal system attains full functionality during puberty[159].

Regarding the passive component of stiffness, Lebiedowska and Fisk[160] have shown that passive knee stiffness increases with stature, within an age range between 6 and 18 years. Furthermore, Kubo *et al*[161] measuring the tendon elongation of the vastus lateralis during isometric knee extension, concluded that the tendon of younger boys was more compliant than older boys and young men. In line with the idea that the MTU is more compliant in children, Asai *et al*[162] demonstrate that children had longer electromechanical delay compared to adults. This could also contribute to their reduced capacity to produce high rate of force development[140-141]. In contrast, series elastic component, quantified with quick-released movements in the knee extensors, revealed decreased stiffness with age[163]. The above differentiations in MTU stiffness between children and adults might influence the force/length relationship of the muscles acting around the knee joint. Stiffer MTU favors more direct force translation from the muscle to the bone[164], whereas the opposite situation requires greater shortening velocity of the contractile apparatus, in which children are inferior[140,141]. The concept of differences in MTU stiffness that are reflected to changes in the joint torque/angle relationship has been supported[165] but also questioned[139] in previous studies, and therefore requires further investigation. More particularly, Marginson *et al*[165] demonstrated that children demonstrate their maximal knee extension torque at more flexed joint angle (longer muscle) than adults, whereas O' Brien *et al*[139] showed no difference in the optimal joint angle between children and adults.

It is apparent that the function of the knee depends on multiple factors, which are influenced during the developmental ages. Despite this complexity, O'Brien *et al*[138] concluded that children's and adults' specific tension (the ratio between muscle strength and size) of the quadriceps is the same, taking into account differences in physiological cross sectional area, moment arm, level of activation, and co-activation. This implies that the muscle tissue is qualitatively very similar in children and adults. It is concluded that regardless of structural differences in muscle size, moment arm-joint angle relationship, central voluntary activation, H:Q ratio, and muscle-tendon stiffness, children's neuromuscular system is highly adaptive, although further systematic research with longitudinal studies are required to improve our understanding on the effects of growth and development in the force and power output of children.

## NEUROMUSCULAR INTERACTIONS AROUND THE KNEE IN THE ELDERLY

The aging process is associated with a significant decline in muscle strength (dynapenia) and strength development that might be caused by alterations of skeletal muscle properties as well as by neural modulations[166,167]. Regarding the knee joint, the reported age-related decrease in the measured isometric muscle force/moment of the knee extensors ranges from 19% to 38% when comparing groups of similar physical activity level[166,168-173] (Table 1). Even greater differences (50% or more) have been reported for people in their ninth decade and beyond[166]. When comparing the specific tension of the knee extensors between young and old women, a reduction of 17% during isometric contraction has been reported[174] (Table 1).

**Table 1 Information provided by cited articles about age-related reduction in muscle force**

| Ref. | Age-related reduction in muscle force/torque | Age of participants, yr | Testing condition | Physical activity level |
|---|---|---|---|---|
| Baroni *et al*[171] | 30%-36% | y: 30 ± 6 | Isometric KE | No systematic training |
| | 40%-53% | o: 69 ± 5 yr | Concentric KE (60-360°/s) | No systematic training |
| Laudani *et al*[173] | 36.9% | y: 28 ± 2 | Isometric KE | Sedentary adults |
| | | o: 70 ± 3 | | |
| Karamanidis *et al*[169] | 21% | y: 21-32 | Isometric KE | Endurance runners |
| | 18.9% | o: 60-69 | Isometric KE | Not active |
| Mademli *et al*[170] | 28% | y: 30 ± 7 | Isometric KE | Physically active |
| | | o: 65 ± 3 | | |
| Savelberg *et al*[172] | 33% | y: 23 ± 2 | Isometric KE | Active runners |
| | 43% | o: 65 ± 3 | Isometric KF | Active runners |
| Macaluso *et al*[174] | 17% | y: 23 ± 6 | Isometric KE | Active |
| | 30% | o: 70 ± 2 | Isometric KF | Active |
| Frontera *et al*[195] | 15.5%-22% | 12-yr longitudinal study, initial mean | Isokinetic KF (60 and 240°/s) | Healthy |
| | 17%-23% | age 65 ± 2 | Isokinetic KE (60 and240°/s) | Healthy |

KE: Knee extension; KF: Knee flexion; Y: Young; O: Old.

The age-related decline in muscle strength is gender specific, with men losing almost twice as much strength as women[175]. Nevertheless, in absolute values, older women demonstrate significantly lower strength than men[176,177], which can be explained predominantly by their higher fat mass[176]. Indeed, when investigating the decline in muscle quality of the knee flexors and extensors, *i.e.*, peak torque per unit of muscle mass, it was found that the rate of the decline was the same for both genders[178]. The higher proportion of body fat in women may put them at significant biomechanical disadvantage for greater disability in old age[176]. It seems that due to their gender-related lower average strength, old women may be at greater risk than old men of becoming impaired in certain motor tasks[177].

Furthermore, when measuring knee extensor moments at different knee angle positions, the percentage loss of muscle strength was different at the different positions[168,179]. Karamanidis *et al*[168] found that the aging process revealed a clear reduction in maximal knee extension moment at intermediate knee joint angles (140° and 110°), but there was virtually no age effect at more extended (160° and 170°) or flexed (80°) knee joint positions. The authors proposed among other, two potential explanations for this phenomenon: (1) The discrepancy in the age-related reduction in muscle strength within the quadriceps muscles, with greater decline in Vastii (monoarticular) than in rectus femoris (biarticular) muscle[172]. It has been reported that, while the moment-knee-joint angle relationship of the Vastii muscles described by a parabolic curve having its vertex (maximum value) between 100° and 120°, the rectus femoris demonstrates a rather flat joint-moment-length curve[172]. Thus, it is possible that the relative contribution of the rectus femoris to the total knee extension moment is higher at more extended or flexed knee joint positions[172], where no age-related effect on quadriceps muscle strength was found; and (2) The modulation of the EMG activity. In their study, Karamanidis *et al*[168] found that older adults have an increased quadriceps femoris EMG activity at more extended (160° and 170°) as well as at moreflexed (80°) knee joint angles in comparison to younger adults. This was not the case at intermediate knee joint angles (110° and 140°).

Knee flexors have been reported to demonstrate similar decline as knee extensors due to the aging process[166]. Nevertheless, Ogawa *et al*[180] found no significant change in muscle volumes and average CSA for the hamstring muscles between young and old adults, whereas quadriceps muscle volume and average CSA were 20% and 16% lower, respectively. This resulted to greater age-related decline in the specific tension for the knee flexors compared to knee extensors (Table 1)[174,180]. In contrast to the knee extensors, for the knee flexors the strength reduction is mainly caused by deterioration of the biarticular muscles, and not of the monoarticular muscles[172]. Furthermore, for the knee flexors, the age-related reduction of joint moment is almost invariant to joint angle[172], something that does not hold for the knee extensors, as already mentioned above.

Age-related muscle weakness is associated with the well described decline of skeletal muscle mass. Yet, more recent studies have shown that this relationship is less robust than once believed[167]. Goodpaster *et al*[175], when measuring knee extensor strength by isokinetic dynamometry, found that although the loss of muscle mass is associated with the decline in strength of older adults, this strength decline is much more rapid than the concomitant loss of muscle mass. Moreover, they reported that maintaining or gaining muscle mass does not prevent aging-associated reduction in muscle strength. Furthermore, there are age-related alterations in torque production capability that are not explained by a reduction in muscle mass, including reduced specific tension and slower rate of isometric torque production (expressed relative to peak torque)[167]. The altered neuromuscular activation is another critical component of the weakness observed in senescence[167].

Nevertheless, the studies focusing on the underlying neuromuscular mechanisms of age-related reduction in knee extensors force generation capacity are limited. Moreover, the reported results are partially conflicting, especially the ones concerning alterations in neural drive to the quadriceps muscle. While some studies find greater activation deficit in the elderly, compared to young adults[181,182], other studies do not find any significant differences between young and old in the ability to activate the knee extensor muscles to a high degree (93%-96%)[183-186]. Harridge *et al*[187] found that very old adults (85-97 years) demonstrated significant impairment in central activation, with mean knee extensor voluntary activation level of only 81% (range: 69%-93%)[187]. This outcome suggests that deficits in the neural drive essentially contribute to the weakness of the knee extensor muscles observed in very old age[188]. On the contrary, Miller *et al*[189] found that the ability to activate the quadriceps muscle was generally very high, and there was no significant difference between older (96%) and younger (98%) subjects. The study was conducted on 20 moderately active older subjects (mean age 75 years) and 12 younger (mean age 25 years). The above described inconsistency in reported findings may be primarily related to methodological limitations and differences in the techniques used to estimate muscles voluntary activation[181], as well as to different physical condition of participants[188]. Mau-Moeller *et al*[181] estimated the neural drive to the knee extensor muscles during maximal isometric contractions by means of both interpolated twitch technique and the root mean square of the EMG signal normalized to maximal M wave[181]. Both techniques led to the same outcome, *i.e.*, there was an age-related decline in the neural drive to the muscle which resulted in muscle weakness. Regarding the knee flexor muscles, to our knowledge there is no study investigating their voluntary activation.

Another neuromuscular mechanism of age-related reduction in knee extensors force generation capacity, regards the age-related changes in antagonistic muscle coactivation. The mechanical opposition to the agonist action can contribute to the reduced exerted moment at the knee joint. Studies investigating the effect of aging on the coactivation during knee extension are limited and their findings lack of consensus. Laudani *et al*[173] found that old (mean, 70 years) and young (mean, 28 years) adults with similar physical activity level do not demonstrate significant difference in the coactivation during maximum isometric contractions (26.2% ± 22.8% *vs* 29.6% ± 20.5%). The increased standard deviation in their measured values indicates high intra-group variability, assigning to coactivation a rather person-dependent instead of age-related nature. Regarding dynamic contractions, no association was found between normalized antagonist activation and velocity, indicating that changes in coactivation cannot be responsible for age-related deficit in force production[190]. On the contrary, Tracy *et al*[191] found that old subjects (mean, 71.5 years) exhibited during submaximal isometric and anisometric contractions, greater coactivation of antagonist muscle compared to young ones (mean, 22 years). Similar findings have been reported for measurements over women during isometric knee extension contraction[174]. Furthermore, there is a highly determinant effect of coactivation on the capacity to produce isometric force on a short period of time[192]. However, significantly higher antagonistic coactivation was only found during contraction of the knee extensors and not during knee flexion[174]. During knee flexion, the co-contraction of knee extensors was found to be significantly lower for both old and young adults[173].

The transfer of force between the muscular and skeletal systems may be affected by age-related changes in muscle architecture, as well as in the length and compliance of tendons[167]. An age-related reduction in vastus lateralis tendon and aponeurosis stiffness has been reported[168-170] (Figure 3). Thus, the greater compliance of the aged tendon and aponeurosis can influence the force-length and force-velocity relationship of the muscle (contractile element) and consequently its force generating potential[193]. The result is a more deteriorate function of the knee extensor muscles in the older population.

The above mentioned age-related alterations in neuromuscular interactions around the knee joint lead to differences in the way old adults perform activities of daily living. For example, when older adults descend and ascend stairs and ramps, they demonstrate an altered control strategy compare to young adults, causing a redistribution of the mechanical load at the tibiofemoral joint[194]. This has effects on the initiation and progression of knee osteoarthritis in the elderly, which in turn makes movement even more difficult[194].

## CONCLUSION

In this review, we attempted to provide a global view of the neuromuscular mechanisms associated with knee joint injuries across lifespan. It is certain that neuromuscular strategies and mechanisms differ between children, adults and the elderly. However, there are some interesting similarities in the mechanisms by which children or elderly differ compared with adults.

Both children and elderly display a lower absolute muscle strength capacity than adults. This deficit may be due to a lower muscle mass (especially of the quadriceps) displayed by children and elderly, obviously for different reasons. The effects of a lower muscle mass are more evident in older individuals. However, when variations in muscle mass are taken into consideration, there are still differences between different age categories.

Quadriceps activation failure is a common symptom of all knee injuries, irrespective of age. However, for those individuals who have a lower quadriceps strength capacity, it is reasonable to suggest that functional impairment will also be higher. If we assume that knee injury conditions (swelling or pain and inflammation) are constant amongst different age groups, an initial differ-

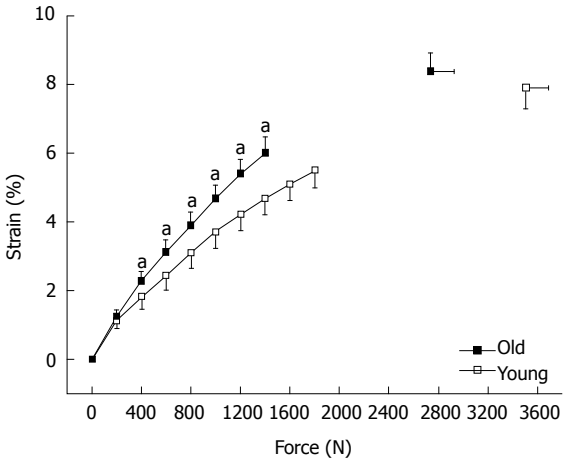


**Figure 3 Strain-force curves of the vastus lateralis tendon and aponeurosis.** The strain values at every 200 N and at maximum calculated tendon force during maximal voluntary isometric knee flexion contraction are displayed. The curves end at 1400 N for the old adults and at 1800 for the young ones, these values correspond to the maximum common force achieved by all subjects in either group, old and young adults. Y: Young ($n$ = 12); O: Old adults ($n$ = 14); Means and SEM; Age effect: ($^aP < 0.05$) *vs* young.

ence in the ability to recruit the entire motor unit pool of the muscle would also contribute to a higher impairment after injury. Our review indicates that this is the case for both children (probably due to maturation) and elderly (due to age effects on neuromuscular system).

Another factor which might have affected the impaired ability to produce maximum muscle strength is a higher antagonist co-activation. Although co-activation levels may contribute to a high joint stability and stiffness, it appears that co-activation levels do not differ between children and adults or between elderly and adults, at least during isolated (static or dynamic) joint strength testing conditions. This indicates that it is the reduced muscle mass and central activation of the agonist muscles rather than higher co-activation by the antagonists that contributes to age related differences in absolute strength. It follows, that this particular neuromuscular mechanism, central or peripheral, is not age specific.

While extensive research has examined the strength balance around the knee through the H:Q ratio, there is a marked difference in the amount of research performed in adults compared to that performed in children and the elderly. Nevertheless, it appears that H:Q ratio levels are altered after knee injury mainly as a result of a lower quadriceps muscle strength. Current evidence does not indicate whether H:Q ratio differs between different age groups. Sparse data indicate that hamstring muscle strength tends to be relatively less affected by age compared with quadriceps muscle strength, but this is only a speculation.

It appears that stiffness of the muscle-tendon units around the knee differs between age groups. Interestingly, there is a common pattern regarding age variations in muscle-tendon stiffness: both children and the elderly display less stiffness of the quadriceps MTU than adults. While in children this may be due to sexual maturation and in elderly due to deterioration of tissue, it could be suggested that the main characteristic is similar: both children and elderly show a more compliant muscle-tendon unit. It seems that tendons adaptations follow muscle's force capacity. Muscle force determines the strain of tendon cells, *i.e.*, the higher the force applied to tendon the higher its deformation. There is evidence that strain of tendon cells is an important regulator for the homeostasis of connective tissues. The resulted more compliant tendon in children and elderly affects both the force-length and force-velocity relationship of their muscles and, in turn, leads to an altered strength capacity.

Finally, an interesting question is whether age-related differences in neuromuscular strategies around the knee depend on gender. There have been no studies that specifically addressed such a question. Neverthless, current evidence indicates that females display a higher injury rate than males. Such variation is observed from an early age where, there is evidence that muscle strength and co-activation profiles may place girls to a greater injury risk than boys. Similar results are also reported for older individuals, where additional factors, such as body mass, also contribute to gender variations.

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TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (6): Osteoporosis

# Bone three-dimensional microstructural features of the common osteoporotic fracture sites

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## Abstract

Osteoporosis is a common metabolic skeletal disorder characterized by decreased bone mass and deteriorated bone structure, leading to increased susceptibility to fractures. With aging population, osteoporotic fractures are of global health and socioeconomic importance. The three-dimensional microstructural information of the common osteoporosis-related fracture sites, including vertebra, femoral neck and distal radius, is a key for fully understanding osteoporosis pathogenesis and predicting the fracture risk. Low vertebral bone mineral density (BMD) is correlated with increased fracture of the spine. Vertebral BMD decreases from cervical to lumbar spine, with the lowest BMD at the third lumbar vertebra. Trabecular bone mass of the vertebrae is much lower than that of the peripheral bone. Cancellous bone of the vertebral body has a complex heterogeneous three-dimensional microstructure, with lower bone volume in the central and anterior superior regions. Trabecular bone quality is a key element to maintain the vertebral strength. The increased fragility of osteoporotic femoral neck is attributed to low cancellous bone volume and high compact porosity. Compared with age-matched controls, increased cortical porosity is observed at the femoral neck in osteoporotic fracture patients. Distal radius demonstrates spatial inhomogeneous characteristic in cortical microstructure. The medial region of the distal radius displays the highest cortical porosity compared with the lateral, anterior and posterior regions. Bone strength of the distal radius is mainly determined by cortical porosity, which deteriorates with advancing age.

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**Key words:** Osteoporosis; Fracture; Microstructure; Trabecular bone; Cortical bone; Vertebra; Femoral neck; Distal radius

**Core tip:** The most common sites of the osteoporotic fractures include the vertebra, femoral neck and distal radius, where the microstructural information is a key for fully understanding osteoporosis pathogenesis and improving the prediction of fracture risk. Vertebral strength is mostly preserved by trabecular bone, which is microstructurally inhomogeneous, with lower bone volume in the central and anterior superior regions. Increased fragility of osteoporotic femoral neck is attributed to low cancellous bone volume and high compact porosity. Distal radius shows significant variations in cortical porosity, which is the major element attributed to bone strength of the distal radius.

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## INTRODUCTION

Osteoporosis is a common metabolic skeletal disorder characterized by decreased bone mass and deteriorated

**Table 1 The main bone histomorphometric parameters and their significance**

| Parameters | Meaning | Significance |
|---|---|---|
| BV/TV | Trabecular bone volume per total tissue volume | In osteoporotic patients, BV/TV significantly decreases, accompanied by low BMD |
| Tb.Th | Trabecular thickness | Trabeculae become thinner with the progression of osteoporosis for both women and men |
| Tb.N | Trabecular number | In osteoporotic patients, the decrease in Tb.N is usually greater in women than in men |
| Tb.Sp | Trabecular separation | Tb.Sp increases with the progression of osteoporosis |
| Co.Po | Cortical porosity | With the progression of osteoporosis, Co.Po increases, accompanied by low cortical BMD |

BV/TV: Bone volume fraction; Tb.Th: Trabecular thickness; Tb.N: Trabecular number; Tb.Sp: Trabecular separation; BMD: Bone mineral density.

bone structure, resulting in an increased susceptibility to fractures[1,2]. With the rapid growth in the elderly population, osteoporotic fracture is a global public health problem with enormous socioeconomic consequences[3]. Osteoporosis is estimated to affect more than 200 million people around the world. Osteoporosis leads to approximately 9 million new fractures annually, 1.4 million being in the vertebra, 1.7 million in the forearm and 1.6 million in the femoral neck[4]. A key characteristic of osteoporosis is fracture that occurs with little or no injury. Osteoporotic fractures might affect functioning of body movement, which can lead to disability, limit daily activities and affect the quality of life.

Osteoporosis can affect any bone in the body. However, osteoporotic fractures are some skeletal sites are more easily fractured than would normally be the case. However, osteoporotic fractures are more easily and more likely to occur at some special skeletal sites. Consistent with current clinical experience, the most common sites of fractures in osteoporotic patients include bones that are under certain strain as they bear body weight such as vertebra and femoral neck or take the stress when a person falls on an outstretched hand such as distal radius[5]. To prevent fractures is the major purpose of osteoporosis screening. When the external force applied to a bone exceeds its strength, a fracture would occur. The ability of a bone to tolerate loading depends on the quantity and quality of the bone. The intrinsic material properties of bone are bone mineral density (BMD), bone size, geometry, bone mineralization, microstructure and bone turnover[6].

The decline in BMD is related to decreased bone strength, increased bone fragility and elevated fracture risk. BMD is a major important predictor of subsequent osteoporotic fracture risk. Many techniques are available to determine BMD value. Low BMD is correlated with increased fracture risk[6]. Clinical studies demonstrate that BMD only accounts for bone strength partially and that there is a limitation of BMD measurements in evaluating fracture risk[7,8]. Recent studies show that bone microstructural information can detect early changes in osteoporotic process. Knowledge of bone microstructure is important to fully understanding the pathogenesis of osteoporotic fracture[9-11]. The microstructural properties of vertebra, femoral neck and distal radius are critical for predicting the fracture risk of these sites. Bone microstructure typically refers to histomorphometric parameters originally obtained from two-dimensional (2D) stained sections. The sample preparation process of this 2D approach is tedious and destructive. Bone structure is three-dimensional (3D). Owing to the substantially improved spatial resolution, it has been possible recently to analyze quantitatively 3D bone microarchitectural properties. Micro-computed tomography (CT) can provide excellent 3D spatial resolution of 10 m. A High-resolution peripheral quantitative CT (HR-pQCT) technique has been implemented on the XtremeCT scanner. The scanner provides 3D images with isotropic voxel size of 41 m or 82 m, the latter resulting in isotropic spatial resolution of about 130-150 m[12]. With these newly developed techniques, many studies have been carried out to investigate the variations of 3D cancellous bone microstructure, such as bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N) and trabecular separation (Tb.Sp). Cortical parameters such as BMD, thickness and porosity are also calculated[13]. All these parameters are important for evaluating bone quality (Table 1). This review article will discuss the bone microstructural parameters obtained from 3D work and newer technologies, especially the vertebra, femoral neck and distal radius, the common sites of the osteoporotic fractures according to the existing literature.

## VERTEBRA

The vertebrae are made up of 24 individual bones to bear the weight of the upper body and withstand substantial loads. Vertebral body is a thick oval segment of bone, composed of internal cancellous bone and a thin coating of compact bone. Intervertebral disc is a massive pad of fibrocartilage, which is firmly attached to vertebral body above and below, forming a flexible column. This lightweight structure contains a minimal amount of material in its structure. Cancellous bone of vertebral body is crucial for the function of the whole spinal column[14,15]. Osteoporotic fractures most often occur in the vertebrae. Approximately 700000 new vertebral fractures occur in the United States annually[16]. They are nearly twofold as common as other fractures, such as osteoporosis-related femoral neck and radial fractures. When osteoporosis is involved, a vertebral compression fracture generally is a patient's earliest sign of a deteriorated skeleton from osteoporosis.

Cancellous bone of vertebra is metabolically more active than cortical bone and trabecular BMD may act as an initial predictor of spinal osteoporotic fracture[17].

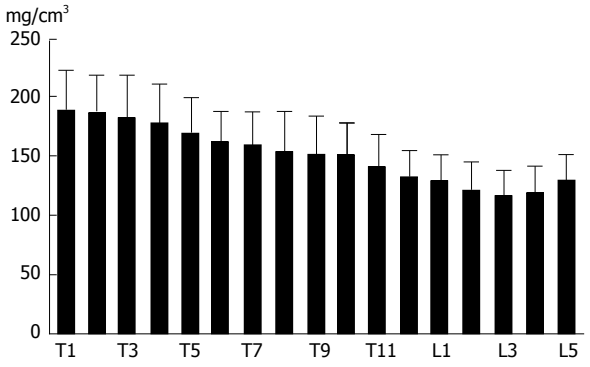


**Figure 1 The trabecular bone mineral density of the thoracic and lumbar vertebrae[22].** The bone mineral density tends to decrease from the first thoracic to third lumbar vertebra.

There is a negative correlation between vertebral cancellous BMD and spinal fracture[14]. It is necessary to examine regional BMD separately in different levels, as osteoporosis-related spinal fractures occur frequently in the midthoracic region and thoracolumbar transitional area, as described by Wasnich[18]. Vertebral BMD can be explored using QCT-based BMD measurement approach[19-22]. Trabecular BMD of the cervical spine is significantly higher than that of the thoracic and lumbar one. Trabecular BMD of the first sacral vertebra is significantly higher than that of the lumbar vertebrae. In an age- and gender-stratified population-based non-invasive study, we examined trabecular volumetric BMD (vBMD) of thoracic and lumbar vertebrae[19-22]. Trabecular vBMD of vertebral body gradually decreased craniocaudally from the first thoracic (Th1) to third lumbar spine (L3) for both genders. Compared with Th1, vBMD at L3 declined around 30% (Figure 1). There was a very high correlation between adjacent vertebral BMD, though the BMD correlation became lower between vertebrae with increasing distance from each other. It might be suitable to use any vertebra for evaluating bone strength of spine. By using our knowledge available for BMD correlations, one can estimate the BMD of any vertebra, provided that one vertebral BMD is known.

The regional variation of vertebral microstructure has been examined extensively[23-25]. We studied 3D microstructure of L4 from Japanese cadaver donors by quantitative micro-CT and electron microscopic methods[25]. BV/TV and Tb.N of vertebral cancellous bone declined with advancing age. BV/TV decreased by 22%-24% from 60 to 90 years of age for both males and females. Age-dependent decreases of BV/TV were similar for males and females. Tb.N also decreased with age by 19% in males and 16% in females. Tb.Sp consistently increased with age. There was no significant decline of Tb.Th with advancing age. Thus, age-related decrease of BV/TV is mainly related to increased Tb.Sp and decreased Tb.N[17,23,25].

Cancellous bone of vertebra is complicated morphologically that contains numerous plate-like and rod-like trabeculae[24-27]. Trabecular plate-like or rod-like characteristic might be assessed by determining the structure model index (SMI). SMI is a crucial morphometric parameter which effects intensely on bone intrinsic properties. Vertebral cancellous bone has a more rod-like than plate-like structure. SMI of the vertebral cancellous bone increases by about 20% from 60 and 90 years of age. Vertebral trabeculae are gradually converted from plate-like to rod-like and consequently are more fragile and are especially prone to fracture. Cancellous connectivity density (Conn.D) is a basic characteristic of 3D network and is critical for the preservation of bone strength. When the amount of cancellous bone declines, the value of Conn.D would decrease correspondently, perhaps attributable to the small trabecular bone loss[25,26,28]. Vertebral trabecular Conn.D decreases significantly with advancing age. Age-dependent change of Conn.D is almost identical for males and females[25,28].

Determination of BMD locally is achievable using QCT owing to its high spatial resolution. However, clinical assessment is limited to just a few thin slices and QCT is commonly carried out in the central area of the vertebral body. As cancellous bone is heterogeneous microarchitecturally in the vertebral body[19,22,25], localization of low BMD value within the vertebral body is beneficial clinically and may play a role in clarifying pathophysiology of spinal osteoporosis-related fracture. QCT and micro-CT studies show that BV/TV is lower in central and anterior superior regions, compared with the posterior region of the vertebral body (Figure 2). The cancellous regional differences of the microarchitectural characteristic within the vertebrae is important for assessing the bone quality of vertebra and may also contribute to the pathogenesis of osteoporosis-related spinal fracture.

By using scanning electron microscopy, it is easy to examine the trabecular resorption state, that is critical for cancellous structural integrity, possibly deciding if the bone strength is sustained or declined[25,29,30]. The decrease of spinal cancellous bone with advancing age is predominantly through trabecular perforation rather than trabecular general thinning[25,28]. It is demonstrated that osteoclasts resorb some perforated trabecular bone and the trabecular connectivity is destroyed. When the newly formed bone is insufficient adequately to replace missing bone, the trabecular connectivity will reduce and the bone will become more brittle and fragile[25,29,30]. Microcallus is a nodular aggregation of woven bone, which is often found predominantly on the thin vertical trabeculae (Figure 3A). Microcallus acts to preserve or repair a trabecula[25,31-33]. However, what triggers the microcallus formation is still subject to debate.

The conventional view is that a compressive load on vertebrae is mainly carried by the vertical trabeculae, whereas the horizontal trabeculae serve to prevent buckling of the vertical trabeculae[34,35]. This view is reinforced by finite element analyses of human vertebral bone specimens, which demonstrates that vertical trabeculae are more highly strained than horizontal ones under normal compressive loading, the[14,36]. Consequently, it is important to quantify the trabecular thickness as well as bone volume fraction for horizontal and vertical trabecular bone

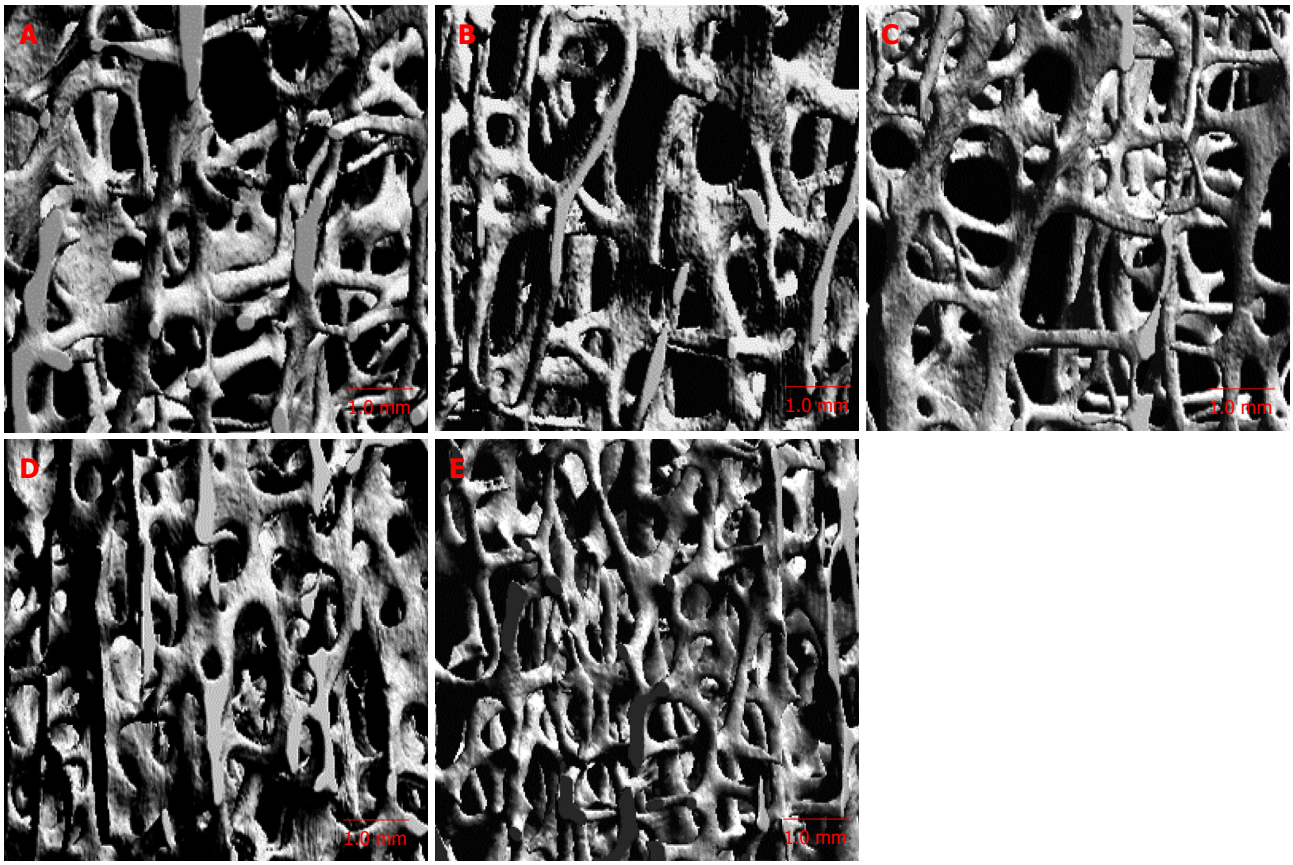


**Figure 2 Micro-computed tomography image in different regions of vertebral body[25].** A: Anterosuperior; B: Anteroinferior; C: Central; D: Posterosuperior; E: Posteroinferior regions. The trabecular bone is lower in the anterosuperior and central regions.

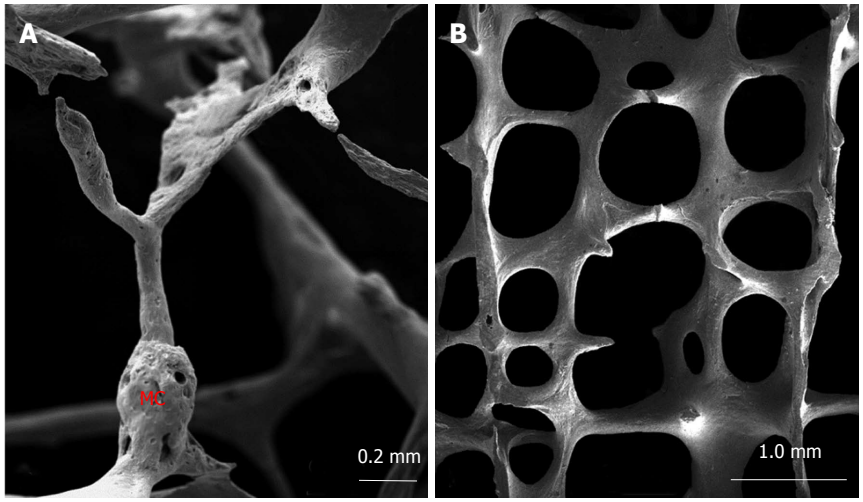


**Figure 3 Scanning electron microscopic image of vertebral trabecular bone[25].** The microcallus (MC) is seen on the vertical trabecula (A). Tertical trabeculae are relatively thicker than the horizontal ones (B).

independently. Recently, a 3D approach was introduced to segment a trabecular network into vertical and horizontal trabeculae of the vertebral body[37-39]. Fields *et al*[37,38] found that vertical trabeculae played a particular important role for the compressive bone strength of vertebrae with low BMD and presumed that vertebral bone strength is better explained by the vertical trabecular bone volume fraction alone, than by the total trabecular bone volume fraction. The scanning electron microscopic images confirmed that the horizontal trabeculae were thinner, whereas the vertical ones were relatively thicker (Figure 3B). Both vertical and horizontal trabeculae decreased with age and vertical trabeculae were lost more rapidly in females than in males. Furthermore, the vertical as well as horizontal trabecular thickness were independent of age, however the ratio of horizontal/vertical trabecular thickness declined significantly with age suggesting a more pronounced thinning of horizontal trabeculae[39]. Age-related bone loss of trabecular elements results in compensatory hypertrophy of vertical trabeculae in females, but not in males[40].

Vertebral trabecular bone is inhomogeneous micro-

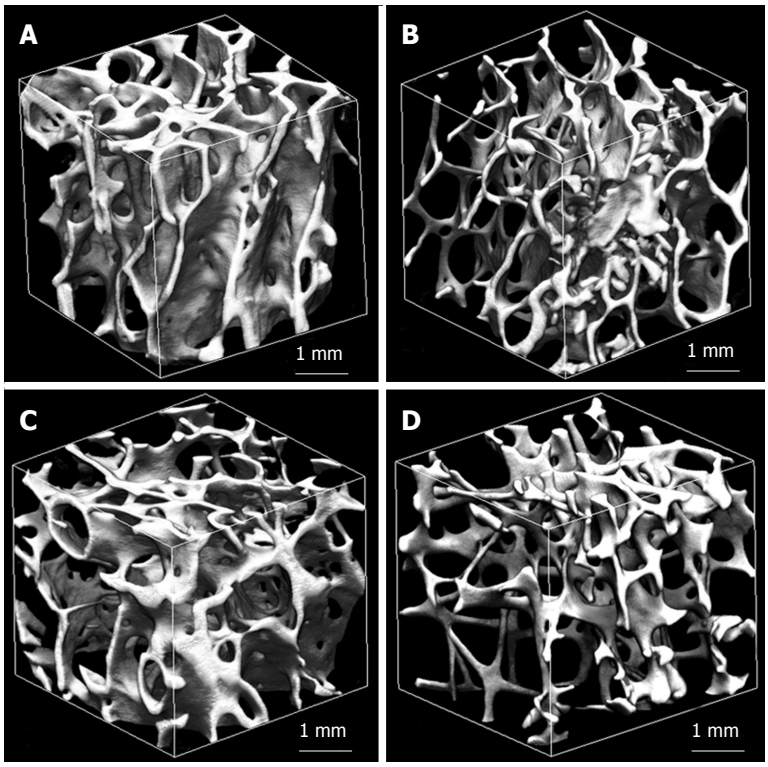


**Figure 4 Trabecular microstructure of femoral neck from a man aged 62 years (A), a man aged 92 years (B), a woman aged 62 years (C), and a woman aged 92 years (D)[49].** The trabecular bone is higher in a man aged 62 years and is lower in a woman aged 92 years.

structurally. Age-dependent declines of BV/TV and Conn.D are similar in males and females. There are significant differences of some morphometric parameters between males and females. Age-dependent bone loss of vertebral trabeculae may be induced by elevated bone resorption activity. These findings elucidate the possible mechanisms of vertebral fractures[17,25].

Highly porous cortical bone of the spine is very thin. Therefore, it is difficult to sort out the role of cortical bone, especially in aged individuals. It is difficult to determine the cortical thinness accurately with non-destructive methods. It is unclear whether the compact bone significantly contributes to biomechanical strength of whole vertebral bone. Cortical thickness of vertebral body ranges from 180 to 600 m, with a mean thickness of 380 m[40-43]. The compact bone of the cervical and lumbar vertebrae is relatively thicker than that of the thoracic one. The dorsal cortex is generally thinner than that of the ventral one. There is no significant gender difference in vertebral cortical thickness. There is a slight age-related decline in vertebral cortical thickness. Most studies highlight the importance of trabecular bone for maintaining bone strength of vertebrae, however recent studies indicate a crucial role of the cortical bone, especially in elderly individuals whose cancellous bone is lower[40-43].

## FEMORAL NECK

Femoral neck has to bear high compressive and shear forces continually. These forces are approximately 1 × body weight (BW) during standing, but they are much higher during physical activities[44]. Femoral neck fracture is generally induced by a fall, but may be caused by impact to the hip. When the bone becomes weak due to osteoporosis, only a slight external force is enough to make femoral neck more susceptible to fracture. This type of fracture is very serious and debilitating osteoporotic fracture. Osteoporosis-related femoral neck fractures are a major cause of mortality and morbidity in elderly people worldwide[45,46]. Gullberg *et al*[47] estimated that there were 1.25 million new femoral neck fractures occurred in the world annually and that the fracture number will increase by 310% in males and 240% in females by 2025. There have been many studies conducted to investigate the underlying causes of femoral neck fracture. It is suggested that 3D microstructures play a significant role in assessing the bone quality and provide compelling evidence to explain the bone strength[48-50].

The proximal femur was isolated by cutting at the base of femoral head and femoral neck. Cancellous bone specimen of 8 mm × 8 mm × 8 mm cube was prepared from the central part of femoral neck for quantitative micro-CT examination. Alterations of the femoral neck cancellous bone with advancing age include a decline in BV/TV and Tb.N, and an increase in Tb.Sp[49,51,52]. BV/TV decreases by around 20% from 60 to 90 years of age (Figure 4). Tb.N and Tb.Th decline, while Tb.Sp increases in males and females. The decrease of BV/TV with age is related to decreases in Tb.N and Tb.Th, and increases in Tb.Sp[49,50]. There are a few studies regarding SMI of femoral neck trabeculae[49,50,53]. It is found that SMI increases with age. Trabecular structure of the femoral neck becomes more rod-like with advancing age. Therefore it is more brittle and more likely to fracture. Conn.D decreases significantly with age[49,50]. When the trabecular bone volume fraction declines, Conn.D will decline concomitantly, probably because of small trabecular bone loss[25,49]. Ciarelli *et al*[48] examined 3D micro-

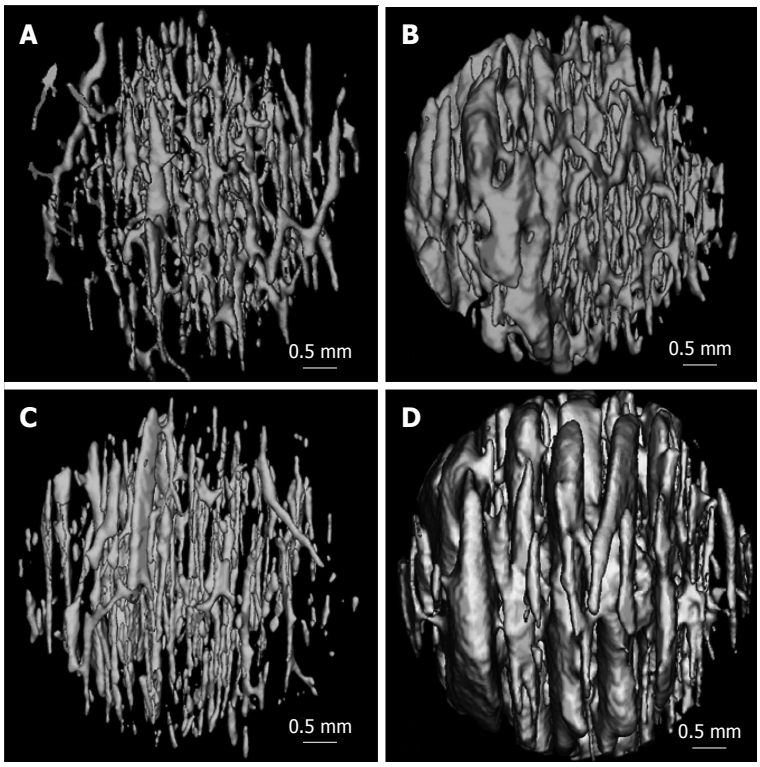


**Figure 5 Three D reconstructed images of the canal networks in the inferior femoral neck cortex from a man aged 62 years (A), a man aged 92 years (B), a woman aged 62 years (C), and a woman aged 92 years (D)[49].** There are more enlarged canals in the 92 years than those of the 62 years.

architecture of femoral neck in hip fracture patients and nonfracture controls. There were more anisotropic 3D microstructures and relatively fewer cancellous elements transverse to the primary load axis in fracture cases. The changed 3D microstructures would be supposed to influence bone biomechanical characteristics. Relatively fewer transverse cancellous bones in fracture patients might produce diminished cross bracing and a high susceptibility to buckling of cancellous bone oriented along the loading axis, and the decreased resistance of transverse loads. This changed microstructure may distinguish between patients of high fracture risk and low fracture risk with identical trabecular bone volume[48].

The femoral neck displays noted regional heterogeneity morphologically[49,54-56]. When the hip joint bears entire body weight vertically, compact bone of the inferior region is thicker than that of the superior region. Compact bone of the aged subjects is very thin in the upper region, while that of the lower region remain relatively thicker[54-56]. Cortical thickness of the superior posterior region decreases by 6.4% per decade in females between the ages 60 to 90 years. Similar but a significantly lesser effect is evident in males. The thinning of femoral cortex compromises the functional capacity of femoral neck to absorb energy independent of osteoporosis[49,55]. Cortical porosity (Ct.Po) of femoral neck varies from 5% to 13%[49,55-57]. With advancing age, the diameter of cortical pores increases and some pores adjacent to the endosteum coalesce, leaving the remnant cortexes that resemble to cancellous bone. The remained cortical bone close to the periosteum is kept with normal appearance including several enlarged pores. In elderly female individuals, enlarged cortical pores are present at the endosteal surface, as well as at the periosteal surface. Figure 5 indicates the age-dependent variations of cortical porosity in the inferior region of femoral neck. Cortical thickness (Ct.Th) declines by 3% to 5% and Ct.Po increases by 31% to 33% per decade between ages of 60 to 90 years[49]. The number of cortical pores has no marked age-related changes, whereas the diameter of cortical pore increases significantly with age[49,55-57]. Accordingly, increase of cortical porosity with advancing age is predominantly attributable to enlarged cortical pores. Compared with males, females have a greater Ct.Po and larger cortical pore. Consequently, in addition to age, gender is also an important factor to influence cortical porosity. With advancing age, especially in females several intracortical pores coalesce into a giant pores larger than 385 m[46,52,55]. The giant intracortical pore formation might have a pivotal function in the process of local cortical bone loss during aging.

Osteoporotic fractures of femoral neck are considered to be caused by both cancellous bone loss and compact bone thinning. The relative contribution of compact bone and cancellous bone to whole bone strength of the femoral neck is still poorly understood. It has been shown that an increase in Ct.Po is the most noticeable age-dependent change of femoral neck. The decline in BV/TV with age is more apparent than that of Ct.Th. There is a statistically significant negative correlation between BV/TV and Ct.Po. Ct.Th and BV/TV are lower, and Ct.Po is higher in females, when compares with males. The above results might be used as reference for racial comparison with age and gender, and contribute to the pathogenesis of osteoporosis-related fracture at the femoral neck[49,55,58].

## DISTAL RADIUS

Distal radius fractures are very common in osteoporosis patients[59]. The most common cause of the distal radial fracture is a fall on the outstretched hand in people with normal or low bone mineral density[60]. When people fall from standing position, the sudden external force can cause fracture of the distal radius. However, the severity of fall required to cause radial fracture in osteoporotic patients is much less than the subjects with normal BMD, because of the greater skeletal fragility.

Population-based cross-sectional studies by HR-pQCT imaging technique uncovered that BV/TV of the radial cancellous bone declines by 26% in males and 27% in females from 60 to 90 years of age[61]. Trabecular bone volume of distal radius remains relatively stable until midlife and thereafter decreases[61-63]. Trabecular bone volume is higher in males than in females of the same age. Age-dependent decreases in the trabecular BV/TV and BMD are similar for males and females from 20 to 90 years of age[61-63]. There is a different microstructural basis for the decline of cancellous bone volume with advancing age between males and females. Gender difference of cancellous bone loss with age is present at the distal radius. Decreases of Tb.N and increases of Tb.Sp are observed in females, whereas in males the decrease of BV/TV is primarily caused by trabecular thinning, leading to a substantial decline in Tb.Th and unchanged Tb.N[61-63].

Recent studies highlight the importance of the cortical microstructure in the maintenance of the radial strength[62,64]. Cortical bone at the distal radius can be analyzed structurally with HR-pQCT method[63]. Cortical porosity significantly increased with age. Cortical porosity parameters of the distal radius provided an important decade-wise discrimination for females in their fifties and sixties[62,63,65]. Cortical vBMD is dramatically decreased in older women than in younger women[66,67]. There is no significant alteration in the cortical vBMD with age in males. As compared with younger subjects, older men and women have elevated values of Ct.Po and cortical pore diameter. Bone strength of distal radial cortex strongly correlated inversely with Ct.Po, which has a major impact on bone quality[63-65]. Age-dependent increase of Ct.Po in females is more than twice as high as in males. Cortical bones have a tendency to become thinning more with age in females than in males. Compared with males, females have lower bone strength of the distal radius. The gender difference is perhaps attributable higher cortical porosity in females.

As compared with young subjects, older women and men had significantly worse microstructure of cortical bone, including increased Ct.Po, but generally similar trabecular bone parameters of the distal radius. The main effect of age independent of BMD is on cortical morphometric parameters[62]. The spatial inhomogeneous characteristic in cortical porosity is particularly noticeable at the distal radius. The anterior region exhibits the lowest Ct.Po, while the medial region shows the highest. Ct.Po is more than twofold higher in the medial region than in the anterior region. Ct.Th is lowest in the lateral region and highest in the anterior and posterior regions. Ct.BMD is lowest in the lateral region and highest in the posterior region. Increased Ct.Po is investigated in the medial region of the distal radius, which is adjacent to the ulna[66]. Assessment of region-dependent cortical parameters is critical for evaluating therapeutic effect and for understanding osteoporosis and its related fracture. Histomorphometric changes of the cortical bone display significant deficits in cortical structure at the distal radius with age as an important base for osteoporotic fracture mechanism[54,67]. Collectively, these findings suggest that cortical porosity is a crucial element of bone strength that deteriorates with advancing age.

## CONCLUSION

Osteoporosis is a skeletal disorder with a decreased bone mass and a deteriorated bone microstructure, resulting in reduced bone strength, elevated bone fragility and increased fracture risk. Bone microstructural properties can detect early alterations in bone fragility process and are an important predictor of bone strength. The changes of bone microstructure with osteoporosis in the axial and peripheral bone are complex. Cancellous and compact bone work effectively together to preserve biomechanical competence of the skeleton. Cancellous bone microstructure is crucial to preserve bone quality of the axial skeleton, while cortical bone is critically important for maintaining skeletal integrity, especially at the appendicular sites where the cortical bone is a major contributor to bone strength[64]. The bone strength of vertebra is preserved predominantly by cancellous bone. Trabecular bone mass of vertebra is much lower than that of the peripheral bone. Trabecular bone of vertebral body has a complex heterogeneous microstructure, with reduced BMD in the central and anterior superior regions. Elevated fragility of femoral neck in osteoporotic subjects is attributed to decreased cancellous bone volume and increased compact porosity. The main microstructural characteristic of cortical bone is cortical porosity, which is significantly higher at femoral neck in osteoporotic fracture patients than that of the controls[68]. Distal radius demonstrates obvious differences in cortical microstructure. The medial region of the distal radius has the highest Ct.Po compared with the lateral, anterior and posterior regions. Cortical porosity of the distal radius plays an important role in maintaining local bone quality that deteriorates with advancing age. There has been remarkable progress in our understanding of the pathophysiology of osteoporosis and its related fracture. However, greater effort is needed to elucidate precise mechanism of the bone fragility at the common sites of osteoporotic fractures.

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TOPIC HIGHLIGHT

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

# Protein kinase small molecule inhibitors for rheumatoid arthritis: Medicinal chemistry/clinical perspectives

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## Abstract

Medicinal chemistry strategies have contributed to the development, experimental study of and clinical trials assessment of the first type of protein kinase small molecule inhibitor to target the Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway. The orally administered small molecule inhibitor, tofacitinib, is the first drug to target the JAK/STAT pathway for entry into the armamentarium of the medical therapy of rheumatoid arthritis. The introduction of tofacitinib into general rheumatologic practice coupled with increasing understanding that additional cellular signal transduction pathways including the mitogen-activated protein kinase and phosphatidylinositide-3-kinase/Akt/mammalian target of rapamycin pathways as well as spleen tyrosine kinase also contribute to immune-mediated inflammatory in rheumatoid arthritis makes it likely that further development of orally administered protein kinase small molecule inhibitors for rheumatoid arthritis will occur in the near future.

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**Key words:** Clinical trials; Protein kinase; Signal transduction; Small molecule inhibitor; Rheumatoid arthritis

**Core tip:** Signal transduction is a regulator of gene expression in cells. Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling is activated by pro-inflammatory cytokines which contributes to immune-mediated inflammation in rheumatoid arthritis. Medicinal chemistry was employed to develop JAK small molecule inhibitors for determining their clinical efficacy in active rheumatoid arthritis patients. Tofacitinib, a JAK small molecule inhibitor, is now generally used to treat moderate to severe rheumatoid arthritis patients who have not adequately responded to disease-modifying anti-rheumatic drugs or various biologic agents. The clinical efficacy of JAK small molecule inhibitors provides the impetus for future drug discovery targeted at other signal transduction pathways in rheumatoid arthritis.

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## INTRODUCTION

Medical therapeutic intervention of rheumatoid arthritis

(RA) was dramatically altered with the introduction of biologic drugs with monoclonal antibody or fusion protein structures[1-5] into the armamentarium of disease-modifying anti-rheumatic drugs (DMARDs), which had previously included, non-steroidal anti-inflammatory drugs, immunosuppressive drugs, (*e.g.*, glucocorticoids, methotrexate, sulphasalazine), anti-malarial agents (*e.g.*, hydroxychloroquine), and modifiers of DNA synthesis (*e.g.*, leflunomide)[6-10] or various combinations of these DMARDs. Among the biological drugs chosen for development for RA were those whose mechanism of action was attributed to their capacity to neutralize the downstream effects of the elevated levels of the pro-inflammatory cytokines in RA sera and synovial fluid[11-15], tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6[16-18], among other interleukins[11-13] as well as possessing activity towards the inhibition of proliferation and dysfunctional RA T-cells and B-cells[19-23].

However, the general requirement that the biologic drugs need to be employed in RA therapy for long periods of time has caused problems inherent in their chronic use, including, but not limited to, the elevated relative risk for developing cancers and infections, inadequate drug responses and drug refractoriness and death as well as the potential for antibodies to be produced that are directed against the monoclonal antibodies or fusion proteins themselves[24-27] thus neutralizing their effectiveness. These crucial considerations have resulted in the contention that there needs to be continual identification of novel therapeutic targets coupled to drug development for intervention in RA and autoimmune diseases in general[28,29].

## IDENTIFICATION OF PROTEIN KINASES AS POTENTIAL DRUG TARGETS FOR RA

### The JAK/STAT pathway

A central theme for considering which component of RA pathology should be targeted for novel drug development first involves identifying a pathway(s) that is involved in the aberrant cell and humoral-mediated immune response and inflammation which regulate abnormal survival of T-, B-cells, macrophages and synoviocytes as well as the loss of chondrocyte viability and vitality, all of which are characteristic elements of RA progression[29]. In that regard, the Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway perfectly fits this viewpoint because JAK/STAT signaling has been shown to regulate so many of the diverse cellular functions critical to RA pathogenesis and progression, including, cell survival and proliferation, immune cell-fate determination and apoptosis[26,28,30,31]. There are 4 members of the JAK family, namely, JAK1, JAK2, JAK3 and TYK2[32] and 7 STAT proteins, STAT1-4, STAT5A, STAT5 and STAT6[33].

The elevated gene expression of several pro-inflammatory cytokines, including interferon-γ (INF-γ), IL-2, IL-6, IL-7, IL-7 receptor, *IL-17*, *IL-15*, *IL-19*, *IL-21*, *IL-23* genes as well as other genes and transcription factors germane to RA pathology are all regulated by phosphorylated (*i.e.*, activated) STAT proteins[33-37]. In addition, there are several STAT-target genes relevant to cell differentiation, survival, apoptosis and cytokine signaling (*e.g.*, cyclin D1, c-Myc, Bcl-xL, Mcl-1, survivin, MKP-1, TNFRSF13b and SOCS-3), all of which play important roles in RA. For example, the complex interaction involving IL-7 and IL-7R appears to be critical for regulating the T-cell receptor-γ-locus *via* phosphorylated STAT5 and histone acetylase. Thus, the findings reported by Hartgring *et al*[38] that RA synovial fluid contained elevated levels of IL-7R made the *IL-7R* gene an even more attractive target for SMI drug development, perhaps through the inhibition of STAT5 activation.

### Tofacitinib (CP-690,550)

The development and FDA approval of the first small molecule inhibitor (SMI) of a protein kinase, for use in the therapy of moderate-to-severe active RA in which methotrexate did not work well, arose from a series of sequential optimization protocols involving pyrrolopyrimidine based-JAK3 inhibitors[39], which eventually resulted in the drug CP-690,550, now called tofacitinib[40]. The efficacy of this drug for RA was established in numerous RA clinical trials[41,42] (see below) and tofacitinib has now entered general rheumatology practice.

### Ruxolitinib (INCB018424)

Ruxolitinib/INCB018424 now referred to as ruxolitinib is a JAK1 and JAK2 SMI[43]. The results of studies conducted on normal volunteers[44] and RA patients[44] concluded that ruxolitinib was generally safe and well-tolerated and also exhibited acceptable oral bioavailability with dose-proportional systemic pharmacokinetics and pharmacodynamics with low oral dose clearance and a small volume of distribution. Additional results from that study showed that ruxolitinib inhibited the phosphorylation of STAT3 in whole blood that was correlated with the plasma levels of the drug. Additional clinical trials involving patients with mild-to-moderate psoriasis[43] or active RA[45] administered ruxolitinib have now been conducted. In the RA trial, Williams *et al*[45] showed that ruxolitinib achieved an American College of Rheumatology (ACR)-70 criteria in 33% of patients compared to 0% in the placebo arm. Pharmacokinetic analysis determined that ruxolitinib inhibited JAK1 and JAK2 and also reduced plasma levels of IL-6 and CD40, the latter a co-stimulatory protein found on antigen-presenting cells. Ruxolitinib was also a potent p-STAT3 SMI in *ex vivo* studies conducted on blood cells obtained from RA patients.

### Pre-clinical studies and development of JAK SMIs

Clinical trials are presently being conducted with RA and psoriasis patients to determine the clinical efficacy of several JAK SMIs, including INCB020850 (specificity, JAK1

**Table 1 Janus kinase small molecule inhibitors in development**

| SMI | JAK Specificity/other kinase inhibitory activity | Ref. |
|---|---|---|
| SAR302503 (Fedratinib) | JAK2 | [46] |
| CEP701 (Lestaurtinib) | JAK2 | [47] |
| SB1518 (Pacritinib) | JAK2/FLT3[1] | [48] |
| XL-019 | JAK2 | [48] |
| LY2784544 | JAK2/V617F[2] | [49,50] |
| AZD1480 | JAK2 | [51] |
| NS-108 | JAK2/Src[3] | [52] |
| BMS-911453 | JAK2 | [53] |

[1]FLT3: Fms-like tyrosine kinase 3; a receptor-type tyrosine-protein kinase; [2]V617F: A point mutation in JAK2 (V617F) identified in the hematopoietic cells of patients with several chronic myeloproliferative disorders; [3]Src: V-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog; JAK: Janus kinase; SMI: Small molecule inhibitor.

= JAK2), INCB39110 (JAK1 > JAK2), LY3009104 (specificity, similar to INCB020850), PF-956980 (specificity, JAK3) and CYT387 (specificity, JAK1/JAK2; with activity towards TYK2 as well). Clinical studies in normal volunteers and patients with various malignancies are also being conducted with the ultimate goal of developing additional JAK SMIs for use in clinical therapy (Table 1).

According to the PubMed Central database at the time of this writing there are as yet no published Phase 3 RA or psoriasis clinical trials results for INCB020850, INCB39110, LY3009104 or PF-956980. However, Kyttaris[54] recently reviewed the status of the JAK3-selective SMI, VX-509, which showed "promising" results in a Phase 2b clinical trial. In that regard, Genovese *et al*[55] recently reported the results of a 12-24 wk placebo-controlled double-blind phase 2 clinical trial involving RA patients maintained on a stable dose of methotrexate. VX-509 administered orally at 100, 150 and 200 mg QD was employed. The subjects receiving VX-509 showed statistically significant ACR20, ACR50 and ACR70 responses *vs* placebo (*i.e.*, methotrexate) as well as a statistically significant improvement from baseline in the DAS-28-CRP, Health Assessment Questionnaire-D1 (HAQ-D1) and Clinical Disease Activity Index *vs* placebo. However, the adverse event rates were higher in the VX-509 arm, most notably the incidence of infection relative to the placebo.

In a recent preclinical evaluation comparing the effects of tofacitinib with INCB028059 on STAT protein activation, Migita *et al*[56] showed that both tofacitinib and INCB028050 suppressed activation of JAK1/JAK2/JAK3 as well as inhibiting phosphorylation of STAT1/STAT3/STAT5 while also reducing monocyte chemotactic protein-1 (MCP-1) and serum amyloid A1/2 (SAA1/2) levels by oncostatin-stimulated RA synovial fibroblasts. However, another JAK SMI, PF-956980, only inhibited the activation of STAT1/STAT5 and MCP-1, but not SAA1/2.

The efficacy of a JAK3-selective SMI in RA compared to several of the JAK1/JAK2 SMIs now in development for treatment of myeloproliferative diseases and malignancies (Table 1) may be a more desirable result because JAK3 is known to be less involved in hematopoietic cell development than is JAK2[57].

## THE MAPK, PI3K/AKT/MTOR AND SYK PATHWAYS

### *MAPK and PI3K/Akt/mTOR*

Signal transduction pathways other than JAK/STAT which are relevant to RA are the mitogen-activated protein kinase (MAPK) and phosphatidylinosotide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) (PI3K/Akt/mTOR) pathways and intracellular signaling involving spleen tyrosine kinase (Syk)[58,59]. There is strong evidence for "cross-talk" between the JAK/STAT, MAPK and PI3K/Akt/mTOR pathways[26]. There are also many overlapping characteristics in the cellular events that promote the abnormal survival of cancer cells when compared to cells involved in the RA synovial joint which also involve MAPK and PI3K/Akt/mTOR signaling. Thus, it was not surprising that future drug development for RA has taken a page from those experimental interventions which particularly focus on inhibiting the proliferation of cancer cells. In that regard, insights gleaned from studies of MEK1/2, the upstream activator of extracellular signal-regulated kinase1/2 (ERK1/2) and mTOR activity[60] in mutant BRAF-metastatic melanoma[61,62] and other experimental models of malignancy may shed light on whether or not these molecules may be eventually applied to RA.

In that regard, the MEK1/2 SMI, AZD6244 (selumetinib) when used in combination with the mTORC1/mTORC2 SMI, AZD8055, showed significant anti-tumor activity in nude mouse xenograft models of human lung adenocarcinoma and colorectal carcinoma[60], whereas the MEK1/2 inhibitor, AZD6244, sensitized apoptosis-resistant NRAS-mutant lines of melanoma cells to undergo apoptosis. This was correlated with negative regulation of the Wnt/β-catenin signaling *via* ERK1/2 and increased levels of the downstream scaffolding protein, AXIN1[61]. Of note, a Phase 2 trial of selumetinib in patients with the BRAFV600E/K-mutated type of melanoma[62] resulted in tumor regression in 3 of 5 patients with BRAF-mutated low p-Akt activity. However, no response was observed in the AZD6244 treatment group with high p-Akt activity. These results provide a rationale for the dual targeting of MEK1/2 and p-Akt, especially in those melanoma patients with documented high p-Akt activity.

Although there was persuasive pre-clinical data supporting the targeting of p38 kinase-α in RA[63], the results from several clinical trials in which the efficacy of pamapimod was compared to methotrexate in RA patients was disappointing in favor of methotrexate. Thus it is unlikely that pamapimod will be further developed for treating RA[64-66] although the jury is still out, so to speak, regarding whether or not VX-702, another p38 kinase SMI should be further developed and assessed for clinical efficacy in RA patients[67].

### *SyK signaling*

The clinical trial evidence is somewhat stronger, but not persuasive, for promoting the further development of the SyK inhibitor, fostamatinib (R-788)[68], although in 3 RA clinical trials with this drug, the ACR20 response rate ranged from only 35%-38%[69,70]. Moreover, in one of these clinical trials the ACR20 response in the fostamatinib (100 mg twice daily group) was 38%, compared to 35% in the placebo group after 3 mo and no significant differences were achieved in the ACR20, ACR50, or ACR70 response levels at that time.

### *Protein kinase C-θ*

There is also increasing evidence for targeting protein kinase C-θ in RA[71]. This is because protein kinase C-θ is known to play an integral role in regulating T-cell viability and cytoskeletal reorganization by regulating the activities of Vav, PI3K and Rac1 (guanyl-nucleotide exchange factor)[72,73].

## THE CLINICAL PERSPECTIVE

Data on the efficacy and safety of tofacitinib in RA was presented to the FDA in May 2012[74]. In November 2012, tofacitinib was approved for use in the US for the treatment of adults with moderately to severe active RA with an inadequate response to, or intolerance to methotrexate. Assessment of the efficacy in RA clinical trials has become fairly standardized[75] and the outcome measures used in the tofacitinib studies were similar to those used in previous clinical trials of biologic drugs for RA. The raw data included a measurement of the tender joint count and the swollen joint count by an examiner, the patient's assessment of pain on a visual analog scale, the patient's global assessment of disease activity on a visual analog scale, an examiner's global assessment of disease activity on a visual analog scale, the patient's assessment of physical function using the HAQ[76], blood testing to determine erythrocyte sedimentation rate (ESR) or CRP, and radiographs of the hands and feet[76]. In most RA studies the raw data is further "manipulated" to produce composite measures of drug efficacy. The ACR has defined the ACR20 response rate as a measure of efficacy in RA to be $\geqslant$ 20% improvement in tender joint count, $\geqslant$ 20% improvement in swollen joint count, and $\geqslant$ 20% improvement in 3 out of 5 of the following parameters: patient pain assessment, patient global assessment, physician global assessment, patient self-assessment of disability and blood acute phase reactant (ESR or CRP)[77]. In the Phase 3 tofacitinib clinical trials, approximately 25%-30% of study patients achieved an ACR20 efficacy when placebo was added to their prior therapy with methotrexate or to another oral immunosuppressant. This was a result that was similar to that previously reported in clinical trials with biologic therapies for RA[74]. In order to demonstrate efficacy that is less likely to be achieved by placebo alone, ACR50 and ACR70 data are also commonly reported, representing $\geqslant$ 50% and $\geqslant$ 70% improvement in the composite ACR score, respectively. Thus, the tender joint count of 28 joints, swollen joint count in 28 joints, serum ESR or CRP and the patient's global assessment of disease activity can be entered into a formula to generate a DAS28-4 score ranging from 0 to 10[78]. If the patient's global assessment of disease activity is omitted, the resulting score is a DAS28-3. A DAS score of $\leqslant$ 2.6 is considered to represent clinical remission, although such a DAS28 score does not necessarily represent a cessation of all joint inflammation. However, DAS28 efficacy measurements are potentially relevant to clinicians, since the DAS28 can be used to track efficacy in clinical practice and a DAS28 $\leqslant$ 2.6 is often the therapeutic goal in treat-to-target clinical trials. Radiographs are also assessed to determine joint space narrowing and the presence of periarticular erosions, which are used to calculate a radiographic score. The method of Sharp as modified by Van der Heijde is commonly employed[79]. This method generates a joint space narrowing score and an erosion score as secondary endpoints, which are combined to generate the primary endpoint, the total Sharp score[76]. Although the publication of this type of radiographic data has become standard over the past 15 years, there are some methodological flaws in this analysis. When efficacy of a new pharmaceutical is assessed, the study population usually adds the new drug to a stable dose of an oral immunosuppressant such as methotrexate. The efficacy data of this population is compared to a group randomized to receive a stable dose of oral immunosuppressant plus placebo. As a result, both groups of subjects receive medication with potential efficacy in RA, and the rise in the modified Sharpe/Van der Heijde score can be slow to rise, even in the placebo group. Therefore, to discern a meaningful difference between the new drug and placebo it may become necessary to choose study subjects with a high risk for the rapid accumulation of joint damage (for example, high serum levels of rheumatoid factor or anti-cyclic citrullinated peptide antibody), to continue to collect radiographic data for 1-2 years or more, or more often to enroll larger numbers of patients.

Ultrasound and Magnetic Resonance Imaging have been proposed as potential substitutes for radiography. However, issues of standardization, reproducibility, potential cost and correlation with other clinical outcome measures are still being worked out, but clinical trials employing these imaging techniques are beginning to appear in published reports.

The dose of tofacitinib used to treat RA in the US is 5 mg orally twice daily. The subjects enrolled in the 5 phase 3 clinical trials were those patients who had experienced an inadequate response to prior treatment with methotrexate, another oral immunosuppressant, or a TNF inhibitor[74]. Most of the study subjects were given either tofacitinib or placebo under a double-blind study design while continuing a stable dose of methotrexate or other oral immunosuppressant. In one of these studies, subjects on a stable dose of methotrexate were given subcutaneous injections (either adalimumab or placebo) plus a pill (placebo pill to recipients of adalimumab, placebo or tofacitinib to recipients of placebo injections). A small

number of subjects were enrolled in a 3 mo study of tofacitinib *vs* placebo without therapy with another immunosuppressant, but there were ethical concerns about randomizing patients with active RA to a study arm in which they were to receive no treatment. In most RA trials the new drug is compared to an active immunosuppressant commonly used in RA (usually methotrexate). The outcome data demonstrated statistically significant efficacy for tofacitinib 5 mg twice daily *vs* placebo as determined by the following outcome measures: ACR20, ACR50, ACR70, DAS-4 (ESR) $\leqslant$ 2.6, DAS-4 (ESR) improving $\geqslant$ 1.2, and HAQ-Disability Index. When compared to 199 subjects receiving adalimumab, 40 mg by subcutaneous injection every 14 d, plus methotrexate plus placebo pills, tofacitinib plus placebo injection plus methotrexate was not inferior using the following outcome measures: ACR20, ACR50, ACR70, DAS-4(ESR) $\leqslant$ 2.6, DAS-4(ESR) improving $\geqslant$ 1.2, HAQ-Disability Index. One of these 5 studies also provided radiographic outcome data. Only 20% of the subjects receiving a stable dose of methotrexate plus placebo demonstrated worsening of the radiographic score at 1 year. In the tofacitinib 5 mg twice daily plus methotrexate treatment group there was a trend toward decreased progression of the total Sharp score, but the difference did not meet statistical significance at either 6 or 12 mo.

Tofacitinib was the first JAK SMI submitted to the FDA for approval in the treatment of RA. As a result the safety assessment was broad in scope, with data collected on mortality, total adverse effects, serious adverse effects, infections, malignancies other than non-melanoma skin cancer, cardiovascular events, and bowel perforations, with monitoring of cell counts, creatinine, liver enzymes, creatinine phosphokinase, and lipid levels in the blood. Data was available for the blinded placebo controlled phase of the study and also the unblinded long-term extension clinical trial. Treatment with tofacitinib was associated with drug dose-dependent neutropenia and lymphopenia, a rise in total HDL and LDL cholesterol, but without associated cardiovascular events, and a rise in serum creatinine[74]. The increased LDL cholesterol improved after the addition of atorvastatin. Overall, the rates per 100 patient-years for all-cause mortality, serious infections, malignancy other than non-melanoma skin cancer, lymphoma, lung cancer, myocardial infarction and gastrointestinal perforation were similar to those reported in published clinical trials of biologic therapies for RA[80]. However, the rate of Herpes zoster infection was higher in the subjects treated with tofacitinib than the infection rates for Herpes zoster reported in prior clinical trials of biologic drugs for RA. After review of the clinical trial data, tofacitinib was considered to be sufficiently safe and effective to be approved for use in the US for moderate to severe active RA not responsive to methotrexate. Of note, post-FDA approval monitoring of the long term safety of tofacitinib is ongoing.

Published RA treatment trials of other small molecule inhibitors have employed a study design similar to those used to assess the safety and efficacy of tofacitinib. As stated above, a phase 2 clinical trial of fostamatinib in RA has now been concluded. Outcome criteria included ACR20, ACR50, ACR70, and DAS28 as measures of efficacy[81]. Imaging outcomes in that study were assessed by MRI. Patient-reported quality of life was assessed using the HAQ-Disability Index, multiple domains of the SF-36 questionnaire, and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire[82]. A 12 wk trial of pamapimod *vs* placebo added to a stable dose of methotrexate used ACR20, ACR50, ACR 70, DAS28, change in mean serum CRP, HAQ-DI, SF-36, and FACIT-F as efficacy outcome measures[83]. Clinical trials of other small molecule inhibitors currently under development are likely to have a similar study design.

## CONCLUSION

The development of SMIs of the JAK/STAT (including the newly developed JAK3 SMI, VX-509)[84], MAPK, PI3K/Akt/mTOR and SyK signaling pathways has recently been the target of additional pre-clinical experimental arthritis studies and RA clinical trials assessment. The phase 3 clinical trial data for the JAK SMI, tofacitinib, illustrates the therapeutic potential of this class of SMI drug. For example, by comparison with the relative ease of storage and oral administration of these SMI drugs, the treatment of RA with biologic drugs such as the TNF blockade drugs, etanercept, adalimumab, golimumab, certolizumab, the T-cell co-stimulator inhibitor, abatacept, and the IL-6/IL-6R neutralizing monoclonal antibody, tocilizumab, requires that the medication be shipped by rapid delivery, stored at 2 ℃-8 ℃ and maintained in a cool storage temperature during travel. Administration of these drugs also requires mastery of the correct injection technique, and safe and proper disposal of hypodermic needles. Therefore, if the efficacy and safety of protein kinase SMIs proves to be comparable to the injectable types of biologic drugs, many RA patients may prefer the convenience of an oral medication. However, the relatively short half-life of tofacitinib means that twice daily dosing will be necessary to achieve optimal clinical efficacy. This can be an advantage to the RA patient if the patient develops an infection such that the treating clinician may wish to reverse the immunosuppressive effect of the drug. Thus, at present, treatment with tofacitinib is a therapeutic option for moderate-to-severe RA where disease progression cannot be controlled with methotrexate.

Although SMIs have been primarily targeted to inhibit the activity of JAKs, specific members of the MAPK pathway (*e.g.*, p38-α) and PI3K/Akt/mTOR signaling pathways were also shown to be relevant to the pathogenesis of immune-mediated inflammation associated with RA. Therefore, there are likely to be signaling components of the MAPK pathway, such as the upstream protein kinase, MEK1/2, whose activity is required for phosphorylation of ERK1/2 that may be targeted for further drug development[57]. In addition, since one tar-

get of STAT activation is it's potential to increase the expression of anti-inflammatory cytokines, such as, IL-4 and IL-10[37] and the signaling pathways these cytokines activate, it appears justified to consider developing SMIs that inhibit those protein kinases which can suppress the expression of anti-inflammatory cytokine genes.

However, as an example of the continuing SMI drug development for JAKs in RA, Baricitinib, (formerly known as LY3009104/INCB028050) an inhibitor of JAK1 and JAK2 is presently under investigation in clinical trials in RA with the results from an open extension of the phase 2b trial having been recently reported[85] with additional studies entering the recruitment phase[86]. In the open-extension phase 2b trial, among all patients, the proportions of patients achieving ACR20, ACR50, ACR70, clinical disease activity index (CDAI) Remission, simplified disease activity index (SDAI) Remission, DAS28CRP $\leqslant$ 3.2, DAS28CRP < 2.6, DAS28ESR $\leqslant$ 3.2, DAS28CRP < 2.6 or the ACR/European League Against Rheumatism (EULAR) Boolean remission at the start of the open label extension (week 24) were similar or increased at week 52.

The ultimate place of protein kinase SMIs in RA therapy is not yet known. It is likely to be determined by the following conditions; more patient-years of follow-up to better understand the long-term efficacy and safety of this drug class as well as head-to-head safety and efficacy comparisons with conventional and biologic DMARDs already in use including cost issues relative to other RA treatment options

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TOPIC HIGHLIGHT

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

# Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis

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## Abstract

Tofacitinib is the first in a new class of nonbiologic disease-modifying antirheumatic drugs (DMARDs), a targeted, synthetic DMARD, approved for the treatment of rheumatoid arthritis (RA) as monotherapy or in combination with methotrexate or other non-biologic DMARD. Tofacitinib, an orally administered Janus kinase (JAK) inhibitor, decreases T-cell activation, pro-inflammatory cytokine production, and cytokine signaling by inhibiting binding of type I cytokine receptors family and γ-chain cytokines to paired JAK1/JAK3 receptors. The net effect of tofacitinb's mechanism of action is decreased synovial inflammation and structural joint damage in RA patients. To date, six phase 3 trials have been conducted to evaluate the safety and efficacy of tofacitinib under the oral rheumatoid arthritis triaLs (ORAL) series. This review describes the pharmacology of the novel agent, tofacitinib, and details the safety and efficacy data of the ORAL trials.

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**Key words:** Tofacitinib; Rheumatoid arthritis; Janus kinase inhibitor

**Core tip:** Tofacitinib, a Janus kinase inhibitor, is a targeted, synthetic, disease-modifying antirheumatic drug (DMARD) approved for the treatment of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to methotrexate. In numerous phase 2 and 3 trials, tofacitinib has proven to be safe and effective as monotherapy or in combination with methotrexate or other non-biologic DMARDs.

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## INTRODUCTION

The 2012 American College of Rheumatology (ACR) guidelines on management of rheumatoid arthritis (RA) recommends the use of disease-modifying anti-rheumatic drugs (DMARDs) in early RA of less than six months duration as monotherapy for patients with low disease activity and combination therapy for moderate or high disease activity[1]. They also recommend the use of anti-tumor necrosis factor (TNF) alpha biologic DMARDs with or without methotrexate for early RA with high disease activity and poor prognostic factors. Approved biologic DMARDs include cytokine inhibitors of TNF alpha (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab), interleukin-6 (IL-6) receptor (tocilizumab), and interleukin-1 receptor (anakinra); cell depleting agent targeting of CD20 of B cells (rituximab); and costimulation blocker of cytotoxic T lymphocyte antigen 4 (abatacept). Limitations of biologic DMARDs, which require parenteral administration (intravenous or subcutaneous), has necessitated the development of orally effective treat-

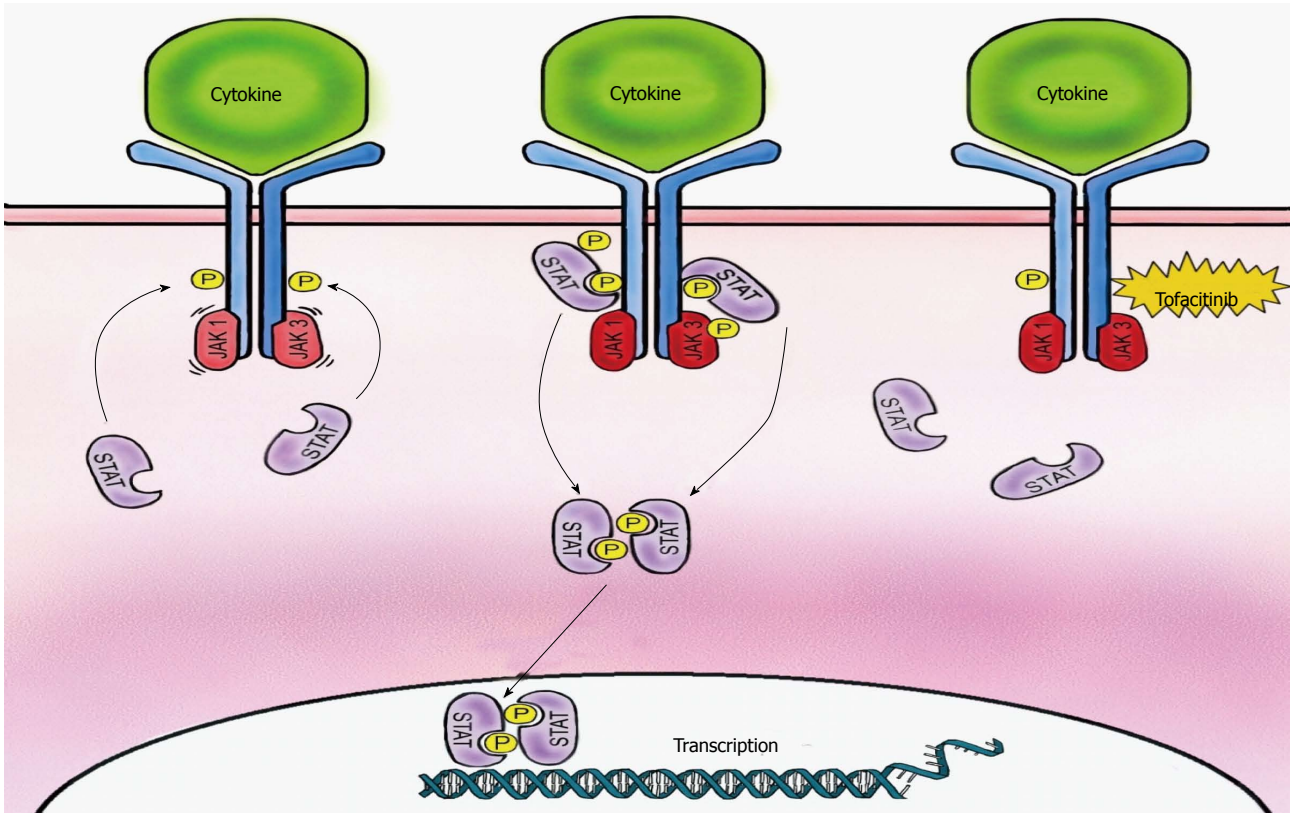


**Figure 1 Mechanism of action of tofacitinib.** JAK: Janus kinase; STAT: Signal transducer and activator of transcription.

ment options for RA. Although, the European Medicines Agency has twice refused the marketing authorization for tofacitinib based on major concerns of the overall safety profile, tofacitinib, a Janus kinase (JAK) inhibitor, is the first oral non-biologic DMARD approved by the United States Food and Drug Administration in more than a decade[2].

## PHARMACOLOGY, MECHANISM OF ACTION, AND PHARMACOKINETICS

Cytokine signaling, pro-inflammatory cytokine production and immune cell activation are key functions of activated JAK in the perpetuation of autoimmune inflammatory disease[3]. The JAK family, JAK1, JAK 2, JAK 3 and Tyk2, are nonreceptor tyrosine kinases with a variety of intercellular domains, a pseudokinase domain, and SH2- and FERM domains[4]. Binding of cytokines to paired JAK receptors (JAK1/JAK3, JAK1/JAK2, JAK1/Tyk2, JAK2/JAK2) induces autophosphorylation, phosphorylation of tyrosine residues on the cytokine receptor, and phosphorylation with subsequent activation of various signal transducer and activator of transcription (STAT) molecules. This leads to increased JAK activity, further recruitment of cytokines, and changes in gene expression through JAK-STAT pathway. The synovium of RA patients has increased expression of the JAK-STAT pathway[3]. JAK1 and JAK2 play a role in growth, neurodevelopment, hematopoiesis, and host defense while JAK3 and Tyk2 are engaged in immune responses. Tofacitinib is a pan JAK inhibitor with potent inhibition of JAK3 and JAK1 and to a minor degree JAK2. JAK3 binds to the common IL-2Rγ chain of the type I cytokine receptor family (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21), which is crucial for T-cell activation. JAK1 binds with γ-chain cytokines (IL-6, IL-10, IL-13, IL-22, granulocyte colony-stimulating face, interferons). Inhibition of JAKs is responsible for decreased pro-inflammatory cytokines signaling *via* IL-2 and IL-4 inhibition, decreased IL-6 production by synovial fibroblasts, decreased receptor activator of nuclear factor-κB ligand production, decreased IL-8 production by $CD14^+$ monocytes, and decreased production of TNF-stimulated fibroblast-like synoviocytes. The net effect of tofacitinib is decreased synovial inflammation and structural joint damage in RA patients by limiting T cell and other leukocyte recruitment[3]. Other immune cells involved in RA pathogenesis express JAKs and may also be affected by tofacitinib inhibition. Figure 1 illustrates tofacitinib's mechanism of action.

Tofacitinib is well absorbed from the gastrointestinal tract following oral administration[2]. Peak plasma concentration ($T_{max}$) occurs within 0.5-1 h with an absolute oral bioavailability of 74%. Administration of tofacitinib with a high-fat meal resulted in a decrease in maximum plasma concentration ($C_{max}$) by 32% with no changes to the area under the plasma concentration time curve (AUC); therefore, tofacitinib was given without regard to meals during clinical trials. Steady state concentrations are achieved in 24-48 h with twice daily administration with minimal accumulation.

Tofacitinib is distributed between plasma and red blood cells equally with a half-life of approximately 3 h and is 40% bound to plasma proteins, mainly albumin[2]. Hepatic metabolism, *via* CYP3A4 (major) CYP2C19 (minor) accounts for 70% of tofacitinib clearance with the remaining 30% excreted in the urine. The activity of tofacitinib is related to the parent compound, with 8 metabolites retaining less than 10% of potency. No dosage adjustments are necessary for patients with mild hepatic impairment; however, tofacitinib should be reduced to 5 mg once daily in patients with moderate hepatic impairment or moderate to severe renal impairment. Safety and efficacy for patients with severe hepatic impairment, or positive Hepatitis B or Hepatitis C serology has not been established.

Tofacitinib is predominately metabolized *via* CYP3A4 and drug-drug interactions are of concern[2]. Results from a recent, small *in vitro* study utilizing midazolam, a highly sensitive CYP3A4 substrate used to evaluate CYP isoenzyme drug interactions, and *in vitro* data has established a relative lack of effect of tofacitinib on the CYP enzyme system[5]. However, the manufacturer recommends the dose of tofacitinib be reduced by 50% (*i.e.*, 5 mg once daily) when administered with potent CYP3A4 inhibitors (*e.g.,* ketoconazole) or drugs exhibiting both moderate CYP3A4 inhibition and potent CYP2C19 inhibition (*e.g.*, fluconazole)[2]. Concomitant administration of tofacitinib with potent CYP3A4 inducers (*e.g.*, rifampin) can significantly reduce AUC and clinical efficacy necessitating dosage adjustment, though specific recommendations are not provided by the manufacturer. Caution should be exercised during concomitant administration of tofacitinib with cyclosporine and tacrolimus, given the risk of severe infection due to added immunosuppression when co-administered.

## EFFICACY STUDIES

Tofacitinib has demonstrated significant ACR20 response in phase 2 trials as monotherapy and with background therapy with methotrexate[6-10]. Six phase 3 trials have been conducted to evaluate the efficacy of tofacitinib under the oral rheumatoid arthritis triaLs (ORAL) series. To date, five trials were available as full publications[11-15] and one as a conference abstract[16]. Three primary efficacy outcome measures were central to the five fully published trials: (1) percentage of patients achieving an ACR20 response, which is defined as 20% reduction from baseline in tender and swollen joints and at least 20% improvement in three of the five ACR core set measures; (2) change from baseline in the Health Assessment questionnaire disability index (HAQ-DI), in which scores range from 0-3 and higher scores indicate greater disability; and (3) percentage of patients with a Disease Activity Score for 28 joint counts based on erythrocyte sedimentation rate (DAS28-4[ESR]) of less than 2.6 with score ranging from 0-9.4. A summary of the phase 3 trial details and results can be found in Tables 1 and 2, respectively.

ORAL Solo was a 6-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[11]. Primary endpoints of this trial were percentage of patients with an ACR20 response, the change from baseline in physical function measured by HAQ-DI, and the percentage of patients with a DAS28-4(ESR) less than 2.6 at month 3. Secondary objectives included percentage of patients with ACR20, ACR50, and ACR70 response rates at all visits, the change in baseline at all visits in the HAQ-DI and DAS28-4(ESR), and the score at month 3 on the functional assessment of chronic illness therapy (FACIT) fatigue instrument. The use of nonsteroidal anti-inflammatory drugs and glucocorticoids ($\leqslant$ 10 mg of a prednisone equivalent) were permitted. A total of 555 patients completed the trial. All patients who received tofacitinib had statistically significant improvement in ACR20, ACR50, and ACR70 response criteria and HAQ-DI scores at month 3 ($P < 0.001$ for all comparisons). There were not significant benefits of tofacitinib seen in DAS28-4(ESR). The changes in the FACIT-fatigue score from baseline at month 3 were statistically significant compared with placebo ($P < 0.001$).

ORAL Step was a 6-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[12]. Primary endpoints of this trial were percentage of patients with an ACR20 response, the change from baseline in physical function measured by HAQ-DI, and the percentage of patients achieving DAS28-4(ESR) less than 2.6 at month 3. Secondary objectives were the percentage of patients with ACR20, ACR50, and ACR70 response over time, changes from baseline in the HAQ-DI and DAS28-4(ESR) over time, pain (rated from 0-100), and fatigue measured by the FACIT. Stable doses of methotrexate 7.5 mg to 20 mg weekly for 6 wk prior to the start of the trial were required. The use of nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, or glucocorticoids ($\leqslant$ 10 mg of a prednisone equivalent) were permitted. A total of 399 patients completed the trial. At month 3, ACR 20, ACR50, ACR70 response rates were significant ($P < 0.01$ for all comparisons) and changes from baseline in HAQ-DI were significant ($P < 0.0001$) for tofacitinib compared to placebo. The proportion of patients with DAS28-4(ESR) less than 2.6 at month 3 were significant in tofacitinib 10 mg twice daily group compared to placebo. Improvements in arthritis pain and FACIT assessments were statistically significant for tofacitinib groups compared to placebo.

ORAL Standard was a 12-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[13]. Primary endpoints of this trial were percentage of patients with an ACR20 response at month 6, the change from baseline in physical function measured by HAQ-DI at month 3, and the percentage of patients achieving DAS28-4(ESR) less than 2.6 at month 6. Secondary objectives were the percentage of patients with ACR20, ACR50, and ACR70 response over time and changes from baseline in the HAQ-DI and DAS28-4(ESR) over time. A total of 717 patients were included in the full analysis. Patients receiving active treatment achieved a significantly greater percentage of ACR20 response

**Table 1 Summary of published phase 3 tofacitinib studies**

| Study | Duration | Participants | Demographics | Intervention | Primary outcome |
|---|---|---|---|---|---|
| Oral solo | 6 mo | Active RA patients with inadequate response to at least one DMARD (biologic or nonbiologic) receiving stable doses of antimalarial | *n* = 611<br>Age: 49.7-52.4 yr<br>Female: 85.2%-88.2%<br>Duration of RA: 7.7-8.6<br>Baseline HAQ-DI: 1.50-1.53<br>Baseline DAS-28: 6.65-6.71 | Tofacitinib 5 mg *bid*;<br>Tofacitinib 10 mg *bid*;<br>placebo for 3 mo then Tofacitinib 5 mg *bid*;<br>placebo for 3 mo then Tofacitinib 10 mg *bid* | ACR20 response at month 3;<br>DAS 28-4 ESR < 2.6 at month 3;<br>HAQ-DI at month 3 (change from baseline) |
| Oral step | 6 mo | Moderate to severe RA patients with inadequate response to TNF alpha inhibitors | *n* = 399<br>Age: 54.4-55.4 yr<br>Female: 80.3%-86.36%<br>Duration of RA: 11.3-13.0 yr<br>Baseline HAQ-DI: 1.5-1.6<br>Baseline DAS-28: 6.4-6.5 | Tofacitinib 5 mg *bid*;<br>Tofacitinib 10 mg *bid*;<br>placebo for 3 mo then Tofacitinib 5 mg *bid*;<br>placebo for 3 mo then Tofacitinib 10 mg *bid* | ACR20 response at month 3;<br>DAS 28-4 ESR < 2.6 at month 3; HAQ-DI at month 3 (change from baseline) |
| Oral standard | 12 mo | Active RA patients receiving stable doses of methotrexate | *n* = 717<br>Age: 51.9-55.5 yr<br>Female: 75.0%-85.3%<br>Duration of RA: 6.9-9.0 yr<br>Baseline HAQ-DI: 1.4-1.5<br>Baseline DAS-28: 6.3-6.6 | Tofacitinib 5 mg *bid*;<br>Tofacitinib 10 mg *bid*; adalimumab 40 mg SC every 2 wk;<br>placebo for 6 mo then Tofacitinib 5 mg *bid*;<br>placebo for 6 mo then Tofacitinib 10 mg *bid* | ACR20 response at month 6;<br>DAS 28-4 ESR < 2.6 at month 6; HAQ-DI at month 3 (change from baseline) |
| Oral sync | 12 mo | Active RA patients with inadequate response to one or more DMARD | *n* = 792<br>Age: 50.8-53.3 yr<br>Female: 75.0%-83.8%<br>Duration of RA: 8.1-10.2 yr<br>Baseline HAQ-DI: 1.24-1.45<br>Baseline DAS-28: 6.14-6.44 | Tofacitinib 5 mg *bid*;<br>Tofacitinib 10 mg *bid*;<br>Placebo | ACR20 response at month 6;<br>DAS 28-4 ESR < 2.6 at month 6;<br>HAQ-DI at month 3 (change from baseline) |
| Oral scan | 24 mo | Active RA patients receiving background methotrexate | *n* = 797<br>Age: 52.0-53.7 yr<br>Female: 80.2%-91.1%<br>Duration of RA: 8.8-9.5 yr<br>Baseline HAQ-DI: 1.23-1.41<br>Baseline DAS-28: 6.25-6.34 | Tofacitinib 5 mg *bid*;<br>Tofacitinib 10 mg *bid*;<br>placebo for 3 mo then Tofacitinib 5 mg *bid*;<br>placebo for 3 mo then Tofacitinib 10 mg *bid* | ACR20 response at month 6;<br>DAS 28-4 ESR < 2.6 at month 6;<br>HAQ-DI at month 3 (change from baseline);<br>SHS at month 6 (change from baseline) |
| Oral start | 24 mo | Methotrexate naïve patients with active RA | *n* = 952<br>Baseline TSS: 16.51-20.30 | Tofacitinib 5 mg *bid*;<br>Tofacitinib 10 mg *bid*;<br>methotrexate 10 mg per week with 5 mg increments every 4 wk to 20 mg per week | Modified Total Sharp Score at month 6;<br>ACR70 response at month 6 |

DMARD: Disease-modifying antirheumatic drug; TSS: Total sharp score; TNF: Tumor necrosis factor; SHS: Sharp/van der Heijde Score; HAQ-DI: Health Assessment Questionnaire Disability Index; DAS: Disease activity score.

compared to placebo at month 6 ($P < 0.001$ for all comparisons). Percentage of patients with DAS-28-4(ESR) less than 2.6 at month 6 and mean change from baseline in HAQ-DI score at month 6 were also statistically significant when compared to placebo. For secondary endpoints, greater ACR50 and ACR70 response and significant changes from baseline in DAS28-4(ESR) and HAQ-DI were seen over time ($P < 0.05$ for all comparisons).

ORAL Sync was a 12-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[14]. Primary endpoints of this trial were percentage of patients with an ACR20 response, the change from baseline in physical function measured by HAQ-DI, and the percentage of patients with a DAS28-4(ESR)-defined remission at month 6. Secondary objectives were ACR20, ACR50, and ACR70 response rates, change from baseline HAQ-DI, DAS28-4(ESR) assessments, and FACIT-fatigue score over time. The use of oral corticosteroid therapy (≤ 10 mg of a prednisone equivalent) was permitted. DMARDs disallowed were biologics, cyclosporine, and azathioprine. A total of 792 patients were included in the primary analysis data set with methotrexate being the most frequently prescribe background DMARD (79%). For both tofacitinib groups compared to placebo at month 6, statistically significant differences were seen in ACR20 response rates, improvements from baseline in HAQ-DI and DAS-28 ($P < 0.005$ for all comparisons). For secondary endpoints, changes from baseline in HAQ-DI, DAS28-4(ESR) less than 2.6, and FACIT-fatigue for both tofacitinib groups compared with placebo were statistically significant. For tofacitinib 10 mg twice daily, ACR20, ACR50, and ACR70, significant response rates were observed by week 2. For tofacitinib 5 mg twice daily, significant response rates were observed by week 2 for ACR20 and ACR50, and by week 4 for ACR70.

ORAL Scan is a 24-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[15]. Primary endpoints of this trial were percentage of patients with an ACR20 response at month 6, the change from baseline in physical function measured by HAQ-DI at month 3, percentage of patients achieving DAS-28-4 (ESR) less than 2.6 at month 6, and change from baseline in total modified Sharp/van der Heijde Score (SHS) at month 6. Stable doses of methotrexate were required. The use of nonsteroidal anti-inflammatory drugs and glucocorticoids (≤ 10 mg of a prednisone equivalent)

**Table 2 Results summary for primary outcomes of phase 3 published trials**

| Primary Outcomes | ORAL solo | | | ORAL step | | | ORAL standard | | | Oral sync | | | Oral scan | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (*n* = 122) | Tofacitinib 5 mg *bid* (*n* = 243) | Tofacitinib 10 mg *bid* (*n* = 245) | Placebo (*n* = 132) | Tofacitinib 5 mg *bid* (*n* = 133) | Tofacitinib 10 mg *bid* (*n* = 134) | Placebo (*n* = 108) | Tofacitinib 5 mg *bid* (*n* = 204) | Tofacitinib 10 mg *bid* (*n* = 201) | Placebo (*n* = 159) | Tofacitinib 5 mg *bid* (*n* = 315) | Tofacitinib 10 mg *bid* (*n* = 318) | Placebo (*n* = 160) | Tofacitinib 5 mg *bid* (*n* = 321) | Tofacitinib 10 mg *bid* (*n* = 316) |
| ACR20 response (%) | 26.7 | 59.8[d] | 65.7[d] | 24.4 | 41.7[b] | 48.1[d] | 28.3 | 51.5[d] | 52.6[d] | 30.8 | 52.1[d] | 56.6[d] | 25.3 | 51.5[d] | 61.8[d] |
| Change from baseline HAQ-DI (LSM change) | -0.19 | -0.50[d] | -0.57[d] | -0.18 | -0.43[d] | -0.46[d] | -0.24 | -0.55[a] | -0.61[a] | -0.16 | -0.44[d] | -0.53[d] | -0.15 | 0.40[2] | -0.54[d] |
| DAS-28-4(ESR) less than 2.6 (%) | 4.4 | 5.6[1] | 8.7[1] | 1.7 | 6.7[a] | 8.8[a] | 1.1 | 6.2[a] | 12.5[a] | 2.6 | 8.5[b] | 12.5[d] | 1.6 | 7.2[2] | 16.0[d] |

[b]$P < 0.01$; [a]$P < 0.05$; [d]$P < 0.001$ *vs* placebo trials. [1]Not significant; [2]Significance not declared for this co-primary endpoint. ORAL: Oral rheumatoid arthritis triaLs; HAQ-DI: Health assessment questionnaire disability index; DAS: Disease activity score.

were permitted. A total of 797 patients were randomized and treated. ACR20 response rates for both tofacitinib doses were significant compared to placebo ($P < 0.0001$ for both comparisons). Significant changes from baseline SHS scores ($P < 0.05$), HAQ-DI ($P < 0.0001$), and DAS28-4(ESR) ($P < 0.0001$) were seen with tofacitinib 10 mg twice daily; non-significant results with tofacitinib 5 mg twice daily.

ORAL Start is a 24-mo, multicenter, multinational, randomized, double-blind, placebo-controlled trial[16]. Primary endpoints of this trial were mean change from baseline in van der Heijde modified Total Sharp Score (mTSS) and percentage of patients with an ACR70 response at month 6. To date, complete methodology and results are unavailable as ORAL Start is published as a conference abstract. A total of 952 patients were randomized and treated. At month 6, mean changes from baseline in mTSS and percentage of patients achieving ACR70 were statistically significant.

## SAFETY AND TOLERABILITY

Safety of tofacitinib was evaluated in six phase 3 clinical trials[11-16], four phase 2 trials[6-9], two phase 1 trials[17-18], and a study evaluating the impact on latent tuberculosis infection (LTBI) in a mouse model due to concerns with a risk of reactivation with treatments (*i.e.*, tumor necrosis factor alpha inhibitors) for chronic inflammatory disorders, including rheumatoid arthritis[19]. Several of the phase 2 and 3 trials have been reported in two meta-analyses to evaluate efficacy and safety of tofacitinib for treatment of rheumatoid arthritis[20-21]. In phase 1 studies, including a study with patients randomized to receive supratherapeutic doses of tofacitinib (*i.e.*, 100 mg), there were no serious adverse events reported[17-18]. Additionally, there were no discontinuations or dose reductions of study medication due to adverse events reported. All reported events were mild to moderate and resolved quickly, including two reports of anemia. Additional adverse events reported included headache, nausea, vomiting, dizziness, and disorientation. There were no clinically meaningful changes in laboratory values or ECG parameters.

Adverse events attributed to treatment with tofacitinib were similar in phase 2 trials with the most common events being headache, diarrhea, nausea, upper respiratory tract infections, and nasopharyngitis[6-9]. Patients receiving doses greater than the FDA-approved dose of 5 mg twice daily experienced the highest number of adverse events (*i.e.*, 10 mg twice daily, 15 mg twice daily, and 30 mg twice daily) in phase 2 trials with few treatment discontinuations reported[6,8,9]. In the trials reviewed, two deaths were reported in patients receiving tofacitinib[8,9]. One attributed to cerebrovascular accident in a patient receiving 15 mg twice daily and the other experiencing pneumonia that led to respiratory and cardiac failure with 3 mg twice daily dosing. Although infections were reported in patients receiving tofacitinib, the reports were mainly mild to moderate in severity[6-9]. Serious infections included nasopharyngitis, gastroenteritis, pharyngitis, pneumonia, and pneumococcal sepsis [8,9]. No opportunistic infections were reported in the phase 2 trials[6-9]. In one phase 2 trial, non-infectious serious adverse events were reported including foot deformity, osteoarthritis of the hip, femur fracture, cardiac failure, and acute dyspnea[7]. Each of these events resolved following discontinuation of the study drug with the exception of cardiac failure. Patients receiving tofacitinib also experienced decreased neutrophil counts, thrombocytopenia, decreased hemoglobin, and anemia[6-9]. Most adverse effects were reported to be mild to moderate not requiring discontinuation of the

**Table 3 Summary of safety and tolerability data for tofacitinib from phase 3 clinical trials (month 0-3) *n* (%)**

| | ORAL Solo | | | ORAL Step | | | ORAL Standard | | | | ORAL Sync | | | ORAL Scan | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (*n* = 122) | Tofacitinib 5 mg *bid* (*n* = 243) | Tofacitinib 10 mg *bid* (*n* = 245) | Placebo (*n* = 132) | Tofacitinib 5 mg *bid* (*n* = 133) | Tofacitinib 10 mg *bid* (*n* = 134) | Placebo (*n* = 108) | Tofacitinib 5 mg *bid* (*n* = 204) | Tofacitinib 10 mg *bid* (*n* = 201) | Adalimumab 40 mg once Q2W (*n* = 204) | Placebo (*n* = 159) | Tofacitinib 5 mg *bid* (*n* = 315) | Tofacitinib 10 mg *bid* (*n* = 318) | Placebo (*n* = 160) | Tofacitinib 5 mg *bid* (*n* = 321) | Tofacitinib 10 mg *bid* (*n* = 316) |
| Patients with AE, | 67 (54.9) | 124 (51) | 139 (56.7) | 75 (56.8) | 71 (53.4) | 76 (56.7) | 51 (47.2) | 106 (52) | 94 (46.8) | 105 (51.5) | 97 (61) | 166 (52.7) | 173 (54.4) | 73 (45.6) | 157 (48.9) | 171 (54.1) |
| Patients with SAE | 6 (4.9) | 1 (0.4) | 5 (2) | 6 (4.5) | 2 (1.5) | 2 (1.5) | 2 (1.9) | 12 (5.9) | 10 (5) | 5 (2.5) | 6 (3.8) | 9 (2.9) | 8 (2.5) | 5 (3.1) | 12 (3.7) | 10 (3.2) |
| Discontinuation due to AE | 5 (4.1) | 2 (0.8) | 6 (2.4) | 7 (5.3) | 8 (6) | 6 (4.5) | 3 (2.8) | 14 (6.9) | 10 (5) | 10 (4.9) | 2 (1.3) | 13 (4.1) | 13 (4.1) | 5 (3.1) | 15 (4.7) | 14 (4.4) |

AE: Adverse events; SAE: Serious adverse events; Q2W: Every 2 wk; Oral Rheumatoid Arthritis triaLs (ORAL) Start was not included in the 3-month evaluation since data reported were for all events 0-12 mo.

**Table 4 Summary of safety and tolerability data for tofacitinib from phase 3 clinical trials (final safety analysis) *n* (%)**

| | [1]ORAL Solo | | | | [1]ORAL Step | | | | [2]ORAL Standard | | | | | [2]ORAL Sync | | | | [2]ORAL Scan | | | | [4]ORAL start | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Tofacitinib 5 mg *bid* (after Placebo) (*n* = 61) | Tofacitinib 10 mg *bid* (after Placebo) (*n* = 61) | Tofacitinib 5 mg *bid* (*n* = 243) | Tofacitinib 10 mg *bid* (*n* = 245) | Tofacitinib 5 mg *bid* (after Placebo) (*n* = 66) | Tofacitinib 10 mg *bid* (after Placebo) (*n* = 66) | Tofacitinib 5 mg *bid* (*n* = 133) | Tofacitinib 10 mg *bid* (*n* = 134) | Tofacitinib 5 mg *bid* (after Placebo ) (*n* = 56) | Tofacitinib 10 mg *bid* (after Placebo) (*n* = 52) | Tofacitinib 5 mg *bid* (*n* = 204) | Tofacitinib 10 mg *bid* (*n* = 201) | Adalimumab 40 mg once Q2W (*n* = 204) | Tofacitinib 5 mg *bid* (after Placebo) (*n* = 79) | Tofacitinib 10 mg *bid* (after Placebo) (*n* = 80) | Tofacitinib 5 mg *bid* (*n* = 315) | Tofacitinib 10 mg *bid* (*n* = 318) | Tofacitinib 5 mg *bid* (after Placebo) (*n* = 81) | Tofacitinib 10 mg *bid* (after Placebo) (*n* = 79) | Tofacitinib 5 mg *bid* (*n* = 321) | Tofacitinib 10 mg *bid* (*n* = 316) | Tofacitinib 5 mg *bid* (*n* = 371) | Tofacitinib 10 mg *bid* (*n* = 395) | MTX (*n* = 186) |
| Patients with AE | 22 (36.1) | 24 (39.3) | 97 (39.9) | 101 (41.2) | 24 (36.4) | 28 (42.4) | 57 (42.9) | 58 (43.3) | 18 (32.1) | 21 (40.4) | 89 (43.6) | 84 (41.8) | 83 (40.7) | 34 (43) | 29 (36.3) | 104 (33) | 135 (42.5) | 34 (42) | 35 (44.3) | 166 (51.7) | 174 (55.1) | (70.1)[5] | (74.4)[5] | (69.9)[5] |
| Patients with SAE | 1 (1.6) | 0 | 5 (2.1) | 6 (2.4) | 3 (4.5) | 2 (3) | 5 (3.8) | 6 (4.5) | 1 (1.8) | 4 (7.7) | 10 (4.9) | 6 (3) | 7 (3.4) | 2 (2.5) | 0 | 7 (2.2) | 9 (2.8) | 1 (1.2) | 4 (5.1) | 13 (4) | 9 (2.8) | (6.5)[5] | (6.1)[5] | (7.0)[5] |
| Discontinuation due to AE | 0 | 0 | 1 (0.4) | 3 (1.2) | 1 (1.5) | 2 (3) | 4 (3) | 7 (5.2) | 0 | 2 (3.8) | 6 (2.9) | 3 (1.5) | 4 (2) | 0 | 1 (1.3) | 1 (0.3) | 9 (2.8) | 2 (2.5) | 2 (2.5) | 9 (2.8) | 7 (2.2) | 13 (3.5) | 17 (4.3) | 11 (5.9) |
| Deaths | 0 | 0 | 0 | 1 (0.4) | 0 | 1 (1.5) | 0 | 0 | 0 | 0 | 1 (0.5) | 0 | 1 (0.5) | 0 | 0 | 2 (0.6) | 2 (0.6) | 1 (1.2) | 0 | 2 (0.6) | 1 (0.3) | See note | See note | 0 |
| Patients with serious infection events | 1 (1.6) | 0 | 1 (0.4) | 3 (1.2) | 1 (1.5) | 0 | 2 (1.5) | 2 (1.5) | 2 (3.6) | 0 | 7 (3.4) | 8 (4) | 3 (1.5) | 0 | 0 | 2 (0.6) | 7 (2.2) | 1 (1.2) | 2 (2.5) | 11 (3.4) | 5 (1.6) | (31.8)[6] | (38.7)[6] | (27.4)[6] |
| Pulmonary Tuberculosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (1) | 0 | 0 | 0 | 0 | 2 (0.6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [3]Opportunistic infections | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.3) | 1 (0.3) | 0 | 0 | 3 (0.9) | 4 (1.3) | 8 (2.2) | 11 (2.8) | 3 (1.6) |
| Malignancies | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NR | NR | NR | NR | NR | NR | NR | NR | NR | 0 | 0 | 5 (1.6) | 4 (1.3) | NR | NR | NR |

AE: Adverse events; SAE: Serious adverse events; Q2W: Every 2 wk; NR: Not reported. [1]3-6 mo data point; [2]6-12 mo data point; [3]Excludes pulmonary tuberculosis; [4]0-12 mo data point; [5]data reported as total number of events; [6]All infections and infestations; serious infection events, pulmonary tuberculosis, opportunistic infections, and malignancies reported for all trial data.

study drug; however, several cases of severe anemia were reported leading to the temporary discontinuation of tofacitinib in one patient secondary to gastrointestinal bleeding. In addition to hematologic effects, increases in serum creatinine and lipid parameters [*i.e.*, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)] were observed. Most were not of clinical relevance; although, several reports of discontinuation were noted with increases in serum creatinine. Changes in blood pressure were minimal and not considered to be clinically relevant. Increased in transaminase concentrations, including aspartate aminotransferase and alanine aminotransferase were reported with treatment discontinuation in few patients. Most cases resolved spontaneously during treatment and did not require discontinuation of the study medication.

In six phase 3 clinical trials, the adverse events profile for tofacitinib was similar to that observed in phase 2 trials. Safety analyses were conducted at 3 and 6 mo for ORAL Solo and ORAL Step and at 3, 6, and 12 mo for ORAL Standard, ORAL Sync, and ORAL scan[11-15]. Safety information from ORAL Start is currently limited to abstract data and reported for the entire 12-mo period[16]. Table 3 summarizes the number of patients experiencing an adverse event, a serious adverse event, or discontinuation of the study medication due to an adverse event during the analysis period. Table 4 provides a summary of adverse events experienced by patients receiving study medication in the last analysis period for the respective trial. Deaths, serious infection events, reports of tuberculosis, other opportunistic infections, and malignancies are also provided. With concern for reactivation of LTBI in patients receiving immunologic agents, it is important to note that reports of tuberculosis infection in patients receiving tofacitinib were rare in phase 3 trials, with two cases reported in two trials, ORAL Standard and ORAL Sync. Additionally, malignancies reported with tofacitinib were rare and reported only in patients receiving tofacitinib in ORAL Scan.

Tofacitinib was associated with changes in laboratory tests, specifically lymphocytes, neutrophils, liver enzymes, lipid parameters, and serum creatinine[11-16]. Patients in the tofacitinib groups had decreases in lymphocyte and neutrophil counts. While patients with decreases in lymphocyte counts were more likely to experience an increased incidence of infections, there was no identifiable association between the decrease in neutrophil count and occurrence of serious infection in clinical trials. Similar to results from phase 2 trials, patients receiving tofacitinib experienced increases in liver enzymes greater than 3 times the upper limit of normal; however, normalization of liver enzymes was achieved with modification of study treatment (*e.g.*, dose reduction, interruption, discontinuation). Lipid parameters, including total cholesterol, LDL, and HDL, were also associated with dose-related elevations following initiation of tofacitinib therapy and remained stable throughout the study periods. Dose-related elevations were also observed with serum creatinine; the clinical significance remains unclear given the propensity for elevations to remain within the normal range. However, several trial discontinuations were attributed to elevations in serum creatinine. In addition to more serious events and laboratory changes, other adverse events reported during phase 3 trials included diarrhea, nasopharyngitis, upper respiratory infection, headache, and hypertension. Headache and diarrhea appear to be more common with tofacitinib treatment versus placebo.

Given the risk of reactivation of tuberculosis in patients with LTBI receiving other immunomodulating agents, such as tumor necrosis factor alpha inhibitors, Maiga and colleagues studied the impact of tofacitinib on LTBI in a mouse model[19]. Results indicated a reactivation of latent infection in the presence of tofacitinib due to an increase in bacterial replication and reduction in containment of the bacteria. The investigators concluded that tofacitinib should be prescribed with caution in patients with chronic inflammation and screening for LTBI is warranted prior to use. These results are consistent with reports of tuberculosis cases identified in the phase 3 trial by Kremer and colleagues[14].

## CONCLUSION

ACR 2012 guidelines for treatment of rheumatoid arthritis with use of DMARDs and biologic agents do not specifically address the place in therapy for tofacitinib. However, European League Against Rheumatism (EULAR) recommendations suggest tofacitinib should be considered a targeted, synthetic DMARD for use after treatment failure of at least one biologic DMARD[22]. Safety and efficacy of tofacitinib have been demonstrated in six phase 3 trials [11-16]. Tofacitinib, a Janus kinase inhibitor, offers a novel mechanism of action in the treatment of rheumatoid arthritis and is administered orally, which may be a benefit for patients.

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TOPIC HIGHLIGHT

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

# Arthrodesis of the wrist in rheumatoid arthritis

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## Abstract

In rheumatoid arthritis the small joints of the feet and hands are the first targets of the autoimmune process. In about one half of the patient the wrist is involved in the first stages of the disease (two years) increasing up to nearly 90 percent after a decade often including both sides. Osteoarthritis of the wrist is one of the most common conditions encountered by hand surgeons. One aim of all treatment options is to achieve the best possible hand function without pain. If conservative treatment fails, operative treatment is necessary. Choice of surgical treatment depends on the soft tissue and bone situation. Techniques can be differentiated by joint preservation or joint replacement. The first include radio-synoviorthesis, synovectomy and tendon repair, the latter resection-arthroplasty, total joint arthroplasty and arthrodesis. In this paper arthrodesis of the wrist as one treatment option is reviewed.

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**Key words:** Arthritis; Rheumatoid; Wrist; Treatment; Surgical; Arthrodesis

**Core tip:** This paper discusses the pathophysiology of wrist destruction due to rheumatoid arthritis. A short overview of different treatment options is given with a special reflect on wrist arthrodesis, surgical techniques and outcomes are presented.

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## INTRODUCTION

### *The natural course of joint arthritis*

If once the inflammatory cascade is activated progressive autoimmune mediated joint destruction is the result. Joints are affected by immune cell mediated inflammation of the soft tissue which is progressive and with the time affects the bone, too. It starts with swelling and stiffness of small joints in the morning, postive blood tests and pain. The disease can be associated with rheumatic nodules in one fifth oft he patients in combination with postive rheuma factors. The disease is classified by American Rheumatoid Association, which enables dignostis and therapy and is based on a disease period of more than six weeks[1]. The course oft he disease can vary from patient to patient. Self limiting forms are possible, but if not joint destruction is the result. First targets oft he autoimmune system are the small joints of the feet and hands (Figure 1). In about one half of the patient the wrist is involved in the first stages oft he disease (two years) increasing up to nearly 90 percent after a decade often including both sides. Many social impairments such as long illness periods and loss of employment are the result in many cases[2-6].

## RADIOLOGICAL CLASSIFICATIONS FOR RHEUMATOID ARTHRITIS

Due to arthritis and soft tissue inflammation pathological changes can be diagnosed and classified radiologically. The pathologies include bone and cartilage and result in periarticular sclerosis, metaphyseal osteoporosis and bone cystes, cartilage loss and consecutive joint space loss and instability. Different classifications are available, three of

**Table 1 Radiographic classification of rheumatic changes according to Larsen**

| X-ray findings | Larsen scoring |
|---|---|
| No pathologic changes | 0 |
| Osteoporosic bone, soft tissue swelling | 1 |
| Narrowing of joint spaces, bony erosions | 2 |
| Increased erosions, bony destructions | 3 |
| Joint spaces diminished, significant bone destruction | 4 |
| Joint mutilation, ankylosis od the wrist | 5 |

**Table 2 The wrightington classification for wrist destruction in arthritis**

| Scoring | Radiographic signs | Therapeutic suggestion |
|---|---|---|
| 1 | Osteoporosis, cystic erosions | Synovial tissue resection |
| 2 | Instability of the carpus | Soft tissue procedures or limited arthrodesis |
| 3 | Bone destruction, subluxation | Arthroplasty or arthrodesis |
| 4 | Severe radial destruction | Arthrodesis |

them are presented here. The Larsen classification describes five different stages of bone and cartilage changes (Table 1)[7]. The Wrightington classification is a combination radiological classification with regard to therapy describing four different groups (Table 2)[8]. Simmen *et al*[9] classified arthritic changes with respect to progression and is based on stability of bone and soft tissue.

The first type is the ankylosing, the second describes changes due to arthritic and arthritic destruction and the third type describes instability and disintegration, which needs bony stabilisation in the case of progression.

## CLINICAL PRESENTATION

The autoimmune disease can affect all tissues, therefore a careful examination of the patient including all regions should be the first step of the orthopaedic evaluation. The patients history including the onset and expression of different typical symptoms such as swollen, painful, overwarmed, stiff, weak, red or numb changes are evaluated. The nature and character and location of the findings should be noted. The first examination should include the activity level of the patient, the social sourrounding and employment using one of the generally accepted scores for objective documentation of disease stage[10-12]. All medication, including corticosteroid application, immunosuppressive therapy and non-steroidal anti-inflammatory drugs and therapy history are documented. All other diseases should be kept in mind, this can be vascular impairment, diabetes mellitus and all inner organs. The so called "fifth extremity" of the patients, the cervical spine can be affected as often as other joints and can present instability, myelopathy due to compression can result in extremity pathology. In this is the case examination of nerve conduction velocity and electromyography are recommended before joint surgery. Clinical evaluation of the status of the upper and lower extremity include gait analysis, range of motion, test of grip strength. Vascular status or signs of vasculitis should be addressed before surgery to avoid wound complications.

**Figure 1 X-ray showing a rheumatoid hand, note axial deviation of the wrist and severe destruction.** A: a.p.; B: lateral view.

## SURGICAL TREATMENT

If the joint disease progressis for more than three months of medical treatment the rheumatologist should consult an orthopaedic surgeon. If conservative treatment, such as physiotherapy or ergotherapy fails, operative treatment is necessary. One aim of all treatment options is to achieve the best possible hand function without pain. One aim of all treatment options is to achieve the best possible hand function without pain[3,5,6]. Time point for surgery is sometimes discussed controversial, the same is for order of joints started with. This could be for an extremity from proximal to dista or the most affected joint first.

All different options for surgical treatment base on the situation of bone and soft tissue destruction. Basicly two approaches can be differentiated: joint preservation and joint replacement. If cartilage and ligaments are functional present a joint preserving technique should always be used. As a first approach synovectomy of the wrist is recommended and may be combined with soft tissue procedures. When the synovia is removed the target of the autoimmune reaction is removed and in the best case pain and swelling diminish and further joint destruction is prevented. If tendon rupture is associated with arthritis repair must be done in all cases. For extensor tendons different replacing methods exist: they include different transfers from one extensor tendon to another or free grafts. In the case of flexor tendon rupture of the thumb arthrodesis of the distal joint is recommended. Transfer or relocation of tendons are necessary to restore hand function and stability and therefore preventing further progression[3,13,14].

Due to hygienic reasons simultaneous surgery of both hands should be avoided. Surgery of the wrist and proximal or distal joints (for instance the elbow or finger joints) should be avoided because of the risk of extensive swelling and wound healing problems. The same is true for the lower extremity because of limited mobilisation

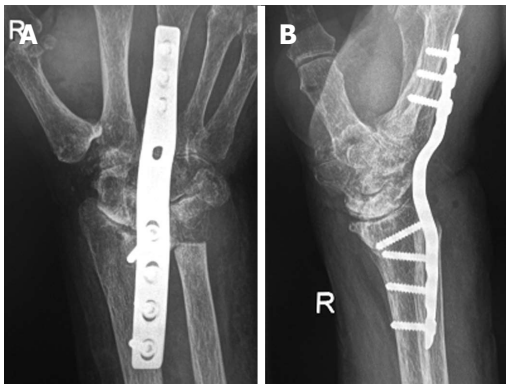


**Figure 2 Postoperative X-ray after wrist arthrodesis of the hand seen in Figure 1.** A: a.p.; B: Lateral view.

postoperatively. For this reason surgery of the lower extremity first is recommended[12].

## WRIST ARTRODESIS IN RHEUMATOID ARTHRITIS

For patients with advanced arthritic changes, wrist fusion is a well-established, safe and reliable method. Several different operative techniques including intramedullary rods or plates for wrist fusion have been retrospectively analysed in long-term studies[15,16]. Osteosynthesis utilising a Rush pin was first described in 1965 by Clayton and was modified in 1971 by Mannerfelt[17,18]. Plate osteosynthesis was introduced by Mueller in 1961 and the original concept was modified in the 1980s with the development of dynamic compression plates which became widely used and have been shown to achieve good primary stability (Figure 2)[19,20].

The position of the fusion remains a matter of debate. In literature, there is a trend towards moderate extension and ulnar abduction. Nevertheless, some surgeons prefer the neutral position which maintains finger balance and allows for better pronation and supination, thus preserving sufficient muscular strength[15,17]. A recent study suggests no statistical difference for position of Mannerfelt arthrodesis in 34 wrists[21]. Another new study on follow up of 93 wrists with Mannerfelt arthrodesis describes this method as an alternative to plate arthrodesis with regard to its good results[22]. For bilateral fusions, it has been recommended to stabilise one side in some flexion and the other in some extension[23]. We compared two methods for arthrodesis, plate and pin fixation, and found comparable clinical outcome with regard to pain and fuction. Subjective satisfaction and strength of grip were higher in the plate group[24]. Despite regained strength and high patient satisfaction, some disadvantages of the fusion have to be considered and which were also observed in our study. Impaired precision mechanics, such as difficulties in performing personal hygiene functions, as well as handling coins and buttons, are the most frequently stated limitations of wrist fusion[24-26]. To overcome these limitations, alternative treatment strategies, including proximal row carpectomy and arthroplasty, have been developed. In conclusion, despite the advances in wrist arthroplasty, wrist fusion represents the method of choice in the treatment of the significant destructed wrist due to rheumatoid arthritis. One aim of this option is to re-establish wrist stability, permitting activities of daily life, to achieve painlessness, and ultimately to improve the quality of life. In selecting the fusion method, the surgeon should consider the need for possible additional surgeries, the quality of the local bone stock, as well as the grade of luxation of the wrist. A comparison of different fixation methods in four studies did not show any differences with regard to surgical technique. Prior to performing the procedure, the planned position of the fusion should be discussed with the patient to address the individual needs[23-30]. Reflecting the long experience and published results, arthrodesis of the wrist is still one of the golden treating standards.

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TOPIC HIGHLIGHT

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

# Interleukins and interleukin receptors in rheumatoid arthritis: Research, diagnostics and clinical implications

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## Abstract

Rheumatoid arthritis (RA) is an autoimmune disease, resulting in a chronic, systemic inflammatory disorder. It may affect many tissues and organs, but it primarily affects the flexible joints. In clinical practice patient care generates many questions about diagnosis, prognosis, and treatment. It is challenging for health care specialists to keep up to date with the medical literature. This review summarizes the pathogenesis, the polymorphisms of interleukin and interleukin genes and the standard available and possible future immunologic targets for RA treatment. The identification of disease-associated interleukin and interleukin receptor genes can provide precious insight into the genetic variations prior to disease onset in order to identify the pathways important for RA pathogenesis. The knowledge of the complex genetic background may prove useful for developing novel therapies and making personalized medicine based on the individual's genetics.

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**Key words:** Rheumatoid arthritis; Interleukins; Polymorphisms; Immunologic targets; Therapy

**Core tip:** Rheumatoid arthritis (RA) is an autoimmune disease, resulting in a chronic, systemic inflammatory disorder. It may affect many tissues and organs, but mainly attacks the flexible joints. This review provides a comprehensive overview about the genetic background, especially with regard to inflammatory cytokines to understand the pathogenesis of the disease. Furthermore it summarizes the current therapy and the future therapeutic agents for RA.

Magyari L, Varszegi D, Kovesdi E, Sarlos P, Farago B, Javorhazy A, Sumegi K, Banfai Z, Melegh B. Interleukins and interleukin receptors in rheumatoid arthritis: Research, diagnostics and clinical implications. *World J Orthop* 2014; 5(4): 516-536 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i4/516.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i4.516

## INTRODUCTION

### *Rheumatoid arthritis*

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune diseases which affects approximately 1% of the population[1-3], which can lead to signifi-

cant morbidity and mortality rates, and can shorten the lifespan by 10 years[4]. RA affects people all over the world, but it is more uncommon in Africa[5]. In contrast, its largest prevalence is registered among North-American Chippewa- and Pima-tribes[5]. Like in other autoimmune diseases females are more often affected than males.

RA is a severely disabling chronic inflammatory disease characterized by inflammation, persistent synovitis, progressive joint destruction, and systemic, extraarticular manifestations (*e.g.*, pericarditis, episcleritis/scleritis, secondary Sjögren syndrome, Felty syndrome, cervical myelopathy, neuropathy, interstitial lung disease, rheumatoid nodules, and vasculitis)[5,6]. Accelerated atherosclerosis is the leading cause of death among patients with RA. The incidence of lymphoma increases twofold in RA patients which is thought to be caused by the underlying severity of the inflammatory process, and not a consequence of the medical treatment[7].

Patients with RA typically present with pain, stiffness in multiple joints, swollen peripheric joints, regional osteoporosis, narrowing of the synovial space and fibrous ankylosis. The wrists, proximal interphalangeal joints, and metacarpophalangeal joints are most commonly affected, however, the clinical appearance can be heterogenous[5,6]. In 2010 the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) developed a new classification criteria, aiming to support diagnosis and facilitate the early introduction of effective RA therapy[8]. The 2010 criteria include tender and swollen joint count, acute phase reactants [C-reactive protein levels (CRP) and erythrocyte sedimentation rate (ESR)], anti-citrullinated protein antibodies (ACPA) or rheumatoid factor (RF), and symptom duration[8]. RF is not specific for RA and it may be present in patients with other diseases, such as hepatitis C and in also healthy older persons. However, patients seropositive for RF are characterized by rapid and more severe course of the disease, and it is frequently coupled with extraarticular manifestations. ACPA is more specific to RA (97.1%)[9]. It is produced against citrullinated proteins which derive from an RA-specific dysregulation of the humoral immune response[10,11]. Likewise RF, the presence of ACPA contributes to a more severe and extended type of RA[10]. The simultaneous presence of these two serological factors predestinates the onset of RA at a 28.9 times higher risk, compared to the population negative for both autoantibodies[10].

RA is an inflammatory arthritis that results from a systemic autoimmune response stimulated by an as yet unidentified antigen. It is commonly believed that the generation of autoantibodies through interactions of the innate immune system (antigen-presenting cells) with the adaptive immune system ($CD4^+$ T cells and B cells) is central to the pathogenesis[12]. Although the clear mechanisms of RA pathogenesis still remain to be defined, cytokines are considered to play an important role in the disease. The imbalance between pro- and anti-inflammatory cytokines promotes the induction of autoimmunity, inflammation and joint destruction. The synovial membrane in patients with RA is characterized by hyperplasia, proliferation, angiogenesis and an infiltrate of predominantly $CD4^+$ T helper (Th) cells. The pro-inflammatory cytokines, especially tumor necrosis factor alpha (TNF-α), and two interleukins (ILs), IL-1B and IL-6 are the key cytokines which drive inflammation and the destructive process[13]. However, it is likely that other cytokines such as IL-23, IL-17A and interferon gamma (IFN-γ) also play crucial roles in the pathogenesis of RA. IL-4 and IL-10, on the other hand, have been suggested to improve arthritis[14]. Joint damage results from the degradation of connective tissue by tissue-destroying matrix metalloproteinases (MMP) and the stimulation of osteoclastogenesis through the receptor activator of nuclear factor-kB ligand (RANKL). Activated $CD4^+$ T cells also stimulate B cells to produce immunoglobulins, including RF[15].

Similarly to other autoimmune disorders, RA is a disease of multifactorial etiology. The genetic predisposition is responsible for approximately 60% of the whole disease risk, while environmental factors, such as infections by microbial agents[16], smoking[17,18], obesity, or schizophrenia of first-degree relatives[19,20], and abnormalities of the autoimmune processes also play a role. The association with the human leukocyte antigen (HLA)-DRB1 locus was the first to be described to confer risk for RA (50% of the overall genetic predisposition)[21]. Linkage and genome-wide association studies identified over 30 validated additional genetic loci associated with RA, example HLA-DRB1, protein tyrosine phosphatase N22 (*PTPN22*), tumor necrosis factor alpha-induced protein 3 (*TNFAIP3*), TNF receptor-associated factor 1 (*TRAF1*), signal transducer and activator of transcription 4 (*STAT4*), chemokine (C-C motif) receptor 6 (*CCR6*), PX domain containing serine/threonine kinase (*PXK*)[22-24]. Further studies have revealed the importance of numerous other predisposing genes and their variants, including several pro-inflammatory and anti-inflammatory cytokine genes, especially interleukins (Figure 1).

## RESEARCH

We conducted a systematic review of the literature of the last 10 years on the polymorphisms of interleukin and interleukin genes associated with RA, and also standard available and possible future therapeutic possibilities of RA. PubMed was searched for papers and abstracts published in English-language journals, using the following terms and/or text words alone and in combination "rheumatoid arthritis", "interleukins", "interleukin receptors", "polymorphisms" and "therapy". No restrictions were placed on race, ethnicity, or geographic area. Extraction from each study was conducted independently by all authors, and consensus was achieved for all data.

## INTERLEUKIN AND INTERLEUKIN RECEPTOR GENE POLYMORPHISMS

ILs are a large group of cytokines which are especially

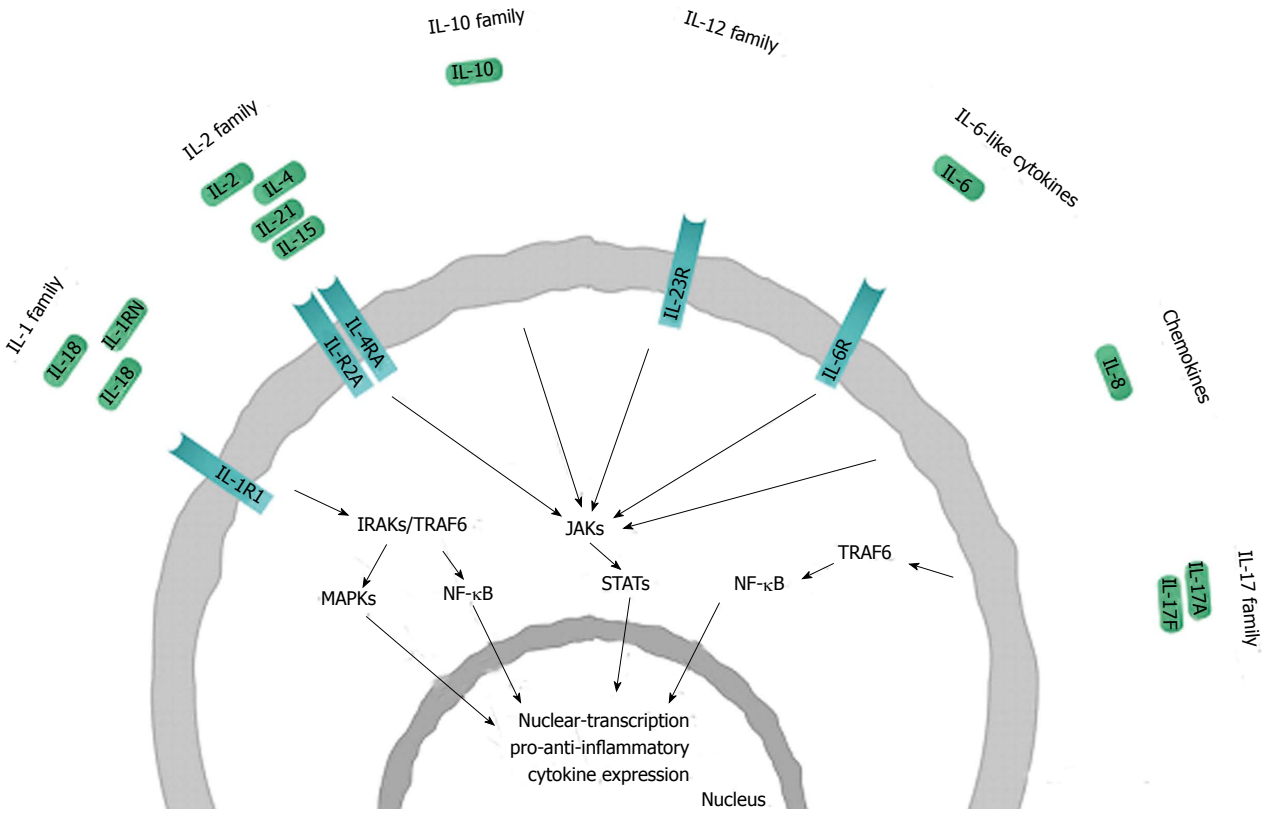


**Figure 1 Schematic representation of the interleukin families and receptors involved in the pathogenesis of rheumatoid arthritis.** Only those interleukins and interleukin (IL) receptors are shown where studies have demonstrated positive association between genes/SNPs and disease phenotype. Interleukins are assigned to each family based on sequence homology and receptor chain similarities or functional properties, considerable overlap between these families exists. Polymorphisms in genes encoding ILs and ILRs have been found to be involved in rheumatoid arthritis. Ligand binding initiates intracellular phosphorylation cascades that are mediated by kinases [i.e., interleukin 1 receptor associated kinase (IRAK); mitogen-activated protein kinase (MAPK); Janus kinase (JAK) and tumor necrosis factor (TNF) receptor associated factor, TRAF], resulting in signal transduction through certain transcription factors [including signal transducers and activators of transcription (STAT); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)]. These transcription factors stimulate the expression of a number of pro-inflammatory and anti-inflammatory cytokine genes involved in the pathogenesis of rheumatoid arthritis.

important in stimulating immune responses, such as inflammation. Once an IL has been produced, it proceeds to its target cell and binds to it *via* a receptor molecule on the cell surface. This interaction triggers a cascade of signals within the target cell which finally alters the behaviour of the cell. Different types of ILs are known. The nomenclature is based on sequence homology and receptor chain similarities or functional nature (www.genenames.org/genefamilies/IL) (Table 1)[25]. Within the interleukin families several *IL* and *ILR* gene polymorphisms have been investigated that are associated with RA (Table 2).

### The IL-1 family

Members of the IL-1 family (IL-1A, IL-1B, IL-1RN, IL-18, IL-33, IL-36A, IL-36B, IL-36G, IL-36RN, IL-37 and IL-38) have similar gene structures and induce a complex network of pro-inflammatory cytokines. IL-1 family has also expanded to 9 distinct genes including coreceptors, decoy receptors, binding proteins and inhibitory receptors[26].

**IL-1:** IL-1 is a key mediator of inflammation which has an effect on cell proliferation and differentiation. It mediates many inflammatory diseases by initiating and potentiating immune and inflammatory responses[25]. IL-1 is involved in several systemic autoinflammatory syndromes and in juvenile RA. It also plays a pathogenic role in inflammation and tissue destruction[27,28]. The most studied IL-1 proteins are IL-1α and IL-1β. *IL-1A* (OMIM 147760) encodes IL-1α which is cell-bound, and *IL-1B* (OMIM 147720) encodes IL-1β, a secreted cytokine. The IL-1 receptor antagonist (IL-1RN) (OMIM 147679) is an anti-inflammatory protein which binds to IL-1 receptor type 1 (IL-1R1, OMIM 147810) without transducing signal[29,30].

Two SNPs, the -511 C/T (rs16944) in *IL-1B* gene promoter and +3953 C/T (rs1143634) in the exon 5 of *IL-1B* are thought to influence *IL-1* expression[31,32]. Both loci may influence erosive damage in RA[33]. The rarer (-511) C-allele is associated with milder erosive disease in patients with a disease duration in excess of 20 years. In a Turkish cohort it was found that patients carrying the 2/2 (T/T) genotype of *IL-1B* +3953 gene are susceptible to RA. However, the 1/2 (C/T) genotype of *IL-1B* -511 has a protective role against RA[34]. In British Caucasian RA patients the *IL-1B* -1464 C/G (rs1143623) G allele showed the possibility to have protective effect in RA.

**Table 1 Characteristics of cytokines in rheumatoid arthritis**

| Family | Cytokine | Cytogenetic location | Molecular weight | Receptor | Cell source |
|---|---|---|---|---|---|
| IL-1 | *IL-1B* (*IL-1F2*) | 2q14 | 17 kD | IL-1R1<br>IL-1R2 | Macrophages, monocytes, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts and synovial lining cells |
| | *IL-1RN* (*IL-1F3*) | 2q14.2 | 16.1-20 kD | IL-1R1<br>IL-1R2 | Monocytes, macrophages, fibroblasts, neutrophils, epithelial cells and keratinocytes |
| | *IL-18* (*IL-1F4*) | 11q22.2-q22.3 | 22.3 kD | IL-18R1<br>IL-18RAP | Macrophages, Kupffer cells, keratinocytes, osteoblasts, astrocytes, and DCs |
| IL-2 | *IL-2* | 4q26-q27 | 15.5 kD | IL-2R | $CD4^+$, $CD8^+$ activated T cells, DCs, NK and NKT cells |
| | *IL-2RA* | 10p15-p14 | 30.8 kD | IL-2R | Activated T and B cells, thymocytes, myeloid precursors and olygodendrocytes |
| | *IL-4* | 5q23-q31 | 15 kD | IL-4R1<br>IL-4R2 | Th2 cells, basophils, eosinophils, mast cells, NKT and γ/δ T cells |
| | *IL-15* | 4q31 | 14-15 kD | IL-15R | Monocytes, activated $CD4^+$ T cells, keratinocytes, skeletal muscle cells |
| | *IL-21* | 4q26-q27 | 15 kD | IL-21R | T and NKT cells |
| IL-10 | *IL-10* | 1q31-q32 | 18.6 kD | IL-10RA/IL-10RB | T and B cells, monocytes, macrophages and DCs |
| IL-12 | *IL-23* | 12q13.13 | 19 kD | IL-12RB1/IL-23R | Macrophages and activated DCs |
| IL-6-like cytokines | *IL-6* | 7p21-p15 | 19-26 kD | IL-6R/IL-6ST | Endothelial cells, fibroblasts, monocytes/ macrophages |
| IL-17 | *IL-17A* | 6p12 | 35 kD | IL-17RA/IL-17RC | Th17, $CD8^+$ T cells, NK cells, NKT cells, γ/δ T cells and neutrophils |
| | *IL-17F* | 6p12 | 44 kD | IL-17RA/IL-17RC | Th17, $CD8^+$ T cells, NK cells, NKT cells, γ/δ T ells and neutrophils |
| Chemokines | *IL-8* | 4q13-q21 | 16 kD | IL-8RA/IL-8RB | Monocytes, macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells, fibroblasts, keratinocytes, chondrocytes, synovial cells, and hepatocytes |

NK: Natural killer cells, NKT: Natural killer T cells, DCs: Dendritic cells; IL: Interleukin.

Meta-analysis revealed that *IL-1B* -511 SNP is associated with increased susceptibility to RA[35].

Variable number of tandem repeat (VNTR) + 2018 (rs419598) SNP of *IL-1RN* gene were investigated in Black South Africans where no significant differences were found in genotype and allele frequencies between RA group and healthy controls. Within the RA group, the *IL1RN*2* (two repeats of an 86bp tandem repeat) at the VNTR locus was independently associated with higher Larsen radiologic damage scores (LDS), corrected for disease duration. Furthermore the *IL1RN*2* and + 2018 C allele defined haplotype was associated with significantly higher LDS on average 15 points higher, compared to the base haplotype of *IL1RN**long (three or more repeats) and + 2018 T allele. The authors concluded that *IL1RN*2* is a marker of erosive joint damage in Black South Africans RA patients[36]. With respect to *IL1R1* loci, negative findings were reported in Indian, Swedish and Chinese RA patients[37-39]. In an Algerian population *IL-1B* (-511), *IL-1* (+3953), and *IL-1RN* VNTR polymorphisms were examined, where no significant differences were observed in the three polymorphisms in genotype, allele and haplotype frequencies between the RA group and the healthy controls. However, the TT genotype of *IL-1B*-511 is more frequent in the patients' cohort with positive ACPA compared with negative ACPA group. The *IL-1RN*1*/*IL-1B*-511T/*IL-1B* + 3953C haplotype was more frequent in the positive ACPA group. The association between *IL-1RN* allele 1 of VNTR, *IL-1B*-511 T allele and *IL-1B* + 3953 C allele seems to predispose to the synthesis of ACPA and therefore to the occurrence of ACPA positive RA[40].

Meta-analysis of 10 European, 7 Asian, and 1 Latin American RA population showed that the *IL-1B* + 3953 polymorphism was associated with the development of RA only in the Asian RA cohort[41]. Similarly to these results the genotype and allele distributions of *IL-1B* + 3953 showed significantly increased risks in a RA cohort from Northwest China compared to controls[42].

**IL-18:** The main function of IL-18 (OMIM 600953) is to promote the production of IFN-γ from T and natural killer (NK) cells, in particular the presence of IL12p70. IL-18 binds to its ligand binding chain, to the interleukin 18 receptor 1 (IL-18R1, OMIM 604494). It also recruits its co-receptor, the IL-18 receptor accessory protein (IL-18RAP, OMIM 604509). With these reactions IL-18 virtually initiates the activation of nuclear factor kappa-light-chain-enhancer of activated B cells/mitogen activated protein 8 (NF-κB/MAPK8)[43]. IL-18 is an important proinflammatory cytokine and plays a potential pathological role in RA[44]. It is highly expressed in sera, synovial fluids and synovial tissues of RA patients; furthermore, elevated IL-18 levels are correlated with RA disease activity, indicating an important role of IL-18 in the pathogenesis of RA[45].

Several studies examined the association of *IL-18* gene polymorphisms with RA, but these studies showed inconclusive and controversial results. In an Egyptian population the -607 C/A (rs1946518) and -137 G/C (rs187238) were analysed in the promoter region. The frequency of -137CC genotype was significantly lower in RA patients compared to controls. As *IL-18* -137CC and *IL-18* -607 were negatively associated with RA, they may not be risk factors for RA in the Egyptian patients[46].The same polymorphisms were analysed in a Chinese Han population. The genotype and allele frequency of -607 of the *IL-18* gene showed significant differences between

**Table 2 The examined interleukin and interleukin receptor gene polymorphisms that are associated with rheumatoid arthritis**

| Gene | Polymorphism | Population | Ref. |
|---|---|---|---|
| *IL-1B* | *rs16944* | Algerian, British, Turkish | [34,35,40] |
| | *rs1143623* | British | [35] |
| | *rs1143634* | Algerian, Asian, Turkish | [34,40-42] |
| *IL1-RN* | *rs419598* | Black South Africans | [36] |
| *IL-2/IL-21* | *rs907715* | Australasian | [72] |
| | *rs6822844* | Australasian, Dutch | [65,72] |
| | *rs17388568* | Australasian | [72] |
| *IL-2RA* | *rs2104286* | Dutch | [64] |
| *IL-4* | *rs2243250* | Egyptian, Polish | [51,52] |
| *IL-4R* | *rs1801275* | African American, Egyptian | [54,55] |
| | *rs1805010* | African American, Egyptian | [54,55] |
| *IL-6* | *rs1800795* | Iranian, United Kingdom, Spain, Spanish, Turkish | [34,114,116, 117,122] |
| | *rs1800796* | Han Chinese, Taiwan, Turkish | [34,43,47,118] |
| *IL-8* | *rs112664* | Taiwan | [118] |
| | *rs2227306* | Caucasian | [137] |
| *IL-10* | *rs1800871* | Malaysian, Polish | [80,81] |
| | *rs1800872* | Chinese, Malaysian, Polish | [80-82] |
| | *rs1800896* | Malaysian, Polish | [80,81] |
| *IL-15* | *rs2322182* | North European | [59] |
| | *rs4371699* | North European | [59] |
| | *rs6821171* | North European | [59] |
| | *rs7665842* | North European | [59] |
| | *rs7667746* | North European | [59] |
| *IL-17A* | *rs1974226* | Japanese | [136] |
| | *rs2275913* | Norwegian | [135] |
| | *rs3748067* | Japanese | [136] |
| | *rs3804513* | Japanese | [136] |
| *IL-17F* | *rs763780* | Polish | [134] |
| | *rs2397084* | Polish | [134] |
| *IL-18* | *rs187238* | Chinese, Egyptian | [46,47] |
| | *rs549908* | Taiwan | [48] |
| | *rs360718* | Japanese | [49] |
| | *rs360722* | Japanese | [49] |
| | *rs1946518* | Chinese, Egyptian, Japanese | [46,47,49] |
| *IL-23R* | *rs1004819* | European, New Zealand, Spanish | [97,100,106] |
| | *rs1343151* | European, New Zealand, Spanish | [97,100,106] |
| | *rs1495965* | Spanish | [97] |
| | *rs2201841* | European, New Zealand, Hungarian | [96,97,100,106] |
| | *rs7517847* | European, New Zealand, Spanish | [97,100,106] |
| | *rs7530511* | Caucasian | [98] |
| | *rs10889677* | Hungarian | [96] |
| | *rs11209026* | European, Caucasian, New Zealand | [98,100,106] |
| | *rs11209032* | Spanish | [97] |
| | *rs10489629* | Europan, New Zealand, Spanish | [97,100,106] |

RA patients and controls. There was no statistical significance in the distribution of genotype frequencies of -137. Significance was found in the data on statistical basis only on allele frequency levels[47]. The controls had significantly higher AA genotype frequency in the Chinese population at position-607 compared to RA patients. At position-137 no significant differences were observed in the distribution of either allelic or genotypic frequencies. Furthermore there was no association between the examined genotypes and the presence of rheumatoid factors. In the Chinese population only the AA genotype at position-607 is associated with a protective effect against development of RA. Meta-analysis was conducted on the associations between these promoter polymorphisms and RA in the Asian population. They found significant differences in genotype and allele frequencies only in the Chinese population which the previous study has also demonstrated[44].

Another polymorphism, the 105 A/C (rs549908) was analysed in a Chinese population living in Taiwan. There were significant differences in the genotype distribution of this polymorphism between patients and controls. The distribution of the AA homozygote in the RA patients was higher compared to the control group. The allele frequency also differed significantly between RA patients and controls[48].

In a Japanese study three haplotype tag SNP, rs1946518 A/C, rs360718 T/G, and rs360722 T/C, spanning from the 5'UTR region to intron 1 were genotyped using allelic discrimination with use of specific TaqMan probes, and three haplotypes (ATT, CTC and AGC). Among these polymorphisms, the T allele frequency of rs360722 which tags the ATT haplotype, was significantly lower in the RA cohort compared with the normal subjects. Having the TT genotype further increased the significance. The presence of the T allele and TT genotype at rs360722 reduces the susceptibility of Japanese people to RA[49].

### The IL-2 family

The members of the IL-2 cytokine family are: IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. This family includes a group of ILs which share a common receptor subunit, the "common γ chain". This acts in unison with a subtype specific α-chain to initiate the signaling cascade. These ILs act mainly as growth and proliferation factors for progenitors and mature cells, and they also have a role in lineage-specific cell differentiation[25].

**IL-4:** IL-4 (OMIM 147780) is a major stimulus of Th2-cell development which regulates allergic conditions and the protective immune response against helminthes and other extracellular parasites[50].

The -590 C/T (rs2243250) promoter polymorphism of the *IL-4* gene was tested in an Egyptian population with RA. In RA patients, the frequencies of TT genotype and T allele were significantly increased compared to controls. Subjects with TT genotype and carriers of T allele were significantly more likely to develop RA. In non-erosive RA patients, the frequencies of TT genotype were significantly increased compared to controls. CT and TT genotypes were significantly increased in erosive RA patients compared to control group. Carriers of T allele had significantly increased risk to develop erosive RA as compared to the control group. The frequencies of -590 CT and TT genotypes were significantly increased in erosive RA patients. RA patients carrying CT, TT genotypes were significantly more likely to have erosive arthropathy. In RA patients with positive anti-CPP, the frequencies

of CT and TT genotypes were significantly increased compared to anti-CCP group. Carriers of T allele were significantly more likely to have positive anti-CCP[51]. The same polymorphism was tested in a Polish RA population, where no significant differences were observed in the genotype and allele frequencies of controls *vs* RA patients[52]. Meta-analysis showed that the -590 C/T polymorphism is a risk factor for RA among Europeans[53].

Two functional polymorphisms in the *IL-4* receptor gene rs1801275 (Q551R) and rs1805010 (I50V) were analysed in African American RA patients. They found that patients positive for *HLA-DRB1* shared epitope (SE) and autoantibodies had a higher risk of developing rheumatoid nodules in the presence of rs1801275 AA and AG alleles, while patients positive for the *HLA-DRB1* SE and RF alone had a higher risk of developing rheumatoid nodules in presence of rs1801275 AA and AG alleles and rs1805010 AA allele[54]. These variants were examined in an Egyptian population as well. In RA patients, the IV genotype frequency was significantly increased compared to controls. Subjects with IV genotype were significantly more potential to have the disease. In patients with erosive RA, the VV genotype frequency was significantly increased compared to patients with non-erosive RA. Subjects with VV genotype were significantly more susceptible to erosive arthropathy. The QR genotype frequency was significantly decreased in patients with erosive RA compared to patients with non-erosive RA. Carriers of V allele and Q allele were significantly more potential to be RF-positive, respectively and consequently develop severe RA[55].

**IL-15:** IL-15 (OMIM 600554) is a T cell activating factor which has pleiotropic and physiological activities in both the innate and acquired immune responses[56]. It plays an essential role in the differentiation, survival and activation of NK cells[56]. These functions are mediated through IL -15 receptor (IL-15R)[57]. IL-15 exerts pro-inflammatory effect in several diseases like allergy, transplant rejection and autoimmune disorders. Abnormalities in IL-15 expression may be involved in the pathogenesis of inflammatory autoimmune disorders like RA[56]. IL-15 may be implicated in the perpetuation of synovial inflammation in RA by generating positive-feedback loop, in which IL-15 synthesis by activated synovial macrophages or fibroblasts could induce a continuous T-cell recruitment[58].

Five SNPs in *IL-15* gene (rs7667746, rs7665842, rs2322182, rs6821171 and rs4371699) were significantly associated with rate of joint destruction in North European RA patients[59]. Thirteen SNPs were screened within the IL-15 regulatory regions [promoter, 5' and 3' untranslated region (UTR) regions]. In addition, an association study of these SNPs was conducted in three independent case-control cohorts with Spanish Caucasian origin. The presence of the 13 selected *IL-15* SNPs was confirmed and no new genetic variants were found. The distribution of the *IL-15* selected SNPs in RA patients and controls showed no statistically significant difference in any studied populations. The haplotype analysis revealed that the three *IL-15* haplotype blocks were not associated with RA susceptibility or severity in the analysed cohorts. It was suggested that the *IL-15* gene polymorphisms may not play major role in RA genetic predisposition, and probably other molecules which are implicated in the IL-15 pathway might possibly be implicated in RA susceptibility[60]. These results are in accordance with two previous studies which analysed the contribution of *IL-15* gene to the genetics of immunity-related diseases. There was no significant association observed in two different Caucasian populations for a number of *IL-15* SNPs and allergic disorders[61].

**IL-2/21:** IL-2 (OMIM 147680) promotes proliferation and expansion of both antigen-specific clones of $CD4^+$ and $CD8^+$ T cells. The *IL-2* receptor (*CD25*) susceptibility locus has recently been reported to be associated with RA[62]. IL-21 is involved in cell-mediated and humoral responses. It has pleiotropic effect on a variety of immune and nonimmune cells. In RA, the synovial fluid and tissue have enhanced inflammatory responses to IL-21 and elevated IL-21 receptor expression[63]. In Dutch RA patients was found that the *IL-2RA* locus may predispose to less destructive course of RA. The minor C allele of *IL-2RA* (rs2104286) was associated with less progression of joint destruction. The *IL-2RA* (rs2104286) protective genotype was associated with lower circulating levels of soluble interleukin-2 receptor A (sIL2RA). Lower sIL2RA levels were associated with a lower rate of joint destruction[64]. The SNP rs6822844 for *IL-2/IL-21* was investigated for associations with the disease and for associations with autoantibody status in a Dutch RA cohort. *IL-2/IL-21* rs6822844 showed a clear trend toward association with RA[65].

The *KIAA1109-TENR-IL2-IL21* region has been associated with a wide variety of autoimmune diseases like type 1 diabetes (T1D)[66], ulcerative colitis[67], Crohn's disease[68], celiac disease, Graves' disease (GD)[66], systemic lupus erythematosus (SLE)[69], psoriatic arthritis[70], and juvenile idiopathic arthritis[71]. The rs6822844 within the *KIAA1109-TENR-IL2-IL21* gene cluster has been linked to RA. Other variants within this cluster, for example rs17388568 is not in linkage disequilibrium (LD), but rs907715 is in moderate LD with rs6822844. The rs17388568 has been described to be in association with a number of autoimmune phenotypes, including T1D. Australasian RA patients and controls of European Caucasian ancestry were genotyped for rs6822844, rs17388568 and rs907715. No statistically significant difference was observed in the Australasian sample set for rs6822844or rs17388568 or rs907715. In a meta-analysis there was a genome-wide level of significance supporting association of rs6822844 with RA. Meta-analysis of rs17388568 showed no significant association with RA, while the meta-analysis of rs907715 only a trend towards association, but this was not independent of the association at rs6822844. The analysis of the *KIAA1109-TENR-IL2-*

*IL-21* gene cluster supported its association with RA and rs6822844 is the dominant association in this locus[72].

### The IL-10 family

IL-10 cytokine family members (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28 and IL-29) are mainly linked through their similar intron-exon structure[73].

**IL-10:** IL-10 (OMIM 124092) is an anti-inflammatory cytokine produced by B cells, T cells, NK cells, monocytes, macrophages, and dendritic cells (DCs). It inhibits both antigen presentation and subsequent release of pro-inflammatory cytokines, so it attenuates the activated immune system[74]. IL-10 has been shown to suppress the inflammatory cytokines IL-1, IL-6, IL-8, IL-12, TNF-α, hematopoietic growth factors and inhibit the synthesis of nitric oxide, gelatinase, and collagenase[75].

Three promoter polymorphisms of *IL-10* rs1800896, rs1800871 and rs1800872 have been studied in some populations with controversial results. The rs1800896 polymorphism is localized within a putative E-twenty six (Ets) transcription factor binding site, while rs1800871 is located within the putative positive regulatory region[76-78]. The rs1800872 is localized within the putative STAT3 binding site and negative regulatory region. These polymorphisms are in strong LD and appear in three potential haplotypes: GCC, ACC and ATA. The production of IL-10 depends on the genotypes. The ACC/ACC, ACC/ATA, and ATA/ATA are correlated with low, ACC/GCC and ATA/GCC with intermediate, whereas GCC/GCC with high IL-10 production[79]. In a Malaysian population the distribution of the *IL-10* genotypes did not differ significantly between RA patients and healthy controls. However, significant difference was found in the allele frequencies of rs1800896CT, rs1800871TT, rs1800872CA and AA between the RA patients and healthy subjects[80].

A Polish population study could not show association between *IL-10* genotypes and age at disease diagnosis, disease activity in a physician's global assessment, joint and extra-articular involvement. They found also no correlation between *IL-10* polymorphisms and disease activity parameters (ESR and CRP), number of swollen and tender joints, and duration of morning stiffness. The frequency of GCC, ACC, and ATA haplotypes in RA patients did not differ from that in the control group. These results suggest that *IL-10* promoter polymorphisms are not risk factors for RA activity[81].

In a Chinese population only rs1800872 was studied. The allele and genotype frequencies were significantly different between the RA patients and controls. In addition, significant differences of allelic and genotypic frequencies were also detected between the patients with or without anti-CCP. The CA genotype is the most frequently observed genotype in both patients and controls. However, the distributions of CC and AA genotype in patients and control were reverse. The AA genotype frequency was higher, whereas the CC genotype frequency was lower in patients than in controls. The A allele frequency showed increased level comparing the results to the controls. It showed decreased A allele frequency, but increased C allele frequency level[82].

In a meta-analysis related to rs1800896, 10 case–control studies were carried out with the result that G allele carriers (GG + GA) had 25% decreased risk of RA, compared to the homozygote AA. In the analysis of Europeans, significantly decreased risks were associated with G allele carriers. The results of this meta-analysis provided evidence for the association between rs1800896 polymorphism and the risk of RA[83].

### The IL-12 family

The IL-12 family consists of IL-12, IL-23, IL-27, IL-30 and IL-35, which are important mediators of inflammatory disorders. The common part is the heterodimeric complex composed of two subunits, the expression of which is regulated independently and have very different biological activities[84].

**IL-23:** IL-23 (OMIM 605580) was first described as a member of the IL-6/IL-12 superfamily[85]. It is a heterodimeric cytokine composed of 2 subunits[86-90]. The α-subunit is homologous to type I cytokines and β-subunit is related to the extracellular domain of other hematopoietin receptor family members[91]. IL-23 is expressed by activated monocytes, macrophages, DCs, T cells, B cells and endothelial cells[85,92] which strongly correlate with the cellular responsiveness to IL-23. IL-23 binds to a heterodimeric receptor complex composed of IL12RB1 (OMIM 601604) and IL23R (OMIM 607562) subunits[93]. IL12RB1 is also part of the IL-12 receptor, while IL-23R is unique to the IL-23 receptor complex.

The genetic variants of *IL-23* and its receptor (*IL-23R*) were first examined in the context of inflammatory bowel diseases (IBDs) in non-Jewish subjects[94]. Previous studies using genetically deficient animals showed experimental evidence that a strong association exists not only between the carriage of certain *IL-23R* gene variants and IBDs, but the correlation also stands for collagen-induced arthritis as inactivation of the *IL-23R* gene resulting in disease resistance[95].

On the basis of these findings, the possible associations between the functional variants of the *IL-23R* gene and RA were studied in the Hungarian population, and it was reported that some allelic variants represent an elevated risk for the disease, particularly in the RF- and/or anti-CCP-seropositive subsets of patients[96]. An increased prevalence of the homozygous rs10889677 AA genotype of the exon-3'-UTR 2370 C/A variant and the homozygous rs2201841 CC genotypes of the intronic SNP could be observed not only in Crohn's disease, but also in the RA groups compared to the controls.

In a Spanish population the examinations were expanded with genotyping of rs1004819, rs7517847, rs10489629, rs1343151, rs11209032 and rs1495965 SNPs, but none of the examined allelic variants and genotypes showed an increased prevalence in RA patients, not even when patients were stratified according to their clinical and demographic features (gender, age at disease onset,

presence of shared epitope, RF, rheumatic nodules and extra-articular disease)[97].

These findings were supported by a large cohort genotyping of Caucasian subjects for rs7530511 and rs11209026 variants of the *IL-23R* gene, but none of these SNPs proved to contribute to the predisposition to RA[98]. A Spanish study proved that the minor allele of the rs7517847 variant is responsible for a slightly elevated risk to RA[99] which is in accordance with the former findings[98]. Also the exonic rs11209026 contributes to the onset of the disease as well. The same variant was reported to be significantly less frequent in RA patients compared to controls[94].

Analyses of six *IL-23R* SNPs (rs11209026, rs1004819, rs7517847, rs10489629, rs2201841 and rs1343151) were analysed in a New Zealand Caucasian set of RA patients and extended by the reanalysis of the Wellcome Trust Case Control Consortium[62] and the previously published Spanish data set[97]. Unfortunately, the results emphasized the lack of association of the exonic rs11209026 with RA, but provided evidence for a weak allelic association of the rs1343151 variant with the disease. The study also tested LD relationships between 11 *IL-23R* markers. Results showed that several SNPs which were reported to confer risk for RA (rs1343151 in the same paper, and rs10889677 and rs2201841 in the Hungarian cohort) seemed to be independent risk factors[96,100], while others, such as rs7530511 in the North America Rheumatoid Arthritis Consortium (NARAC) and the Swedish Epidemiological Investigation of Rheumatoid Arthritis EIRA genome wide scan[101] seemed to confer risk only due to their weak LD with the markers associated in the Hungarian cohort[96]. Additionally, the NARAC plus EIRA data did not support the predisposing nature of the rs1343151 genetic variant which contradicted the results of a New Zealand study and a meta-analysis performed by a Chinese medical research group, who were able to replicate the association in a data set consisting of four European Caucasian populations[102].

As several studies have examined the association between *IL-23R* polymorphisms and RA but the results were contradictory. There was a high need for a carefully designed meta-analysis which can clarify the issue. In 2012, two papers summarized the observations published before February 2012[103,104]. In a meta-analyis, all relevant original papers gathered from electronic databases were selected by strict inclusion criteria[104]. Six studies involving more than 5000 European patients and controls were assessed. The C allele of the rs10489629 and the G allele of the rs7517847 proved susceptibility to RA. Interestingly, these alleles are protective factors in ankylosing spondylitis, but the same genetic variants may not share a common mechanism in different autoimmune diseases[105].

A meta-analysis evaluated the possible role of four other *IL-23R* polymorphisms in the etiology of RA (rs10489629, rs11209026, rs1004819 and rs2201841). It revealed significant association between the A allele of the rs134151 variant and RA in European subjects, and also confirmed the results of the previous meta-analysis on the predisposing feature of the rs10489629. A allele in the overall population[106]. Interestingly, no association was found between the rs7517847 polymorphism and RA, although this variant is in moderate LD with rs1343151. None of the other SNPs in the focus of this meta-analysis (rs11209026, rs1004819, rs2201841) showed association with the disease. Although three, possibly predisposing *IL-23R* variants after the meta-analyses have been convincingly identified; the exact functional significance of these polymorphisms remains unclear.

### The IL-6-like cytokines

Members of this family (IL-6, IL-11, IL-27 and IL-31) signal through receptors containing gp130 which are commonly referred to as the IL-6-like or gp130 utilizing cytokines family[107].

**IL-6:** IL-6 (OMIM 147620) is one of those pro-inflammatory cytokines which are involved in the pathogenesis of RA. It acts as a major mediator of the acute phase response[108]. IL-6 signals through a cell-surface type I cytokine receptor complex consisting of the ligand-binding IL-6R chain (OMIM 147880) and the shared signal-transducing component IL6ST (also called gp130; OMIM 600694)[109].

Conventional radiography is considered a well-established imaging technique for identifying progressive joint damage[110]. The *IL-6* gene polymorphism-174 G/C (rs1800795) have been associated with RA susceptibility and radiographic severity of bone-erosive damage[111-115]. Significant association was observed between *IL-6* -174 C allele and early disease onset of RA[116]. However no relationship was found between disease susceptibility and *IL-6* -174 C allele in a Spanish study[117]. Another SNP, the -572 G/C (rs1800796) of *IL-6* is associated with RA in a Chinese Han population[47] but with no association with RA in Taiwan[118]. Similarly to these studies no association was found between *IL-6* -174, -572, -597 genotype distributions and allele frequencies in Turkish RA patients[34].

Elevated levels of IL-6 and soluble IL-6R (sIL6R) were found both in the serum and also in synovial fluid of joints in Han Chinese patients with RA[119]. IL-6R can be released *in vivo* in sIL6R through differential mRNA splicing and proteolytic rupture controlled by a disintegrin and metalloprotease domain (ADAM17, also called tumor necrosis factor-α-converting enzyme, TACE). This process is influenced by the SNP rs8192284 resulting in an aspartic acid to alanine substitution (D358A) at the proteolytic cleavage site. Trans-signalling extends the IL-6 range of action to cells lacking constitutive IL-6R[120]. It plays a key role in the pathophysiology of RA[121], where synoviocytes and chondrocytes react to IL-6 through this pathway. In a Spanish RA study was found that rs8192284 polymorphism determines the sIL6R plasma level. Furthermore, increased sIL6R plasma levels and expression of spliced isoform generating sIL6R are genotype dependent.

Meta-analysis of different studies with different ethnicities found association between RA and *IL-6*-174

G/C polymorphism in the European population. An Asian study also revealed significant association between the same *IL-6* polymorphism and RA. Regarding to the *IL-6*-572 G/C polymorphism, the ethnicity-specific analysis in the Asian study revealed an association between RA and the *IL-6*-572 G/C. However no association was found between the *IL-6*-174 G/C polymorphism and RA in the Iranian study[122].

### The IL-17 family

This recently discovered interleukin family contains six cytokines (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F). IL-17A was the first member and the others were discovered shortly after the first one by large-scale sequencing of the human genome[123-126]. Members of this family share the highest amino acid sequence homology and perform distinct biological functions[127].

**IL-17:** IL-17A (OMIM 603149) is a pro-inflammatory cytokine which was the first discovered member of this family in 1993[128]. It acts on a variety of cells involving the development of autoimmunity, inflammation, and tumors. IL-17A and IL-17F genes share the highest degree of homology of about 50%, while the others have only 16%-30% of identity at the primary sequence level[126,129-132]. IL-17F (OMIM 606496) is a novel pro-inflammatory cytokine which induces the expression of cytokines and chemokines. Furthermore, it may play a role in skeletal tissue destruction and inflammatory processes in RA. In arthritis, IL-17A and IL-17F induce significant cartilage matrix release, inhibit new cartilage matrix synthesis and directly regulate cartilage matrix turnover[130]. The IL-17 receptor (IL17R) family includes five members: IL-17RA (OMIM 605461), IL-17RB (OMIM 605458), IL-17RC (OMIM 610925), IL-17RD (OMIM 606807), and IL-17RE (OMIM 614995)[133].

The *IL-17F* gene polymorphisms 7488 A/G (rs763780) and 7383 A/G (rs2397084) were investigated in Polish RA patients. The examined polymorphisms were not correlated with susceptibility to RA, but the 7488A/G (His161Arg) variant was associated with parameters of disease activity (number of tender joints), Health Assessment Questionnaire (HAQ) score or Disease Activity Score (DAS-28)-CRP. The authors supposed that the 7383 A/G (Glu126Gly) polymorphism may be correlated with longer disease duration in patients with RA. Probably these two SNPs directly regulate the IL-17F expression. They hypothesized that polymorphisms in *IL-17* gene may cause redundant production of IL-1 and TNF-α which can mediate inflammatory pathology in many autoimmune diseases, including RA[134].

In Norwegian patients with RA, five *IL-17A* SNPs were analysed. They found a weak but significant RA correlation with the *IL-17A* promoter polymorphism rs2275913[135]. A Japanese study concerning early RA examined the association between age at RA onset, radiographic progression and three SNPs (rs3804513, rs3748067, rs1974226) in the *IL-17A* gene. They described a weak association between the intronic rs3804513 and joint destruction (Larsen score), but found no association with the risk of developing RA[136].

### Chemokines

This group contains only two ILs, IL-8 and IL-16.

**IL-8:** In a Taiwan population the 2767 A/G (rs112664) polymorphism in the 3'-UTR of the *IL-8* gene were investigated and no significant differences were found in the genotype and allele frequencies between RA patients and controls. Clinical characteristics such as age at onset, RF positivity, joint erosion and extra-articular manifestations were compared among patients, and it was found that patients with *IL-8* 3'-UTR 2767AA genotype had a significantly younger age of onset of RA than patients without that genotype[118].

In caucasian RA patients and healthy controls the 781 C/T (2227306) SNP of *IL-8* gene was examined with the result that CC genotype is associated with the early onset of RA[137].

## CLINICAL IMPLICATIONS, TREATMENTS

Till the 1950s, aspirin and non-steroid anti-inflammatory drugs (NSAIDs) were the mainstay of RA therapy. Oral, intramuscular or intra-articular corticosteroids are recommended for controlling pain and inflammation. Ideally, NSAIDs and corticosteroids are used only for short-term management of RA. The development of disease-modifying anti-rheumatic drugs (DMARDs) has revolutionized the long-term therapeutic approach of the chronic inflammatory rheumatic diseases, particularly in patients resistant to standard treatment.

In respect of the new nomenclature for DMARDs[138], the term conventional, synthetic DMARDs (csDMARDs) is used to subsume chemical agents such as methotrexate (MTX), sulfasalazine, leflunomide, hydroxychloroquine, minocycline (less commonly used: gold sodium, thiomalate, penicillamine, cyclophosphamide, cyclosporine, azathioprine); whereas tofacitinib, a new sDMARD specifically designed to target janus kinases (JAKs), will be designated as a targeted sDMARD (tsDMARD). Biologic agents (bDMARDs) include monoclonal antibodies (mAbs), soluble recombinant cytokine receptors and natural antagonists to block cytokines which promote the inflammatory cascade responsible for RA[139]. Biological originator (bo) DMARDs encompass the five currently available TNF-α inhibitors (infliximab, etanercept, adalimumab, certolizumab pegol and golimumab), the T cell costimulation inhibitor abatacept, the anti-B cell agent rituximab, and the IL6R-blocking monoclonal antibody tocilizumab, as well as the IL-1 inhibitor anakinra. While biosimilars (bs), such as bs-infliximab, approved newly in the United States and/or Europe, will be named bsDMARDs[140].

The last set of ACR recommendations for the treatment of RA were published in 2008[141] with an update in 2012 for the use of DMARDs[142]. The 2010 EULAR guideline was renewed in 2013[140]. Goals of RA therapy

include reaching a target of remission or low disease activity in every patient. The commonly used indices to depict clinical response to therapy in RA include the ACR response[143], HAQ score[144] and DAS[145]. DAS28 is derived by the number of swollen joints and tender joints using the 28-joint count, and measures the CRP and and the patient's own assessment on a visual analogue scale[145].

Therapy with DMARDs should be started as soon as the diagnosis of RA is made[140]. Methotrexate is recommended as the first-line treatment in patients with active RA, unless contraindicated or not tolerated[138,141]. Leflunomide may be used as an alternative to methotrexate, although gastrointestinal adverse effects are more common. Sulfasalazine or hydroxychloroquine is recommended as monotherapy in patients with low disease activity or without poor prognostic features (*e.g.*, seronegative, non-erosive RA)[141,146]. Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 mo, but should be tapered as rapidly as clinically feasible. Combination therapy with two or more DMARDs is more effective than monotherapy; however, adverse effects may also be greater[15]. If RA is not well controlled with a csDMARD, a biologic DMARD should be initiated with MTX[140,141,146]. Current practice would be to start a TNFα inhibitor. If TNF inhibitors have failed, other biologic therapies can be considered (*e.g.*, abatacept, rituximab or tocilizumab). Simultaneous use of more than one biological therapy (*e.g.*, adalimumab with abatacept) is not recommended because of an unacceptable rate of adverse effects[141]. Tofacitinib, a new tsDMARD, may be considered after biological treatment has failed[138].

Although the precise etiology of RA still remains unknown, improved understanding of the pathogenesis of the disease DMARD treatment has undergone dramatic changes during the past decade. Biological DMARDs have the potential to inhibit the behaviour of cytokine, cellular activation, and inflammatory gene transcription by various means. Cardiovascular disease due to accelerated atherosclerosis is the major cause of excessive mortality in RA. Cytokine antagonists have shown a favourable response in endothelial cell dysfunction in these patients[147].

Because of the elevated levels of TNFα, IL-1 and IL-6 in the synovial fluid of patients with RA, these three cytokines have been targeted at the beginning of RA therapy. Numerous other biological therapies are in various stages of development. We now review the main biological drugs classifing according to the targeted mechanism of action.

### *Tumor necrosis factor inhibitors*

TNFα is a pleiotropic, pro-inflammatory cytokine which plays a pivotal role in the origin and progression of RA. TNF is a 17-kD trimeric protein cytokine that is produced mainly by monocytes and macrophages. Newly synthesized TNFα is inserted into the cell membrane. Subsequently, the TNFα converting enzyme (TACE) cleaves this cell-bound TNFα to release it into circulation[148]. Both soluble (sTNF) and membrane TNF (mTNF) are biologically active when interacting with either of two distinct receptors, TNF receptor 1 (TNFR1, p55) and TNFR2 (p75), expressed on a wide variety of target cells[149]. TNF receptor signalling occurs through two pathways: one arm has death-domain proteins which lead to apoptosis, the second and dominant signalling pathway goes through a series of kinases, leading to the activation of nuclear-factor kappa B (NF-κB).

The mechanism of action of TNF-α antagonists is based on the neutralization of both sTNF and mTNF and has a more global effect on inflammation than the blockade of other cytokines. The interruption of the signal pathways mediated by TNF has numerous consequences, reflecting the pleiotropic effect of the cytokine: apoptosis, inhibition of pro-inflammatory cytokine and chemokine release, but also of chondrocyte, osteoclast, and endothelial cell activation, reduction of leukocyte accumulation and angiogenesis, increase of T reg cell number.

Currently, 5-TNF inhibitors are approved for use by the United States Food and Drug Administration. Infliximab (Remicade®) is a chimeric (75% human + 25% mouse) monoclonal full-length, bivalent IgG1 mAb[150]. Certolizumab Pegol (Cimzia®) is a humanized protein containing amino acid sequences derived from a mouse anti-TNF mAb and inserted into human domains; adalimumab (Humira®) and golimumab (Simponi®) are fully human mAbs[151]. Etanercept (Enbrel®) is a dimeric fusion protein consisting of soluble p75-TNFR2 and the Fc portion of human IgG1. The primary action of etanercept is to bind and inactivate soluble and cell-bound TNF-α and lymphotoxin-α.

Another way to block TNF-α in biological fluids is to inhibit TACE, up to 95% reduction of the TNF production is attainable. TACE inhibitors are under development, but, even after more than a decade no single TACE inhibitor has passed the phase 2 clinical trials[152].

### *IL-1 antagonism*

IL-1 is implicated in the pathogenesis of RA, its level correlates with RA disease activity[153]. IL-1 type 2 receptor (IL-1R2) (OMIM 147811) is a decoy receptor which binds to circulating IL-1[154] and is not involved in signal transduction. An antagonist of these receptors has also been identified (IL1RN) which neutralizes the effects of IL-1, consequently, IL1RN acts as a physiological inhibitor of IL-1. Complete inhibition of IL-1 requires 10-fold to 100-fold molar excess of IL1RN over IL-1. The balance between IL-1 and IL1RN is important in maintaining the normal physiology of the joints and homeostasis of the immune system.

Anakinra (Kinaret®) is a recombinant form of the naturally occurring IL1RN[155], approved in 2001 for the treatment of patients affected by RA. It should also be mentioned that anakinra, while effective in individual patients with RA, did not show a high level of clinical efficacy in clinical trials[156] and therefore has not been recommended as a major biological agent for use in RA[140].

Many IL-1 inhibiting agents are being developed and tested. These include a recombinant form IL-1R2, rilonacept, also known as IL1Trap (recombinant molecule consisting of IL1R1 and IL1RAP fused to human IgG1 Fc portion which acts as a soluble decoy receptor, trapping both IL-1A and IL-1B[155]). Canakinumab, a human anti-IL-1B mAb (currently investigated in phase 3 studies[157]), and an inhibitor of IL-1 converting enzyme[154,158].

### IL-6 antagonism

Evidence has indicated that blocking the effects of IL-6 in RA is effective and safe, especially with the IL-6R inhibitor, tocilizumab[159]. Tocilizumab (Actemra®) is a humanized mAb of IgG1 class against IL-6R which prevents the formation of the IL-6/IL-6R complex and the activation of signal transduction cascade through JAKs and STATs. Over the next few years, new biological agents targeting the IL-6 receptor (sarilumab) or IL-6R (clazakizumab, sirukumab) may become available[160].

### Co-stimulation signal blockade

There are several sets of T cell co-stimulatory molecules like CD40-CD40 ligand (CD40L) and CD28-CTLA4-B7. Blockade of some of these are under various stages of development[139]. Abatacept (Orencia®) is a biologic agent which blocks T cell activation through the inhibition of CD28-B7 mediated costimulation of the T cell. It has been approved for the treatment of RA[161]. Structurally, abatacept is a recombinant dimeric fusion protein consisting of the extracellular domain of CTLA-4 fused with the modified Fc portion of a human IgG1. Blocking anti-CD40 ligand antibody and anti-CD11a monoclonal antibody (efalizumab) could be also beneficial for the treatment of RA.

### B-cell-depleting therapy

B cells behave as antigen presenting cells, stimulating the activation and proliferation of T cells. In addition, the synovium of patients with RA contains a large number of plasma cells producing RF. The easiest method to obtain a reduction in the number of B cells is to use mAbs directed against surface markers such as CD19, CD20, and CD22.

Rituximab (Rituxan®) is a chimeric mouse/human mAb which selectively depletes B cells bearing the CD20 surface marker. Widely used in the treatment of B-cell lymphomas, it has been shown to be surprisingly effective in RA. The rituximab/MTX combination represents a potential therapeutic option for moderate/severe RA patients, resistant or intolerant to at least one TNF antagonist[140]. Epratuzumab is a humanized mAb formed by an IgG1 directed against CD22.

Tumor necrosis family proteins (*e.g.*, death receptors, anti-B lymphocyte stimulator antibodies) are the molecules of the immune system which take part in the negative feedback regulation to eliminate autoimmune cells. Excessive levels of the TNF family ligand B-lymphocyte stimulator (BLyS) have been demonstrated in RA synovial fluid. Approaches targeting the BLyS and other systems (like APRIL) to selectively eliminate the activated autoimmune lymphocytes in RA are under development[162]. Belimumab is a human recombinant IgG mAb which acts by binding BLyS protein and prevents the interaction with the B cell activating factor receptor.

Atacicept is a recombinant fusion protein comprising the extracellular domain of the TACI (Transmembrane Activator and CAML Interactor) receptor joined to a human IgG1 Fc domain. Atacicept also inhibits the survival of long-lived plasmacells directly involved in the pathogenesis of RA and SLE.

### Kinase inhibitors

In the case of RA, kinases play a central role in the aberrant immune system activation and hence have been targeted using small molecule inhibitors. Mitogen-activated phosphokinase p38 (MAPK), spleen tyrosine kinase (Syk), and JAKs have been studied extensively in clinical trials in RA[163]. Several p38 MAPK inhibitors proved inefficient in treating rheumatoid arthritis.

The Syk inhibitor, fostamatinib, proved superior to placebo in Phase 2 trials and is currently under phase 3 investigation. Tofacitinib (Xeljanz®), a JAK1/3 inhibitor, was approved for the treatment of RA in the United States, Japan and Russia in April 2013[164]. This new tsDMARD may be considered for use after biological treatment has failed[138]. Ruxolitinib and baricitinib (JAK1/2 inhibitors) and pan-JAK inhibitors (JAKinibs) have also been studied in RA where preliminary results were promising in terms of efficacy and safety in a Phase 2a trial.

### Upcoming therapies

**IL-1 superfamily:** IL-18 could be an interesting target in the treatment of RA and one opportunity for antibody-based biological therapies in RA. Blocking of IL-18 by the administration of a recombinant IL-18 binding protein (IL18BP, OMIM 604113) which has the ability to prevent binding of IL-18 to its receptor, or anti-IL-18 in mice with collagen-induced arthritis resulted in a clear reduction of the disease severity compared with placebo-treated mice[165].

IL-33 (OMIM 608678), a newly identified IL-1 family member cytokine, is a chemoattractant for Th2 cells and facilitates the production of Th2 cytokines. IL-33 binds to its receptor consisting of the orphan receptor ST2 (IL1RL1, OMIM 601203) and IL-1 receptor accessory protein (IL1RAP). The soluble ST2 (sST) acts as a decoy receptor of IL-33 and is a natural inhibitor of IL-33. Increased serum and synovial fluid levels of sST2 in RA patients reflect an active inflammatory state[166,167]. Furthermore, the inhibition of IL-33 receptor signaling with anti-ST2 antibodies or sST2-Fc fusion protein resulted in reduced severity of collagen-induced arthritis[166,168].

**IL-2 superfamily:** The role of IL-2 in the immunopathogenesis of RA is debated. IL-2 is hardly detectable in the synovial fluid, and only a low percentage of the intra-articular T cells express T cell activation markers (Tac antigen)[169]. IL2-directed therapy may have beneficial effects

in RA patients[170]. The humanized monoclonal antibody daclizumab (Zenapax®) against the α-chain of the IL-2R (CD25) caused significant reduction of joint-inflammation and joint-erosion in collagen-induced arthritis in rhesus monkeys[171]. Antagonistic IL2RA mAbs (anti-Tac/daclizumab, basiliximab) are effective in preventing rejections of organ transplants.

IL-15 is a pro-inflammatory, innate response cytokine. In patients with RA, innate response cytokine IL-15 is expressed in the synovial tissue and the serum levels of IL-15 have been reported to correlate with disease severity[172]. Anti-IL15 monoclonal antibodies are being examined for their anti-arthritic activity. Baslund and colleagues conducted a phase 1/2 clinical trial of a human IgG1 anti-IL15 monoclonal antibody, HuMax-IL15. This antibody could neutralize various biological effects of IL-15 in synovial tissue *in vitro*, and it caused significant improvement in disease activity at 12 wk after treatment initiation[56,173,174]. Clinical trials are underway evaluating the safety and efficacy of monoclonal antibody IL-15 (HuMax-IL15) and CD2 receptor (Alefacept).

IL-21 contributes to joint inflammation and synovial cellular infiltration in RA, as expected for a Th17-related cytokine[25,175]. Increased level of IL-21 has been reported in RA sera, and the concentration of IL-21 in serum and synovial fluid was higher in RA than osteoarthritis[175]. Treatment with IL21RFc chimeric protein in animal models of RA resulted in significantly reduced disease severity[176-178].

**The IL-12 family:** IL-12 and IL-23 bind to the IL12RB1 of T cells and NK cells via their shared p40 subunit. Evidence shows that IL-23 plays a key role in the development of pathogenic Th17 cells producing IL-17, which further induces the production of several pro-inflammatory cytokines, such as TNFα and IL-6, chemokines, which cause the aggravation of synovial inflammation and osteoclast differentiation leading to joint destruction in patients with RA[179,180]. In addition, the serum level of IL-23 in patients with RA correlates with the number of swollen joints, the DAS28 joints. Studies have shown that IL-23 induces receptor activator of RANKL expression on $CD4^+$ T cells and promotes osteoclastogenesis in an autoimmune arthritis[181]. Thus anti-IL23 therapy could be a therapeutic target not only of inflammation but also bone erosion in RA. The level of interest in this target can be seen from the fact that 15 different IL23R antagonists are now reported to be in clinical or pre-clinical development[182] .

Recent clinical studies associated with IL-23 inhibition in arthritis include the use of apilimod mesylate, an orally administered inhibitor of IL-12/IL-23 in RA[183]. Ustekinumab and briakinumab, fully human mAbs directed against the p40, are currently in phase 2 trials. However, due to the common p40 subunit and IL12RB1 chain, the major drawback of anti-IL23 treatment may be the simultaneous inhibition of IL-12 and a possible shutdown of the immune system. Nevertheless, it would be much more useful to design drugs that target the IL23p19 or IL23RA itself, thus inhibiting IL-23 without modifying the effects of IL-12 (*e.g.*, MP-196, FM-303, IL-23 Adnectin)[182].

**The IL-17 family:** Increased levels of IL-17A have been found in sera, synovial fluid, and in the T cell-rich area of the synovium in patients with RA[184,185] and these levels are predictive of a more severe joint damage progression[186]. Besides the enhancement of inflammation commonly observed in arthritis, IL-17A also mediates bone and cartilage destruction through the stimulation of fibroblast-like synoviocytes to produce pro-inflammatory cytokines, IL-6 and IL-8, as well as matrix-degrading enzymes, matrix metalloproteinases. In addition, IL-17 upregulates the receptor activator of RANK on osteoclast precursors causing increased sensitivity to RANK signaling.

Treatment of RA patients with a humanized anti–IL-17 antibody (LY2439821) given intravenously is shown to improve the signs and symptoms of the disease[187]. In another study on RA, treatment with AIN457 (anti-IL17) induced clinically relevant responses, although of variable magnitude[188]. The IL-17 blockers secukinumab (anti-IL-17A), ixekizumab (anti-IL17A), and brodalumab (anti-IL17RA) have shown efficacy in phase 2 trials in RA. The results of the ongoing phase 3 trials should help to shed light on whether IL-17A is truly a viable therapeutic target in RA. The effect of blocking other IL-17 family members including IL-17F has yet to be evaluated in human diseases.

**Agents blocking the chemokines and adhesion molecules:** Agents blocking the chemokines and adhesion molecules are also under trial. These include antibodies to IL-18[165], humanized anti-integrin avb3 monoclonal antibody (MEDI-522) and anti-VCAM antibodies. Suppression of new wessel formation could also be an interesting target in the future treatment of RA.

**Anti-inflammatory cytokines in RA**: IL-10 and IL-4 are cytokines with counter-regulatory mechanism that down-regulates pro-inflammatory responses. Some anti-inflammatory effects are also naturally provided by the presence of IL-1RN, IL-1R2 decoy receptor and soluble TNF receptor. In vitro, IL-10 and IL-4 inhibit the production of inflammatory cytokines including IL-1, IL-6 and TNF-α RA[189,190], furthermore IL-10 has been shown to reverse the cartilage degradation seen in RA[189]. *In vivo*, however, they are inherently weak and proved inadequate.

IL-27 (OMIM 605816) is an IL-12 superfamily cytokine that plays a role in the immune effector responses in autoimmune diseases, including arthritis. The role of IL-27 as a pro-versus an anti-inflammatory cytokine has not yet been fully resolved. In collagen-induced arthritis, treatment of mice with IL-27 reduced the severity of arthritis, as well as the levels of IL-6, IL-17[87]. Another mechanism of IL-27-mediated protection against arthritis involves the inhibition of osteoclastogenesis[191].

It has recently been shown that human Tregs express

IL-35 and require this cytokine for their optimal suppressive effect[192]. These findings reinforce a potential mechanism (*e.g.*, suppression of Th17 response) that Tregs can be used to control pathogenic T cell responses in RA. Treatment of mice with IL-35 reduced disease severity which was associated with reduction in IL-17, IFN-γ, and an increase in IL-10 production[193].

**Small molecular inhibitors of intracellular signalling:** Small molecular inhibitors of intracellular signalling (*e.g.*, NF-κB and associated activator molecules) are in focus of numerous clinical and preclinical research and have shown promising results in animal models[194,195].

**RANKL inhibition :** Denosumab, a human anti-RANKL mAb is approved in the United States for the treatment of postmenopausal osteoporosis but is not currently indicated for the treatment of RA (phase 2).

## CONCLUSION

RA is the most common chronic inflammatory disease of the joints and is characterized by a complex genetic architecture. In our review, we discussed the pathogenesis, the polymorphisms of IL and *IL* genes and also the standard available and possible future immunologic targets for RA treatment. The identification of disease-associated interleukin and interleukin receptor genes could provide precious insight into the genetic variations prior to disease onset in order to identify the pathways important for RA pathogenesis. From the discussed interleukins the IL-1, the IL-6, and the IL-23 were the most investigated.

IL-1 is very important, because it mediates many inflammatory diseases by initiating and potentiating immune and inflammatory responses. Several studies have dealed with the association of *IL-1* gene polymorphisms with RA. The IL-1 expression is influenced by two variants of the *IL-1B* (-511 T/C and +3953 C/T). Carrying the TT genotype of *IL-1B* +3953 gene is susceptible to RA in a Turkish cohort, while the CT genotype of *IL-1B* -511 has a protective role against RA. In a British Caucasian RA patients the G allele of *IL-1B* -1464 C/G was found to possibly have protective effect in RA. In the Asian populations +3953 C/T SNP of the *IL-1B* polymorphism was associated with the development of RA.

IL-6 is the main pro-inflammatory cytokine which is involved in the pathogenesis of RA. Several SNPs of the *IL-6* gene were investigated (promoter polymorphisms: -174, 572, -597, exonic polymorphisms: 869), but with controversial results. In a Spanish, Turkish and Iranian cohort the *IL-6*-174 G/C is not a risk factor for RA, but meta-analyses with different ethnicities showed an association between RA and these SNP in other European population. An Asian study also revealed a significant association between the same SNP and RA. The -572 G/C SNP is associated with RA in a Han Chinese population, while no correlation could be detected in a Taiwan population. Ethnicity-specific analysis in an Asian study revealed an association between RA and *IL-6* -572 G/C polymorphism.

IL-23 is the most extensively studied cytokine. IL-23 is very important in innate and adaptive immunity. The *IL-23R* gene was identified first as a CD susceptibility gene in North American non-Jewish subjects but the studied were extended to RA. Association between independent functional SNPs in the gene and its neighboring region and RA were investigated (rs10889677, rs11209032, rs1495965, rs2201841, rs1004819, rs11209026, rs7517847, rs10489629, rs1343151) in numerous studies. Several SNPs are susceptible, others are protective to the disease but the predisposition was population dependent.

In the lack of knowing genetic variants that influences the development of RA and in default of adequate therapy, the patient's way of life continuously declines, even permanent disability might arise. However, conventional DMARD therapy of RA has several limitations like slow onset of action and induction of partial remission. By targeting molecules that are directly involved in pathogenesis pathways, blocking biologic activity of pro-inflammatory cytokines and their receptors may be more specific, more efficacious, and less toxic in the short-term than current treatment modalities. Because biologics are relatively new, evidence is insufficient to determine their long-term benefits and risks, including the risk of lymphoma and malignancies.

Evidence suggests that although biologics are relative expensive, they remain cost-effective because of the major clinical benefits that patients may experience. Currently, data is available for one biosimilar product (infliximab) which shows similar efficiancy and safety profiles to the original biological agent. It has been estimated that the price for biosimilar products will be 65%-85% of their originators. Nevertheless, combinations of biological agents targeting different disease processes may allow more promising results in future. The knowledge of the complex genetic background may prove to be greatly useful for developing novel therapies and producing personalized medicine based on the individual's genetics.

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REVIEW

# Psoriatic arthritis: Epidemiology, diagnosis, and treatment

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## Abstract

Our understanding of psoriatic arthritis has evolved as new knowledge of the disease has emerged. However, the exact prevalence of psoriatic arthritis is unknown, and its pathogenesis has not been fully elucidated. Genetic, environmental, and immunologic factors have all been implicated in disease development. Early diagnosis and treatment have become primary objectives in clinical rheumatology. Psoriatic arthritis not only causes functional impairment, but also increases mortality risk of patients. The advent of new therapeutic agents capable of arresting the progression of joint damage is expected. However, early psoriatic arthritis assessment remains limited. The objectives of this article are to outline the epidemiology, diagnosis, and treatment of psoriatic arthritis and to suggest a paradigm for identifying early psoriatic arthritis patients.

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**Key words:** Arthritis; Psoriasis; Psoriatic arthritis; Spondyloarthritis

**Core tip:** Psoriatic arthritis, usually seronegative for rheumatoid factor, involves the inflammation of synovial tissue, entheses, skin. Clinical manifestation of psoriatic arthritis varies and is under-diagnosed in psoriasis patients. This article presented the epidemiology, diagnosis, and treatment of psoriatic arthritis and to suggest a paradigm for use in standard clinical practice.

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## INTRODUCTION

Psoriatic arthritis (PsA) is a chronic disease which involves the inflammation of synovial tissue, entheses, skin and usually seronegative for rheumatoid factor[1]. Spondyloarthritis complex includes ankylosing spondylitis, reactive arthritis, arthritis associated with inflammatory bowel disease, undifferentiated spondyloarthritis, and PsA[2,3]. PsA is belonged as one part of the spondyloarthritis complex. PsA patients have heterogeneous clinical presentations, with diverse articular and dermatological features and varied disease courses and outcomes. PsA was initially considered to be a mild disease, but in the past decade, 40%-60% of patients have developed erosive and deforming joint complications[4]. PsA-induced joint damaging complications not only lead to lower articular function and higher mortality but also affect patients' ability to work and affect their social relationships[4]. The remission of PsA symptoms has been attributed to early diagnosis and treatment in recent studies[5,6]. However, PsA is underdiagnosed in psoriasis patients, which may be due to under-recognition of PsA symptoms and a lack of effective screening tools. The aims of this article were

**Table 1 The classification for psoriatic arthritis criteria[7] for diagnosing psoriatic arthritis-related inflammatory musculoskeletal disease (joint, spine or entheseal)**

| |
|---|
| Evidence of psoriasis (any of three) |
| Current[1]: Psoriatic skin or scalp disease present, as judged by a dermatologist or rheumatologist (score of 2) |
| Personal history: May be obtained from the patient, family doctor, dermatologist, or rheumatologist (score of 1) |
| Family history: In a first- or second-degree relative, according to patient report (score of 1) |
| Psoriatic nail dystrophy |
| Typical psoriatic Nail dystrophy, including onycholysis, pitting, and hyperkeratosis, observed on current physical examination (score of 1) |
| Negative rheumatoid factor |
| By any method except latex, but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range (score of 1) |
| Dactylitis |
| Current: swelling of an entire digit (score of 1) |
| Personal history: recorded by a rheumatologist (score of 1) |
| Radiological evidence of juxta-articular new bone formation |
| Ill-defined ossification near the joint margins (but excluding osteophyte formation) on plain X-rays of the hand or foot (score of 1) |

[1]Current: Psoriasis score of 2; others: 1. A PsA patient must have inflammatory articular disease with > 3 points from the following 5 categories.

to present the epidemiology, diagnosis, and treatment of PsA and to suggest a paradigm for use in standard clinical practice.

## DATA COLLECTION

We collected all of the articles published from January 2005 through October 2013 that described patients who were affected by PsA. By searching MEDLINE (National Library of Medicine, Bethesda, Maryland, United States), we used the key words "psoriatic arthritis" and "epidemiology of psoriatic arthritis" or "diagnosis of psoriatic arthritis" or "management of psoriatic arthritis" to obtain these articles. Articles that were not published in English, manuscripts without an abstract (which were assumed to not be original), and opinion articles were excluded from the review. The relevant information was extracted from the selecting articles and classified based on the following: PsA epidemiology, PsA diagnosis, PsA management, the setting of study, and the methodology of study.

The article searches were conducted from August 2013 to September 2013. Using the search terms previously described, a total of 853 papers were collected. All selected articles were reviewed by the authors and 109 articles were considered to be relevant. The study settings mostly located in European countries, the United States, Australia and Japan. The region that produced the most original information was Europe, which accounted for 35% of the articles. After analyzing the abstracts, we found that 85% of the studies were case reports, and 10% were retrospective. Additionally, 5% referenced other designs.

## EPIDEMIOLOGY

It is difficult to determine the epidemiology of PsA due to the absence of universally accepted criteria for its diagnosis. The first classification criteria for PsA were proposed by Moll *et al*[7]. However, the pattern of disease may change over time and, therefore, is not useful for classification. The classification for psoriatic arthritis (CASPAR) criteria were developed in 2006 (Table 1)[7]. The CASPAR criteria are easier to use in epidemiologic studies. The specificity and sensitivity of these criteria are 98.7% and 91.4%, respectively[7].

**Table 2 Comparison of the incidence and prevalence of psoriatic arthritis among several countries**

| Country | Incidence (1/100000) | Ref. | Prevalence | Ref. |
|---|---|---|---|---|
| Asia | | | | |
| China | NA | | 0.02% | [33] |
| Japan | 0.1 | [17] | 0.001% | [32] |
| Europe | NA | | NA | |
| Greece | 3 | [20] | 0.17% | [29] |
| France | NA | | 0.19% | [23] |
| Italy | NA | | 0.42% | [25] |
| Germany | NA | | 0.29% | [24] |
| Finland | 23.1 | [18] | NA | |
| Sweden | 8 | [19] | 0.02%-0.25% | [30] |
| Iceland | NA | | 0.14% | [28] |
| Norway | NA | | 0.2% | [27] |
| Russia | NA | | 0.3% | [31] |
| Americas | | | | |
| United States | 7.2 | [22] | 0.16% | [22] |
| Argentina | 6.3 | [92] | 0.07% | [21] |
| Mexico | NA | | 0.02% | [26] |

NA: Not available.

PsA usually occurs in the age of 40 to 50 years old, and the disease may occur in young children and elderly patients as well[8]. Psoriasis vulgaris is the most common type of psoriasis with PsA[9]. A few proportion (4%-5%) of PSA cases are related to guttate and pustular psoriasis[10]. One to two percent of cases involve single nail without skin involvement[11]. Male-to-female ratio is from 0.7:1 to 2.1:1[11]. Approximately 10%-37% of patients have skin and joint disease simultaneously, and 6%-18% of patients have arthritis preceding psoriasis[12,13]. Environmental factors, including infection (such as streptococcus, human immunodeficiency virus), drug use, and joint trauma (mainly in children), are known to contribute to PsA[14,15]. Emotional stress plays an important role as a trigger for both skin and joint psoriasis[15]. However, the neuroimmunoendocrine mechanisms involved in this phenomenon have not been elucidated. One population-based study suggested that pregnancy and steroid use might trigger PsA in patients with psoriasis[16].

Table 2 shows the incidence and prevalence of PsA worldwide. There is substantial variability in the incidence and prevalence of PsA by country. The incidence of PsA varies from 0.1/100000 in Japan to 23.1/100000 in Finland[17-22]. The prevalence of PsA in Europe and America varies from 0.02%-0.42%[22-30]. The prevalence in Japan is approximately at 0.001%[31]. In China, the disease prevalence is 0.02%[32]. Indians were found to have the highest prevalence of PsA among the multiethnic population in

**Figure 1 Peripheral hand joint involvement along with psoriatic skin lesion and nail changes.** Reproduced with permission from Dhir *et al*[39].

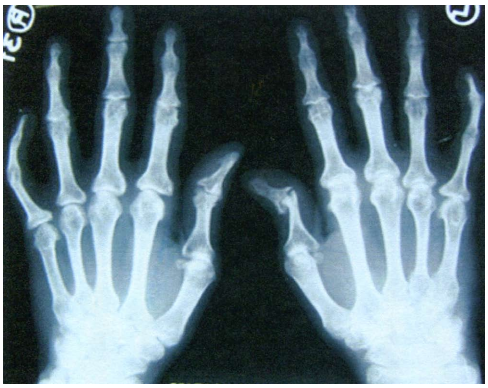

**Figure 2 Ankylosis of distal interphalangeal joint on both hands, pencil in cup deformity in the first left interphalangeal joint on radiography.** Reproduced with permission from Dhir *et al*[39].

Singapore[33].

Collectively, compared to Americas and Europe, Asia has lower incidence and prevalence of PsA. The reasons for the difference of PsA morbidity in different areas are unclear. However, different case definitions and clinical settings in the studies may be one of the reasons.

## DIAGNOSIS

### *Clinical manifestations*

The clinical spectrum of PsA is diverse in nature; psoriatic patients might have axial skeleton disorders, nail changes, peripheral joint inflammation, entheses, tenosynovitis, or dactylitis. Each of these conditions can be found in isolation or in combination with others. The major clinical features of the disease are spondylitis (18%-46%), inflammatory neck pain (23%-39%), thoracic inflammatory pain (13%-21%), and axial symptoms (25%-50%)[8,34]. Most of patients with axial involvement can be no clinical symptoms and maintain their spinal mobility with no reduction in spinal flexion or chest expansion for more than 10 years [34,35].

Sacroiliitis is a common symptom among PsA patients[8,11,12,34,36]. Usually, it occur unilaterally and then become bilaterally in the following years. A study conducted in an Italian patient population using bone scans to detect active sacroiliitis found that the prevalence of sacroiliitis was 32%[37]. A multicenter study from the United States found that the prevalence of sacroiliitis was 78%[38]. It was found that one-third of PsA patients developed sacroiliitis after 5 years of illness and that half of patients developed sacroiliitis by 10 years[35]. Longer period of disease may be the cause of higher prevalence of sacroiliitis. Males have a three-fold greater risk of developing sacroiliitis than females have[11]. The onset time of PsA at younger age has higher risk to hip joint disease, however, there is no significant association between occurrence of enthesitis, dactylitis, and peripheral arthritis with the occurrence of hip joint disease[36].

PsA can simulate rheumatoid arthritis to involve the knee or a large joint with some small joints in fingers or toes (Figure 1)[39]. Polyarthritis is generally symmetrical and has dactylitis and enthesitis[37,39]. Oligoarthritis can be associated with dactylitis[37]. It is also found a shortening of the fingers with pencil-in-cup deformity[40].

Dactylitis was present in 32%-48% of patients with PsA in various studies[37,40-45]. Seventy-five percent of patients have toes with dactylitis and 50% of patients have multiple digits involved simultaneously[43]. The morbidity of dactylitis increases as the duration of disease prolongs[40-45].

Twenty-five to fifty three percent of PsA patients present enthesitis[36,44]. One study in Canada demonstrated that only 15% of patients had enthesitis at the beginning of treatment, but the incidence increased to 36% as the disease progressed[44]. The Achilles tendon, plantar fascia, and greater trochanter are the most common sites affected[44,45].

From 4% to 18% of patients with PsA are found to have acute anterior uveitis[8,46,47]. Uveitis is more common in PsA patients with the spondylitis, with or without peripheral joint involvement[9]. However, uveitis is uncommonly clinical presentation in Spain and Israel. The prevalence of uveitis among PsA patients in these areas is only 1%-3%[11,41].

### *Imaging findings*

Radiography, ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), and bone scintigraphy[48] are imaging techniques for diagnosis of PsA. In recent years, MRI and ultrasonography are increasingly used for assessment of PsA, providing additional information of the pathogenesis of the disease.

The most characteristic radiological finding indicative of PsA is bone destruction and proliferation[49]. Figure 2 shows the characteristics of radiological findings of peripheral PsA: an asymmetrical distribution, distal interphalangeal joints involvement, periostitis, bone density preservation, bone ankylosis, and pencil-in-cup deformity[39]. Axial involvement includes paravertebral ossification, syndesmophytes, interspinous or anterior ligament calcification, apophysis, sclerosis, and asymmetrical sacroiliitis[49]. Cervical intervertebral discs may be narrowed, and ankylosis may be present with atlantoaxial fusion or subluxation[50,51]. Bone erosion and condyle osteolysis

might be found in the temporomandibular joint[52].

Ultrasonography is a reliable method for investigating subclinical enthesopathy in the Achilles tendon and for confirming a diagnosis in symptomatic patients[53]. This method can be used to identify acute or degenerative tendinitis, rupture, peritendinitis, and retrocalcaneal or pre-Achilles bursitis[53]. Ultrasonography has been considered an important tool in the evaluation of PsA. Power Doppler ultrasonography is not only a useful tool to assess musculoskeletal and cutaneous involvement, but also a functional tool to monitor the efficacy of therapy and to guide steroid injections at the level of inflamed joints, tendon sheaths, and entheses[54].

MRI examination has improved our understanding of PsA by establishing that synovial inflammation is usually secondary to extrasynovial involvement, which helps to differentiate PsA from rheumatoid arthritis[55]. However, this diagnosis cannot always be precisely determined. The use of gadolinium contrast increases the odds of differentiation by calculating the relative enhancement and rate of early enhancement[55]. MRI has improved the quality of diagnosis and objective observation of the disease spectrum in PsA[55,56]. In addition, direct visualization of inflammation in the peripheral and axial joints and peripheral and axial entheses is the advantage of MRI. It may show the images among enthesitis, synovitis, and osteitis in PsA and support an spondyloarthritis (SpA) pattern of inflammation of enthuses, in which is the primary target of inflammation[56].

CT is another useful tool for diagnosis of PsA. CT plays a limited role in the diagnosis of peripheral joints, however, it may be useful in assessing spine disease[57]. The sensitivity of CT in the detection of erosions of sacroiliac joint is similar to that of MRI, but MRI is more effective in monitoring synovial inflammation. The specificity of bone scintigraphy for diagnosis of PsA has improved when supplanted with ultrasonography and MRI techniques[57].

Taken together, conventional radiography, ultrasonography, and MRI have similar diagnostic efficacy in the assessment of joint space width[48]. Radiology is less sensitive than ultrasonography and MRI in the assessment of other features of joint inflammation[48]. Radiography allows the detailed analysis of morphostructural and blood flow changes in multiple psoriasis-affected sites (skin, joints, tendons, entheses, and nails)[58]. Ultrasonography with power Doppler has shown that psoriasis patients without PsA more commonly exhibit synovitis and enthesopathy than do patients with other skin diseases. Additionally, ultrasonography has shown a significant prevalence of musculoskeletal asymptomatic involvement (3.2% synovitis and 11.6% enthesopathy)[59]. MRI is more sensitive in detecting small erosions and enthesitis[48].

## TREATMENT

The basic goals of PsA treatment are helping patient to alleviate from the suffering of the disease, to preserve the joint structure, to improve patients' physical activities, and to reduce the risk of mortality. As a rule, all PsA patients must be informed of the characteristics of the disease and given psychological counseling and physiotherapy.

### *Corticosteroids*

Mild forms of the disease may respond to nonsteroidal inflammatory agents, which are occasionally given in combination with intra-articular glucocorticoid injections[60]. Intra-articular corticosteroids may represent a therapeutic option in cases of mono- or oligoarticular joint involvement in PsA. The systemic use of corticosteroids is not recommended due to a lack of evidence regarding its efficacy and due to the risk of severe adverse events and relapse of skin psoriasis upon discontinuation[60].

### *Nonsteroidal anti-inflammatory drugs*

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed as an initial therapy for both peripheral and axial disease[60]. For example, according to the measurement by the American College of Rheumatology Responders Index 20 (ACR20), the treatment of PsA patients with celecoxib at a dose of 200 or 400 mg over two weeks increased their rates of clinical response by 21% and 11%, respectively[61]. However, there was no difference in response between patients treated with celecoxib and untreated patients after 12 wk[61]. Treatment with NSAIDs represents an option for the short-term symptomatic treatment of PsA[60,62-64].

### *Conventional disease-modifying antirheumatic drugs*

Disease-modifying antirheumatic drugs (DMARDs) include methotrexate, oral and parenteral gold, cyclosporine, leflunomide, azathioprine and 6-mercaptopurine, antimalarial agents, D-penicillamine, colchicines, retinoids, photochemotherapy, somatostatin, and sulfasalazine[60]. Moderate to severe forms of the disease are initially treated with the same therapy as in the mild form of the disease, but with the addition of DMARDs[61]. The efficacy of methotrexate in the treatment of PsA is controversial; although this drug is occasionally used in combination with NSAIDs, its use should be carefully monitored due to the possibility of hepatotoxicity[60,63,64]. Cyclosporine is an efficacious option for the treatment of PsA, and its results may be potentiated by combination with adalimumab. Leflunomide may be used in the treatment of PsA but should be carefully monitored due to its hepatotoxicity. Sulfasalazine can be used in PsA to afford pain relief[63,64].

### *Anti-tumor necrosis factor agents*

Table 3 summarizes the current biological therapies for the treatment of moderate to severe psoriasis and PsA[63-65]. Adult patients who have had moderate to severe active PsA (at least three swollen and painful joints) for more than six months and those with psoriatic skin lesions or a history of psoriasis and an intolerance to NSAIDs or DMARDs over three months, whether combined or not combined with methotrexate, are the indi-

**Table 3 Summary of current biologic therapies for the treatment of psoriasis and psoriatic arthritis[65]**

| Drug | Treatment |
|---|---|
| Anti-TNF | |
| Adalimumab | PsA: 40 mg *sc* every other week. Psoriasis: 80 mg *sc* at week 0, 40 mg *sc* every other week thereafter |
| Etanercept | PsA: 25 mg *sc* twice per week. Psoriasis: 50 mg *sc* twice weekly for 3 mo, 50 mg/wk thereafter |
| Golimumab | PsA: 50 mg *sc* every month |
| Infliximab | PsA and psoriasis: 5 mg/kg at week 0, 2, and 6, every 8 wk thereafter |
| Anti-IL-17 | |
| Brodalumab | In clinical trials |
| Ixekizumab | In clinical trials |
| Secukinumab | In clinical trials |
| Anti-IL-12/IL-23 | |
| Briakinumab | In clinical trials |
| Ustekinumab | Psoriasis: 45 mg (weight < 100 kg) or 90 mg (weight > 100 kg) *sc* at wk 0 and 4, followed by 45 mg or 90 mg every 12 wk |
| Anti-T cell activation | |
| Alefacept | Psoriasis: 15 mg IM weekly for 12 wk |

PsA: Psoriatic arthritis; SC: Subcutaneous injection; IM: Intramuscular injection; TNF: Tumor necrosis factor; IL: Interleukin.

cations for the use of anti-tumor necrosis factor (TNF) agents (*e.g.*, infliximab, etanercept, adalimumab, and golimumab)[63,64]. Although it is difficult to quantify the occurrence of adverse effects, there are no statistically significant differences in the safety profiles among the various anti-TNF drugs using for treatment of PsA[63,64].

## CONCLUSION

The incidence and prevalence of PsA vary worldwide. The incidence and prevalence of PsA in Asia are lower than in North American and European countries. Early diagnosis and treatment for PsA improve patient's outcomes. PsA is underdiagnosed among psoriasis patients. Physicians should be alert the possibility of PsA when a patient with preexisting psoriasis has arthritis. If needed, counsel a rheumatologist for help. The treatment of PsA should be considered all aspects of the disease, including clinical manifestations, mental problems, and maintenance of articular function.

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MINIREVIEWS

# Rheumatoid arthritis susceptibility genes: An overview

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## Abstract

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease sustained by genetic factors. Various aspects of the genetic contribution to the pathogenetics and outcome of RA are still unknown. Several genes have been indicated so far in the pathogenesis of RA. Apart from human leukocyte antigen, large genome wide association studies have identified many loci involved in RA pathogenesis. These genes include protein tyrosine phosphatase, nonreceptor type 22, Peptidyl Arginine Deiminase type Ⅳ, signal transducer and activator of transcription 4, cytotoxic T-lymphocyte-associated protein 4, tumor necrosis factor-receptor associated factor 1/complement component 5, tumor necrosis factor and others. It is important to determine whether a combination of RA risk alleles are able to identify patients who will develop certain clinical outcomes, such myocardium infarction, severe infection or lymphoma, as well as to identify patients who will respond to biological medication therapy.

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**Key words:** Rheumatoid arthritis; Gene; Polymorphism; Human leukocyte antigen; Genome wide association study

**Core tip:** This is a comprehensive review concerning genetic factors in rheumatoid arthritis.

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## INTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune disease, afflicting around 0.5%-2% of the human population, especially females, but the precise etiology is still unknown. RA is characterized by chronic, systemic inflammation that may affect many tissues, principally synovial tissue, leading to joint destruction, functional disability and sometimes death[1]. Environmental and genetic factors are responsible for susceptibility and the phenotype. Environmental factors include geography, climate, endemic microbes and lifestyle, such as smoking and diet[2,3]. Native Americans show a relatively higher incidence than African or Asian populations. Familial clustering is important, with the prevalence of RA ranging from 2% to 12% in first degree relatives of patients, 5%-10% in same sex dizygotic twins and almost 12%-30% in monozygotic twins[3,4].

The human leukocyte antigen (HLA) region in the human genome is the most heterogeneous and many diseases are known to be associated with this region. The first risk alleles for RA were identified within 36Mb, the major histocompatibility complex (MHC) region[3]. Several studies beginning in the 1980s explained the strong association of the HLA-DRB1 alleles with RA. The associated alleles encode five amino acids at position 70-74 of the HLA-DRβ1 chain, which is known as a shared epitope (SE). It was established that the HLA-DRB1*01, HLA-DRB1*04 and HLADRB1*10 alleles containing the SE were associated with susceptibility to RA and amino acid sequences QKRAA, QQRAA and KKRAA were known SEs conferring susceptibility, while DERAA sequences were for protective effects[5,6]. Caucasian RA patients have

**Table 1 The most relevant alleles associated with susceptibility in rheumatoid arthritis according to genome wide association studies**

| Gene candidate | Locus | SNP | OR |
|---|---|---|---|
| HLA-DRB1 | | | |
| PTPN22 | 1 | Rs2476601 | 1.23-1.75 |
| PADI4 | 1 | Rs 2240340a | 1.4 |
| STAT4 T/C | 2 | Rs1188934 | 1.22 (0.98-1.53) |
| FCGR2A | 1 | Rs12746613 | 1.1 |
| CTLA4 | 2 | Rs3087243 | 0.75-1.136 |
| CCL21 | 9 | Rs2812378 | 1.1 |
| TRAF1 | 9 | Rs3761847 | 1.1 (0.97-1.32) |
| IRF5 | 7 | Rs10488631 | 1.16 (0.72-1.87) |
| CCR6 | 6 | Rs3093023 | 0.79 (0.64-0.98) |
| CD40 | 20 | Rs4810485 | 0.91-1.02 |
| IL2RA | 10 | Rs2104286 | 0.92 |

RA: Rheumatoid arthritis; HLA: Human leukocyte antigen; IL: Interleukin; PTPN22: Protein tyrosine phosphatase, nonreceptor type 22; TRAF1: Tumor necrosis factor receptor associated factor 1.

been tested for ACPA antibodies, RF and HLA-DR genotype, and the results showed a correlation between the presence of RF and ACPA antibodies within the HLA-DRB1 SE[3,7]. Moreover, current smoking habits and SE, especially homozygous SE, have a strong interaction[3,8]. SE is a risk factor for the development of an extra-articular manifestation and so for more severe, destructive RA. However, the non-SE alleles DRB1*1301, *1302 and *1304 seem to be linked to the DERAA motif[9-11]. The study in Hungarian RA patients recommended that HLA-DRB *1301 allele may protect against ACPA positive or ACPA negative RA[9,12-15]. Also, enhanced production of ACPA has been connected with HLA-DRB1*15 positively in RA[9,16-18]. In a Korean population, heterozygous for HLADRB1 0404 or 0901 have up to a 60-fold increased risk of developing susceptibility to RA[19].

A new taxonomy system for the risk of developing RA has been proposed[9,11]. This new classification depends on whether the RAA (motif which represents susceptibility risk of RA) sequence occupies position 71-74 of HLA-DRB1 but is modulated by amino acids at positions 70; glutamine (Q) and arginine (R) represent a higher risk than aspartic acid (D). Lysine (K) confers the highest risk, arginine (R) intermediate risk and the lowest risk is for alanine (A) and glutamic acid (E) in position 71. According to this new classification, SE alleles are divided into S1, S2, S3P and S3D groups and allele X which denotes all non-RAA motifs. The presence of S2 and S3P alleles are a positive association with RA and also correlated with ACPA production, while S1, S3D and X were found to be low risk alleles[9,11,20].

Genome wide association studies (GWAS), large scale cohorts and Wellcome Trust Case Control Consortium databases have allowed the simultaneous evaluation of thousands of genes[9,21-23] and drawn attention to association with RA susceptibility, determining the phenotype of the disease, and response to therapy. Additional variants in the MHC contribute to the heritability of RA independently of the HLA-DRB1, leading to more consequent results of genetic associations. Alleles associated with the susceptibility with RA according to the GWAS study are shown in Table 1. Loci outside the MHC have been associated in a RA population in approximately 4% to the phenotypic variance of RA risk. One of them is peptidyl arginine deiminase, type Ⅳ (PADI4) encoding peptidylarginine deiminase type Ⅳ.

### *PADI4*

One of the isoenzymes carrying the post-translational conversion of arginine residues to citrulline is known as the type 4 peptidylarginine deiminase type Ⅳ. PADI4 enzyme may be connected to the production of ACPA. PADI4 is present in bone marrow and peripheral blood leukocytes and is one of the four isoforms of PADI enzyme in humans encoded by the *PADI4* gene[3,24]. *PADI4* gene maps on 1p36 locus have been associated with European and Japanese RA populations. A meta-analysis done by Lee *et al*[25] showed that in Asian patients, all 5 researched polymorphisms (PADI4_89, PADI4_90, PADI4_93, PADI4_94 and PADI4_104) were significantly associated with RA, while in Europeans only PADI4_94 was associated with RA risk, much less than in Asian patients[26,27]. The function of this gene in the European RA population is still questionable as the results of large studies from Spain, France and the UK found no association with RA[3,28,29].

Within the genes investigated for susceptibility to RA, protein tyrosine phosphatase type 22 (PTN22) is one of the most strongly associated.

### *Protein tyrosine phosphatase, nonreceptor type 22*

Protein tyrosine phosphatase, nonreceptor type 22 (PTPN22) encodes the intracellular tyrosine phosphatase LYP, known as a powerful inhibitor of T-cell activation. The gene encoding PTPN22 shows the second strongest (just after HLA-DRB1) association with RA. The gene was first associated with type 1 diabetes, systemic sclerosis, Graves disease and lupus erythematosus. Then it was associated with RA in a Caucasian population; rs2476601, C1885T polymorphism leading to an amino acid modification from Arg to Trp at amino acid position 620. This polymorphism resides in a rather large haplotype block encompassing the entire PTPN22 gene[3,30-32]. This SNP has been associated with RF, ACPA positive and SE. ACPA status powerfully supports the early diagnosis of RA. It is worth mentioning that in contrast to SE, C1885T polymorphism may not be associated with smoking[9,33-35]. The important fact is that this polymorphism is not associated with RA in Asian populations, maybe only with Asiatic Indians with RA positive[36].

### *Signal transducer and activator of transcription 4*

The signal transducer and activator of transcription 4 (STAT4) is a transcription factor that intercedes the intracellular signal activation by cytokines such IL-12, IL-23 and IL-27 and type I interferons. STAT4 can be induced

upon activation and maturation of monocytes as well as immature dendritic cells. STAT is also overexpressed in RA synovium. Lee *et al*[37] and Amos *et al*[38] detected linkage at chromosome 2q33 in RA and then revealed that the polymorphism located at 2q33 STAT4 gene is the marker responsible for the linkage signal in 2q33. It has been found that STAT4 rs7574865 polymorphism is associated with European, Asian and Latin American RA patients[37,39-43]. Comparison between ACPA positive and negative patients showed no significant differences[37]. It seems that the intronic variant rs11893432 C/G of *STAT4* gene could also predispose to RA[26,44].

### Cytotoxic T lymphocyte-associated antigen 4

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is expressed on T cells, is a member of the immunoglobulin superfamily and performs a critical role in the inhibition of T-cell activation and peripheral tolerance. Three polymorphisms have been described in the *CTLA-4* gene: first, microsatellite at position 642 of the 3' untranslated region of exon 4; second, the polymorphism 49G/A in exon 1 causes a threonine to the alanine substitution of amino acid 17; and the third, -318 of the promoter sequence C/T transition[45]. The CT60 allele has been associated with autoimmune diseases. In the end, CTLA-4 export to the membrane reduces and decreases the inhibitory function of CTLA-4. CTLA4 increased the development of ACPA positive RA in contrast to RA patients with ACPA negative. The meta-analysis showed a positive connection of 49A/G polymorphism susceptibility with RA in Asians, but only 1 in Asians and Europeans[3,46-48]. However, the exact role of this gene in RA is quite modest and still must be clarified.

### TRAF1-C5

Two biological candidate genes, TNF receptor associated factor 1 (TRAF1) and complement component 5 (C5), were described by GWAS. TRAF1 is a member of the TNF receptor associated factor family, which are a class of proteins that link TNF receptor family members associated with signaling pathways that play a function in apoptosis, cell proliferation and differentiation, activation and inhibition cytokines and bone remodeling. The most strongly associated SNPs are rs3761847 and rs10818488 in the genome. It seems that the maximal genetic signal is located between the TRAF1 and C5 gene[39,49].

### TNF

TNF alpha is a pleiotropic inflammatory cytokine. TNF-308A/G (rs1800629) polymorphism is associated with RA in the Latin American population[26,50] but not in any other ethnic group. Also, the TNF promoter polymorphism -609G/T and -238A/G are not associated with RA[45]. TNF-308A/G polymorphism was associated with radiological damage in a RA patient. Khanna *et al*[51] showed that patients with -308 TNF alpha AA+AG genotypes had considerably higher rates of progression in erosion scores and Sharp scores equal to the GG genotype patients. In contrast, Lacki *et al*[52] suggest that TNF-308 polymorphism cannot serve as an indicator of the disease course in RA patients.

## INTERLEUKIN

Interleukins are a large part of cytokines which promote the development and differentiation of lymphocytes T, B and hematopoietic cells. In RA patients, SNPs of cytokines have been investigated regarding an association with erosive damage. One of them is IL-1. Polymorphism -511A/G (rs16944) in promoter IL-1b was positively associated with RA. +3954T allele was associated with more severe structural damage (mainly with Larsen's score in wrist joints)[3,53,54]. IL-6 is a multifunctional cytokine implied in the inflammatory and immune response. Some studies reported that -174G/C (rs1800795) allele was associated with radiological damage in RA patients who were ACPA and RF positive[55]. The presence of two functional polymorphisms in the promoter region of IL-6, the -174G/C and -572G/C, suggests a strong susceptibility for European RA patients compared to Asians. These two polymorphisms (rs1800795 and rs1800795) may also influence the risk of osteoporosis. Another multifunctional cytokine is IL-10, produced by monocytes and lymphocytes, a protein that inhibits the synthesis of a number of cytokines and has a range of anti-inflammatory and immunoregulatory properties. Three polymorphisms placed in the promoter IL-10 were studied, including -1082G/A (rs 1800896), -892C/T (rs1800871) and -592C/A (rs1800872). The results are controversial as one showed that -1082G/A polymorphism is not associated with RA of either European or Asian populations and the other showed a positive association with RA, indicating that the carriers of the G allele could have a decreased liability of RA[26,56]. Some studies reported that the homozygosity of -592C/A was associated with higher Larsen scores in RA patients with ACPA and RF negative[55]. Polymorphisms of the *IL-2* and *IL-21* genes (region 4q27) have been implicated in several autoimmune diseases, including RA. One of them is intronic change A/G rs13151961[57]. Next studied were polymorphisms in RA susceptibility which may modulate gene expression of IL-2 or IL-21 located in the noncoding region, upstream of IL-21 and downstream of IL-2 is the G/T rs6822844. In a study on European Caucasian and South American populations, significant association with RA was shown[26,58,59].

With the use of GWAS, genetic studies can examine many common genetic variants across the entire human genome. There are a lot of other gene and chromosome loci revalidated as RA susceptible regions, such as CD226, CD40, CDK6, MBP, BLK, REL and more[60].

In conclusion, rheumatoid arthritis has a strong genetic influence mediated by alleles. Human genetics should be able to determine the value of RA risk alleles by providing clinical predictions. One of the most direct clinical applications is to use human genetics to lead the development of treatment for RA. It will be crucial to determine whether a combination of RA risk alleles are

able to identify patients who develop certain clinical outcomes, such as myocardium infarction, severe infection or lymphoma, as well as to identify the patients who will respond to biological medication therapy.

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RANDOMIZED CONTROLLED TRIAL

# Donor's site evaluation after restoration with autografts or synthetic plugs in rabbits

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## Abstract

**AIM:** To investigate donor site's area histological and immunohistochemical knee cartilage appearances after resurfacing iatrogenic defects with biosynthetic plugs orautografts.

**METHODS:** Thirty New Zealand White rabbits were used in this study. A full-thickness cylindrical defect of 4.5 mm (diameter) × 7 mm (depth) was created with a hand drill in the femoral groove of every animal. In Group A ($n$ = 10) the defect of the donor site was repaired with a biosynthetic osteochondral plug, in Group B ($n$ = 10) with an osteochondral autograft, while in Group C (control group of 10) rabbits were left untreated.

**RESULTS:** Twenty-four weeks postoperatively, smooth articular cartilage was found macroscopically in some trocleas' surfaces; in all others, an articular surface with discontinuities was observed. Twenty-eight out of 30 animals were found with predominantly viable chondrocytes leaving the remaining two -which were found only in the control group- with partially viable chondrocytes. However, histology revealed many statistical differences between the groups as far as the International Cartilage Repair Society (ICRS) categories are concerned. Immunofluoresence also revealed the presence of collagen Ⅱ in all specimens of Group B, whereas in Group A collagen Ⅱ was found in less specimens. In Group C collagen Ⅱ was not found.

**CONCLUSION:** The matrix, cell distribution, subchondral bone and cartilage mineralization ICRS categories showed statistically differences between the three groups. Group A was second, while group B received the best scores; the control group got the worst ICRS scores in these categories. So, the donor site area, when repairing osteochondral lesions with autografting systems, is better amended with osteochondral autograft rather than bone graft substitute implant.

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**Key words:** Autografts; Synthetic plug; Osteochondral defects; Rabbit model; animal study; Donor site; Immunofluoresence; Histological evaluation; International Cartilage Repair Society score

**Core tip:** The donor site during the autografting process or during synthetic plugging when dealing with osteochondral defects is usually not well evaluated or addressed. This is an innovative original article, in which

the donor site is repaired with autografts or synthetic plugs and after 24 wk it is histologically and immunohistochemically evaluated and compared.

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## INTRODUCTION

Many different methods have been documented in literature, trying to restore articular cartilage. In the 1950's, the first attempts were made to restore articular cartilage using skin. Even though since then, much progress has been made[1-6], there is still lacking evidence in how to best manage these lesions. The avascular and denervated environment, the immobility of chondrocytes and the limited ability of mature chondrocytes to proliferate, are considered as the main reasons that obstruct intrinsic articular regeneration[7-9].

An abundance of surgical techniques, each with their advantages and disadvantages, have been developed in order to repair articular cartilage defects. The choice of treatment usually depends on the surgeon's preference and the size of the lesion. The current treatments include: (1) palliative (debridement), marrow stimulating techniques (microfractures, drilling, abrasion) and transfer of osteochondral unit (autograft or allograft) for lesions up to 2.5 $cm^2$; and (2) for lesions bigger than 2.5 $cm^2$, use of chondrogenic potential cells (autologous chondrocyte implantation) and osteochondral allografts[10].

Increasing interest appears in one-time surgery techniques as they provide shorter recovery time, with the transfer of an entire osteochondral autograft being the most appealing[2-6,9,11]. Autografting represents a reasonable solution for osteochondral defects. In the most widespread system of mosaicplasty, an osteochondral cylindrical graft is received from a healthy region (donor site) and after appropriate preparation of the osteochondral defect region with special instrumentation, it is inserted in the recipient site (osteochondral defect). The donor site, depending on the surgeon's preference remains uncovered, is covered with biosynthetic implant or is covered with the autograft been taken from the defect region.

To date, the histological faith of the donor site remains unanswered. No consensus exists regarding the best approach to achieve optimal results[4-6,9,12]. The donor site, could be a major source of pain. Nonetheless, it is underestimated because all surgeons and all reports focus on the damaged area. We performed a controlled laboratory animal study in order to find an answer about the faith of the donor site region. In order to identify the method which achieves the best outcomes for the International Cartilage Repair Society (ICRS) scoring system, and which ends up expressing more collagen of type Ⅱ (marking the presence of hyaline cartilage) we used a rabbit model[13] where the same standardized cartilage defect was treated with three different options; bone graft substitute (BGS) plug, osteochondral autograft transplantation and conservative approach. Our null hypothesis was that there would be no significant difference between the control, the OA and the BGS group. $P$ value < 0.05 was deemed to indicate statistical significance.

## MATERIALS AND METHODS

The following controlled laboratory study was approved by the local veterinarian department and the scientific committee of our University's laboratory. Thirty male, New Zealand White rabbits, which were 3 mo old and had a mean weight of 3.8 kg (range, 3.5 to 4 kg) were used in this study. Under moderate sedation we administrated Ⅳ ketamine to achieve general anesthesia according to a previously published protocol[14]. The rabbits were placed in the supine position and have had their right leg shaved and sterilized. A 4-cm medial parapatellar arthrotomy was made and the patella was dislocated laterally. Thus, the femoral condyles and groove were exposed. The region of the femoral groove, which contacted with the patella when the knee was flexed at 90°, was selected as the site for the osteochondral defect[15]. A full thickness osteochondral defect, using the smallest instrument of the provider (Smith and Nephew, Memphis, Tennessee) was made using a hand drill, leading to a defect of 4.5 mm in diameter and 7 mm depth. The defect was then carefully debrided of any cartilaginous remnants and was dilated with a 5 mm dilator, at the same time the bottom of the defect was flattened under the slight load of the dilator. During the drilling process, the depth was checked continuously for an accurate depth of 7 mm. All implants were inserted press-fit without any additional fixation or glue. The rabbits were divided into 3 groups (10 per group) depending on the treatment method used for cartilage repair, In group A, the defect was reconstructed using the Smith and Nephew's *TruFit* (Memphis, Tennessee) BGS (Bone Graft Substitute) plug of 5 mm in diameter and of 7 mm height, which is a composite material of polylactide-co-glycolide, calcium sulfate and polyglycolide fibers. Special attention was paid in order to apply the graft equally to the host cartilage surface, following the specific guidelines of the manufacturer. In group B, an osteochondral autograft (OA), 5 mm in diameter and of 7 mm height, harvested from an area above the recipient site of the same femoral groove was used to restore the cartilage lesion[5,9], following the "mosaicplasty" surgical technique initially described by Hangody *et al*[16]. The donor area was selected in a manner that a minimum critical space of 3 mm was left between the host and the donor area. The region of the donor site of this group had had its cartilage disrupted and destroyed with a curette before harvesting. This was done in order to mimic the unhealthy cartilage seen when osteochondral autograft transfer system (OATS) is performed. In the control

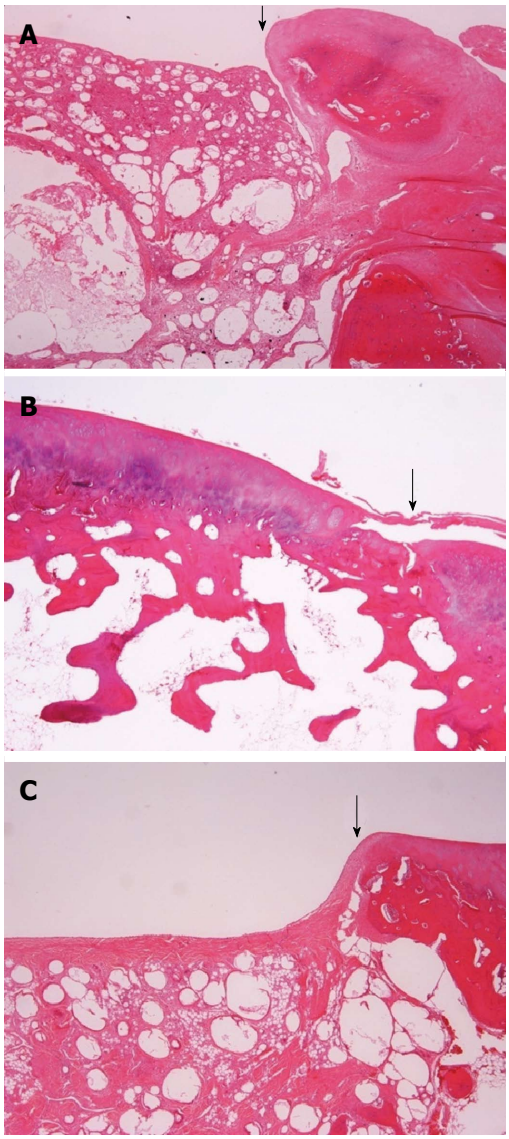


**Figure 1 Group.** A: Group A. The black arrow marks the junction between the host- on the right- and the transplanted cartilage on the left. The surface is irregular. No hyaline cartilage is produced. A foreign body reaction to the BGS is observed (HE, × 200); B: Group B. The black arrow marks the junction between the host- on the right- and the transplanted cartilage on the left. The surface is smooth. Hyaline cartilage is observed (HE, × 200); C: Control group. The black arrow marks the junction between the host- on the right- and the transplanted cartilage on the left. The surface is smooth but not even. The defect is repaired with fibrous tissue. No hyaline cartilage is observed (HE, × 200).

group (group C) the defect was left untreated.

The capsule was closed with simple interrupted sutures (3-0 absorbable), followed by skin closure with a running subcuticular suture (4-0 absorbable). All rabbits underwent a perioperative course of enterofloxin, with post-operative pain control using aspirin. All surgical procedures were made by the same surgeon.

### *Macroscopic/Histological evaluation*

All evaluations were made by the same assessor, who was blind to the procedure used in each specimen. After 24 wk the animals were sacrificed using a lethal dose of phenobarbital IV injection under general anesthesia, which was achieved using the protocol of the surgery[4,14]. The type and degree of integration of reparative tissue were evaluated. Joint surfaces were grossly examined (Figure 1). Repair tissue was assessed macroscopically according to the ICRS recommendations[7]. ICRS Visual Histologic Assessment Scale is used to histologically evaluate the repaired lesions[18,19]. For macroscopic assessment 3 main characteristics are evaluated: (1) the defect depth compared with the surrounding cartilage (control group) and the survival of the initially grafted surface (BGS plug and the autograft); (2) the integration of the repaired tissue to the border zone (size of the gap); and (3) the macroscopic appearance of the repair tissue surface (smooth, fissured, degenerated, *etc.*).

After macroscopic evaluation distal thirds of all femurs were removed and placed for 2 d in 10% neutral buffered formalin. Specimens were decalcified and followed the routine procedure of dehydration of tissues and were embedded in paraffin. 1.5 μm thickness sections were stained for hematoxylin and eosin stain (H and E). The histochemical stains (Toluidine Blue and Wan-Giesson) as well as immunohistostaining with antibodies against collagen type Ⅱ (Dako A/S, Denmark) were performed, as long as the extend of collagen type Ⅱ in cartilage is considered a marker of degree of differentiation towards hyaline cartilage[12,18-20]. Each H and E sample took a score according to the ICRS scoring system[7,18] (Table 1). A total of 30 knees underwent histological evaluation.

### *Statistical analysis*

Data were analyzed using SPSS ver.16. Histological grading scores were analyzed statistically using the Kruskal-Wallis and the Mann-Whitney test. Categorical variables (surface and cartilage mineralization) were analyzed using the $\chi^2$ test.

## RESULTS

Twenty-four weeks after surgery the rabbits were sacrificed and the repaired site was examined macroscopically, histologically and immunohistochemically for an overall assessment, of whether bone graft substitute is better graft than the autograft. All rabbits were left free to move in their cages postoperatively. No evidence of postoperative infection at the wound site was observed, and all wounds healed uneventfully. No rabbit died before the scheduled sacrifice time.

### *Macroscopic findings*

In group A, the grafted areas were well recognized with distinct margins and a reddish appearance. The surface was opaque, almost smooth and seemed well incorporated with the surrounding, healthy cartilage. The BGS plug was even with the host articular surface (Figure 1A). In group B, femurs the margins between the host and the repaired tissue were not easily discerned. The grafted area had a light yellow, smooth, continuous surface (Figure 1B). In group C, the defects sites seemed to be filled with

**Table 1 Mean international cartilage repair society scores per category and standard deviation of all groups**

| | BGS group | OA group | Control group |
|---|---|---|---|
| Surface (0,3) | 1.2 ± 1.55 | 1.5 ± 1.58 | 0.9 ± 1.45 |
| Matrix (0-3) | 1.6 ± 1.35 | 3 | 0.7 ± 0.67 |
| Cell distribution (0-3) | 0.7 ± 0.82 | 2 | 0.1 ± 0.32 |
| Cell viability (0,1,3) | 3 | 3 | 2.6 ± 0.84 |
| Subchondral bone (0-3) | 1.4 ± 0.84 | 2 | 0.9 ± 1.19 |
| Cartilage mineralization (0,3) | 1.2 ± 1.55 | 3 | 0.6 ± 1.26 |

The mean scores are presented in bolt letters, while the standard deviation in simple ones. BGS: Biosynthetic graft substitute. OA: Osteochondral autograft.

**Table 2 The presence of collagen type Ⅱ is verified or not with the antibodies for collagen type Ⅱ**

| | Presence of collagen Ⅱ | | Presence of collagen Ⅱ | | Presence of collagen Ⅱ |
|---|---|---|---|---|---|
| A1 | Yes | B1 | Yes | C1 | No |
| A2 | No | B2 | Yes | C2 | No |
| A3 | Yes | B3 | Yes | C3 | No |
| A4 | No | B4 | Yes | C4 | No |
| A5 | No | B5 | Yes | C5 | Yes |
| A6 | Yes | B6 | Yes | C6 | No |
| A7 | Yes | B7 | Yes | C7 | No |
| A8 | Yes | B8 | Yes | C8 | No |
| A9 | No | B9 | Yes | C9 | No |
| A10 | Yes | B10 | Yes | C10 | No |

white to reddish, soft, irregular tissue. This repair tissue almost filled the defects, which were grossly distinguishable from the surrounding tissue and had irregular surfaces (Figure 1C). No apparent synovitis and no degenerative changes on the opposing articular surfaces in either the tibiofemoral or patellofemoral joints were observed in any of the three groups.

### *Histological/immunohistochemical evaluation and statistical results*

The mean scores of each group for each ICRS category are summarized in Table 1. Immunohistostain evaluation with collagen type Ⅱ antibodies can be seen in Table 2. Significant differences were found between the groups for the ICRS categories of matrix, cell distribution and subchondral bone (Table 3). Furthermore, there was significant difference in the mineralization category (Table 3). No significant difference was found between the three groups for the surface and viability ICRS categories.

Significant difference was found in the ICRS categories matrix, cell distribution, and subchondral bone between the OA and BGS group, with the OA group showing much improved healing. Comparing the OA and the control group significant differences were also found in the same ICRS categories; the OA got better outcome measures than the control group. In the comparison between the BGS and the control group significant difference was observed only in the cell distribution category, with the BGS group receiving a better score.

Utilizing the $\chi^2$ test in order to make the same three comparisons (group A *vs* group B, the A *vs* the control group and the B *vs* the control group) no significant difference was noted as far as the surface category is concerned. No significant difference was observed when comparing all three groups per two for the cell viability category, as well (Table 3).

**Table 3 *P* values for each pair of groups' comparison separately**

| | BGS *vs* OA group | BGS *vs* control group | OA *vs* control group |
|---|---|---|---|
| Surface | 0.653[1] | 0.639[1] | 0.361[1] |
| Matrix | 0.005 | 0.142 | 0 |
| Cell distribution | 0.001 | 0.049 | 0 |
| Cell viability | 1 | 0.146 | 0.146 |
| Subchondral bone | 0.03 | 0.285 | 0.024 |
| Cartilage mineralization | 0.03[1] | 0.329[1] | 0.000[1] |

[1]These *P* values are calculated using the $\chi^2$ test, while the others with Kruskal-Wallis or Mann-Whitney test. $P < 0.05$ was statistically significant. OA: Osteochondral autograft; BGS: Bone graft substitute.

## DISCUSSION

A lot of basic research in articular cartilage repair has been conducted[16,21,22]. The purpose of this study was to evaluate and compare three options when restoring osteochondral defects with OATS (mosaicplasty) in a rabbit model. We used an animal model, which underwent repair of an osteochondral lesion, created by a hand drill, with specified diameter and depth. It is known that cartilage defects smaller than 4 mm tend to heal spontaneously into cartilage in the rabbit model[23]. In order to prevent spontaneous healing, we designed a protocol which included a larger defect. With an exact-fit plug of prespecified measurements, but different composition (OA or BGS) we repaired the site, or left it without intervening (control group). The patella, tibial plateau and menisci did not show any increased degenerative changes as a result of articulating against the donor or recipient sites of the osteochondral grafts a finding which comes in agreement with the Lane *et al*[5] findings. Our transplanted grafts had a similar gross macroscopic appearance at the sacrifice time as the one 24 wk before; an observation stated by Lane *et al*[5], though for a shorter period of time (12 wk). We managed to successfully transfer an osteochondral plug with maintenance of cellular viability which was also recorded by Lane *et al*[5] in the goat model 12 wk post-operatevely.

The underlying subchondral bone appeared to undergo a routine fracture healing, while the superficial cartilage layer appeared to interdigitate with the host cartilage. Lane *et al*[5] stated the presence of a cleft between the host and the transplanted cartilage in the goat model 12 wk post-operatevely, while Nam *et al*[9] in the rabbit model found that the interdigitation of the cartilage is not in all sides of the chondral part 12 wk post-operatevely. Nakaji *et al*[24] report a fracture healing process after the implantation of the graft with "improvement of the continuity of the articular

cartilage surface after the 12th week, which is then almost as normal". Makino *et al*[6] reported full embedding of the autograft in the rabbit model 24 wk post-operatively; an observation which comes in agreement with our findings.

In group B, we noticed subchondral bone healing with excellent trabecular interdigitation with the host bone, something that has been published before by Lane *et al*[5] and Nam *et al*[9]. We did not notice any difference on the thickness of the chondral part of the graft, compared to the host cartilage. It is well known that as the cartilage matures it becomes thinner and the number of cells decreases[25,26]. Makino *et al*[15] reported an increase of the thickness of the chondral part of the graft 24 wk post-operatevely, when - due to their technique- the implanted graft was slightly undersized of the host lesion. When they used slightly oversized graft they did not notice any thickness differences. It can be assumed that the initial stability of the graft was obtained because the size of the graft was slightly larger than the created defect. It should be pointed out that our donor site has less thickness cartilage. Thus, a stable graft changes its biomechanical properties in order to meet the loading needs of the area that it is transplanted to. Consequently, the graft is adapted to the biomechanical properties of the host cartilage.

The quality of the healing response of the control group was not good. The defect was clearly different from the surrounding cartilage, had a white to red-brownish appearance, was softer in palpation and had irregular surface. This observation comes in agreement with previously published data[9,15]. The host surrounding cartilage maintained its normal structure 24 wk post-operatively, something stated by Nam *et al*[9] (12 wk post-op), Lane *et al*[5] (12 wk post-op) and Makino *et al*[6,15] (12 and 24 wk post-op) also.

The articular surface 24 wk post-operatively presented with no significant difference between the three groups, as far the smoothness is concerned. Thus, it has been clearly shown that the congruity of the articular surface can be preserved excellently if the plug is perfectly grafted to the defect. However, the histological examination of the repaired site revealed differences between the three groups. The ICRS categories of matrix, cell distribution, subchondral bone and mineralization had significant differences, with the group B receiving the best scores, group A being second and the control group getting the worst ICRS scores in these categories. The absence of significant difference when comparing the three groups, as far as the surface category and the cell viability are concerned, states that the good macroscopic appearance of the repaired site and the viability of the graft do not imply an equally histologically and immunochemically healthy graft.

This study has provided some new data and insights but also has some limitations. One limitation concerns the rabbit model. It is not an entirely suitable animal model to study articular cartilage repair procedures in preclinical studies. Hunziker noted that "the matrix domain sustained and remodeled by an individual cellular unit is, in the human, approximately 8 to 10 times larger than that in the rabbit"[27]. It likely would lead to substantial enhancement in the rabbit to maintain surrounding cartilage compared to the human. Nevertheless, the rabbit is probably the most often used model for economic reasons and the literature contains interpretations based on rabbit data. Although we believe our rabbit model represents the clinical situation, cartilage repair procedures using this model should still be interpreted with caution before proceeding to clinical studies and conclusions.

Another limitation is that the defects were located on the trochlear of the rabbits. The trochlear were selected in order for us to have the critical space to create a 5 mm cylindrical defect. The patellofemoral joints of rabbits have some degree of compressive force because the rabbit knees are always in the flexed position. However, no direct weight bearing appears in the patellofemoral joint. To find animal knees that resemble the human knee in terms of biomechanics, we would have to use bigger experimental animals. Also, when autografting our animal model suggests an osteochondral repair with an autograft that has been iatrogenically destroyed, whereas in clinical practice the defect from the donor site (which actually is the recipient site of the healthy osteochondral graft) is degenerative most of the times.

Previous studies report no degeneration of the grafted autologous osteochondral graft in 12 wk[9]. We saw no degeneration of the graft in 24 wk either, an observation that agrees with previous reports for other experimental animals in the literature[4,6]. Further investigation concerning the histological, mechanical and immunohistochemical properties of grafted cartilage needs to be done to verify the longer effects of OA and BGS transplantation, bearing always in mind that in the clinical situation a transplanted knee with osteochondral problems continues to improve even after 6 mo post-operatively.

In a conclusion, we repaired full-thickness defects with three different ways. We compared the results per two, showing that outcomes of the OA graft were significantly better than those reported with the BGS, which in turn was significantly better than the control group, shooting this way down our initial hypothesis. Therefore, the donor site in mosaicplasty technique is better amended with osteochondral autograft rather than with BGS implants. Choice of procedure lies upon donor size morbidity, lesion's size, quality and viability of the present cartilage, knee's overall evaluation (possible meniscal lesions, rupture of ACL, *etc.*) and surgeon's preference. Other strategies as well are under investigation, that deserve our attention and more thorough experimental studies[28,29].

## ACKNOWLEDGMENTS

The current experimental work took place in the Laboratory for Research of the Musculoskeletal System, University of Athens, KAT Hospital, Maroussi, 14561, Athens.

## COMMENTS

### Background

Autografting is a well known option as far as resurfacing osteochondral defects

is concerned. Usually the donor site when not left empty, is covered with an autograft or a biosynthetic plug. The donor site area, though a possible source of postsurgical pain, is not well investigated.

### Research frontiers

There are controversial publications in the area. Everybody agrees about the fate of the autografts (inferior than hyaline cartilage) but the fate of the synthetic plugs is not universally agreed. Depending on the post-surgery time and on the publication, synthetic plugs appear in the literature with hyaline-like cartilage to fibrous tissue.

### Innovations and breakthroughs

This is the first study to the knowledge that deals with the donor site area of the autografting procedure.

### Applications

This study proves that the donor site area is better amended with autografts than synthetic plugs. So, when available, an autograft-though its surface injured- could be used for the donor site area.

### Terminology

ICRS score: International Cartilage Repair Society scoring system, which evaluates and scores cartilage appearences in the microscope. BGS: Biosynthetic Graft Substitute.

### Peer review

This is an excellent study evaluating 2 different methods of repairing the donor site following knee cartilage resurfacing. The authors concluded that the donor site in mosaicplasty technique is better amended with osteochondral autograft rather than with BGS implants. The manuscript is well written and easy to follow.

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*INSTRUCTIONS TO AUTHORS*

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*No author given*
6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

*Volume with supplement*
7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

*No volume or issue*
9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

**Books**
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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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**Electronic journal** (list all authors)
15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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