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EDITORIAL

# Induced pluripotent stem cells in cartilage repair

Steven A Lietman

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## Abstract

Articular cartilage repair techniques are challenging. Human embryonic stem cells and induced pluripotent stem cells (iPSCs) theoretically provide an unlimited number of specialized cells which could be used in articular cartilage repair. However thus far chondrocytes from iPSCs have been created primarily by viral transfection and with the use of cocultured feeder cells. In addition chondrocytes derived from iPSCs have usually been formed in condensed cell bodies (resembling embryoid bodies) that then require dissolution with consequent substantial loss of cell viability and phenotype. All of these current techniques used to derive chondrocytes from iPSCs are problematic but solutions to these problems are on the horizon. These solutions will make iPSCs a viable alternative for articular cartilage repair in the near future.

**Key words:** Induced pluripotent stem cells; Articular cartilage; Cartilage repair; Stem cells

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**Core tip:** Herein we review the challenges in articular cartilage repair. Further we explain that induced pluripotent stem cells (iPSCs) represent an exciting theoretically limitless source of autologous cells for articular cartilage repair. We also discuss a novel systematic approach to optimally derive articular chondrocytes from iPSCs.

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## INTRODUCTION

Nearly 1 in 2 people develop symptomatic knee osteoarthritis (OA) by age 85 years, two in three people who are obese develop symptomatic knee OA in their lifetime[1], and 1 in 4 people develop painful hip arthritis in their lifetime[2]. Over 30 million Americans suffer from arthritis and other rheumatic conditions that affect joint and connective tissue; and by 2030 nearly 25% of the American

population is expected to be affected by such conditions[3]. Joint Replacement.

Perhaps as a result or as a testament to the inability of articular cartilage to heal, knee replacement is now the most common elective surgery in the United States (Figure 1). Knee replacement though is not appropriate for young patients as it only lasts for an average of 15 years[4] so alternative cellular treatments for osteoarthritis have been sought.

Articular cartilage is made up of cells (5%) with extracellular matrix and water (95%)[5]. Articular chondrocytes express high levels of COL2A1, SOX9 and AGGRECAN[6]. Endogenous attempts at cartilage repair are ineffective in composition (primarily creating fibrocartilage with type Ⅰ rather than type Ⅱ collagen) and the reparative tissue does not provide durable healing to the adjacent normal cartilage Figure 1[6]. During embryonic cartilage formation, mesenchymal condensation is the prerequisite for the induction of chondrogenesis. Initiation of limb development starts with the lateral plate mesodermal cells, which proliferate, aggregate and form mesenchymal condensations[7]. These primordial cells differentiate into chondrocytes and form cartilage anlagen[7-10].

One major limitation when studying primary chondrocytes in culture is their loss of phenotype[11]. Research in cell-based cartilage tissue engineering has focused on identifying a cell source suitable for regenerating cartilage. Mesenchymal stem cells (MSCs) would seem to be well suited for tissue engineering and are multipotent cells able to differentiate into chondrocytes, osteoblasts, adipocytes and myocytes[12-15]. However, even though MSCs can be easily obtained from bone marrow, fat and skin, these primary cells have limited proliferation capacity when cultured *in vitro* and relatively low numbers of MSCs are capable of chondrocyte differentiation[16-21]. Autologous chondrocytes and MSCs have still been used in regeneration of articular cartilage[22-24]. However there are limitations in terms of the ability of adult differentiated chondrocytes to heal a cartilage defect, the numbers of cells that can be obtained using these autologous cells due to their obscurity, and due to the limited maintenance of their phenotype with cell division[16]. The only exception to the inability of a cartilage defect to heal effectively and seamlessly appears to be in a fetal lamb model in which partial thickness articular cartilage defects did heal to subsequently normal appearing cartilage[25].

As a result our group and others have become interested in the use of induced pluripotent stem cells (iPSCs) that can be derived from a patient skin biopsy, transformed into iPSCs and then into articular chondrocytes with theoretically large numbers of cells without the concerns of disease transmission from allogeneic cell transfer. In this review we will discuss the current status and recent progress in the development of articular chondrocytes from iPSCs.

## DEVELOPMENT OF IPSCS

Many attempts have been made in the last decade to obtain various MSCs, derived from iPSCs, in ample quantity and high purity after differentiation *in vitro*[26-33]; and the International Society for Cellular Therapy has defined three primary criteria for cells to meet the definition of MSCs. First, MSCs must be plastic-adherent when maintained in standard culture conditions. Second, MSCs must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14, CD11b, CD79alpha or CD19 and HLA-DR surface molecules. Third, MSCs must be able to differentiate into osteoblasts, adipocytes and chondrogenic cells *in vitro*[34]. In the past, undifferentiated iPSCs have contaminated the differentiated population of MSCs, and they can contribute to teratoma tumor formation; and a uniformly differentiated cell population is necessary for clinical use[35]. iPSCs were developed by Yamanaka by taking differentiated cells and reprogramming them to an embryonic-like state by transfer of nuclear contents into oocytes or by fusion with cells. Specifically he demonstrated induction of pluripotent stem cells from mouse adult fibroblasts by introducing four factors, Oct3/4, Sox2, c-Myc, and Klf4, under ES cell culture conditions[36,37]. These cells, which his group designated iPSCs, exhibit the morphology and growth properties of ES cells and express ES cell marker genes. Subcutaneous transplantation of these iPSCs into nude mice resulted in tumors containing a variety of tissues from all three germ layers. Their work demonstrated that pluripotent stem cells could be directly generated from fibroblast cultures by the addition of only a few defined factors[38].

The fibroblasts used to derive iPSCs can be obtained from a skin punch biopsy done in clinic at the time of patient presentation. iPSCs have the potential to self-renew and differentiate into many adult cell types[39] and represent a theoretically nearly unlimited supply of cells for studying normal cell function and modeling of disease[16,17,27,31,40]. More recent publications have proven the beneficial effect of cells derived from stem cells[41,42]. Stem cell derived cardiomyocytes improve myocardial performance in animal models[42]; and stem cells derived from neuroprogenitor cells lead to regeneration of functional neurons in *in vivo* models[4,43]. Stem cells derived from retinal epithelial cells improve vision in rodents and humans[33,44]. iPSCs, also potentially provide cell sources for the development of regenerative therapy in articular cartilage repair[45-48]. The chondrogenic cells derived from iPSCs are similar to the fetal lamb chondrocytes, (effectively able to repair cartilage) based on their rapid proliferation and ability to make healthy appearing tissue[38,47-51]. iPSCs can also be manipulated to correct genetic defects, a very important consideration for genetically inherited diseases, including RA. Genetic manipulations could indeed allow *de novo* produced articular cells to be resistant to inflammatory stimuli and to produce tissues insensitive to degrading enzymes. Based on these considerations and evidence that human iPSCs can be directed to undergo differentiation into various cell types, iPSCs are currently the best option to develop strategies for tissue repair in articular cartilage.

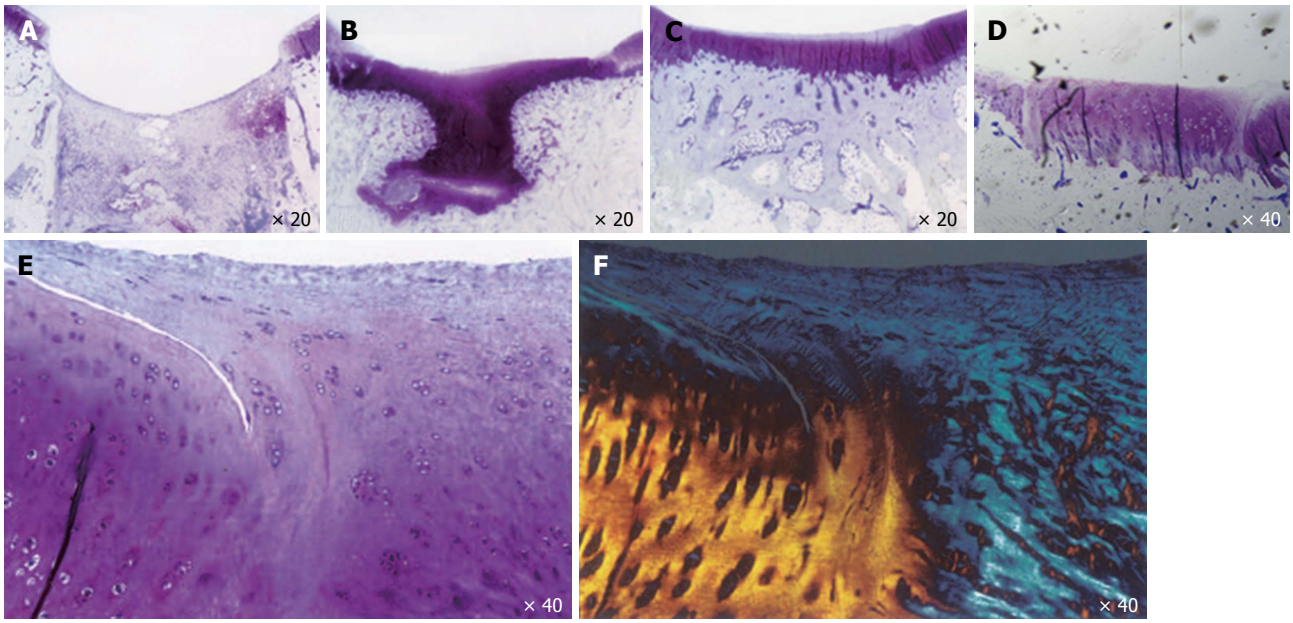


**Figure 1 Articular cartilage healing in a microfracture model in adult rabbits.** Articular cartilage healing at day 7 (A), 21 (B), 42 (C), and day 84 (D-F). E and F: Lack of healing of reparative cartilage to "normal cartilage" is shown by toluidine blue and polarized light micrographs at day 84.

## DEVELOPMENT OF ARTICULAR CHONDROCYTES FROM IPSCS

iPSCs can be derived from a small skin biopsy done with minimal intervention before orthopaedic surgery and can be amplified into virtually limitless amounts of homogeneous cell populations. iPSCs could thus be better than other cell sources to create highly reproducible orthopaedic biologic implants such as for articular cartilage (requiring large amounts of cells). Interestingly, iPSCs apparently produce differentiated cells that exhibit young rather than adult properties, including faster proliferation and creation of healthier, longer-lasting reparative tissues such as the cartilage repair observed in the fetal lamb[25,36,47-50,52-55].

Recent reports have demonstrated the ability to induce differentiation of iPSCs into different lineages (similar to embryogenesis) by using small molecules, cytokines and overexpression of transgenes[40,45,56-62]. There are several existing protocols for generating mesenchymal progenitors or MSCs from ESCs and iPSCs that utilize embryoid bodies and/or co-culture with primary cells[26,29,30,40,46]. These protocols are important steps in developing the use of iPSCs for articular cartilage repair but they have limitations in terms of using either an embryoid body stage or feeder cells which lead to cell heterogeneity or the sue of serum which decreases reproducibility.

Two large groups have had a specific interest in chondrogenic differentiation from iPSCs. Tim Hardingham's group has developed techniques using a number of growth factors to differentiate iPSCs to impressive chondrogenic cells with feeder cells and use fibrin as a control group which we believe actually inhibits *in vivo* cartilage repair[63,64]. Craft *et al*[65] developed a protocol with an embryoid body stage with healing in an *in vivo* model with impressive cartilage formation without an adequate control group. Recently, a third group made chondrogenic cells without the use of feeder cells and do not use an embryoid body stage but at the end of their protocol it is not clear why the cells are in suspension, moreover their toluidine blue staining is not similar to that of the adjacent articular cartilage indicating a difference in the sulfated glycosaminoglycans[30,51,66-69].

## CURRENT CHALLENGES IN THE USE OF IPSCS IN ARTICULAR CARTILAGE REPAIR

Chondrogenic differentiation from iPSCs has been demonstrated by monolayer cell culture and in coculture experiments with primary chondrocytes in 3D culture systems such as condensed cell bodies and pellet cultures, but the necessity of coculture conditions increases the chance of contamination of differentiated cells with feeders or other undesired cells[6,28,70].

A strategy for large-scale production of chondrogenic cells from human ESCs and iPSCs *in vitro* without the use of serum or feeder cells and without the necessity of a condensed cell body step. To aid in the development of an optimal protocol and to avoid the use of feeder cells, serum and the formation of embryoid bodies we plan to use a Quality-by-Design (QbD)-based method similar to that used in the pharmaceutical industry. Specifically the FDA recommends using QbD-based methods to develop new drugs and cell-based treatments for patients[71]. QbD is a systematic approach that utilizes experimental design and statistical methods in order to gain an in-depth understanding of the effects of input parameters

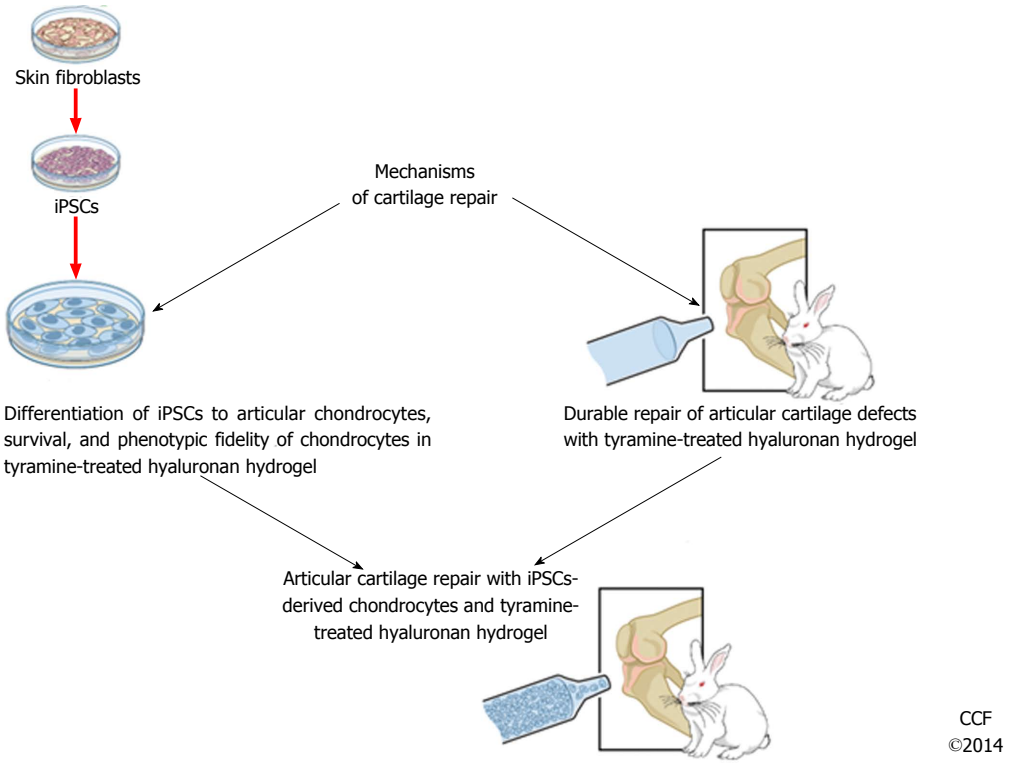


**Figure 2 A broad outline for the use of induced pluripotent stem cells in articular cartilage repair.** iPSCs: Induced pluripotent stem cells.

and obtain optimal results and quality[72]. We have begun to apply QbD by implementing the Design-of-Experiment theory and by combining it with Multivariate Data Analysis will more thoroughly and systematically optimize protocols for chondrocyte differentiation from iPSCs.

## DISCUSSION

One of the main challenges in using iPSCs for either therapeutic applications or *in vitro* modeling is the difficulty in achieving uniform differentiation of the desired cell type. One cause for a lack of uniform differentiation is the use of serum in the differentiation process of cells, which is imprecise due to batch variability and the presence of undefined extracellular factors within serum. The other primary cause for heterogeneity is the use of feeder cells or an embryoid body stage.

Coculture of MSCs with primary chondrocytes to get chondrogenic differentiation has been used to avoid the inconsistent differentiation of primary MSCs in a cartilage regeneration model[73-75]. However coculture is problematic as there are contamination issues when the desired cells need to be separated from the feeder cells as mentioned above[30].

Thus current issues which need to be addressed to further the use of iPSCs in articular cartilage repair and are critically important in cartilage regeneration in an articular cartilage repair model are: (1) Chondrogenic potential and fidelity of the cells; (2) Long term survival of the cells in the repair tissue; (3) Healing to the adjacent endogenous "normal" cartilage in comparison to an adequate untreated control group; and (4) Contamination with (a) undifferentiated cells that form teratomas with embryoid body formation or (b) with feeder cells used in coculture (Figure 2). Despite these hurdles our group and others have preliminary solutions to these issues. Our group believes that a more systematic approach similar to that used in the pharmaceutical industry could add important information to optimize chondrocyte generation from iPSCs with QbD techniques. We predict that the use of iPSCs clinically for cartilage repair holds the most promise to provide a biologic solution for cartilage damage in the near future and that we and others will be able to optimize protocols applicable for clinical use in cartilage repair in the near future.

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EDITORIAL

# Evidence base and future research directions in the management of low back pain

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## Abstract

Low back pain (LBP) is a prevalent and costly condition. Awareness of valid and reliable patient history taking, physical examination and clinical testing is important for diagnostic accuracy. Stratified care which targets treatment to patient subgroups based on key characteristics is reliant upon accurate diagnostics. Models of stratified care that can potentially improve treatment effects include prognostic risk profiling for persistent LBP, likely response to specific treatment based on clinical prediction models or suspected underlying causal mechanisms. The focus of this editorial is to highlight current research status and future directions for LBP diagnostics and stratified care.

**Key words:** Low back pain; Diagnostics; Prognostics; Stratification; Treatment

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**Core tip:** Knowledge of the current research status and future directions for low back pain diagnostics and stratified care is essential to help engage clinicians in evidence based practice and to potentially improve patient management.

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## INTRODUCTION

Low back pain (LBP) is a prevalent and burdensome problem for individuals and society worldwide[1,2]. LBP is often defined in terms of its localization, duration, severity, frequency, and interference on activities of daily living[3]. Most episodes of LBP are self-limiting but approximately 20% develop chronic symptoms[1]. The etiology of LBP is often classified as specific or non-

specific, based upon if a pathoanatomical cause can be identified through objective diagnostic assessment and confirmed by medical imaging[4]. The prevalence of LBP caused by specific pathology of serious nature such as malignancy, spinal fracture, infection, or cauda equine syndrome requiring secondary or tertiary health care has been reported to range between < 1%-4% in the primary health care setting[5,6]. Furthermore, nerve root problems associated with radiculopathy or spinal stenosis are thought to explain approximately 5%-15% of cases[7,8]. Medical imaging studies have highlighted that approximately 50% of younger adults and 90% of older adults have degenerative findings and large variations in lumbar spine morphology[9]. This is however evident in both symptomatic and asymptomatic individuals which renders diagnosis of specific LBP prone to false-positive results. The choice of treatment merely based on benign anatomic impairment or individual clinical assessment techniques with low diagnostic accuracy is controversial and may result in suboptimal outcomes[10]. Treatment focused on patient specific and modifiable pain mechanisms assessed with accurate diagnostics has the potential to improve patient outcomes. Therefore, research in these topics is of utmost importance.

## EVIDENCE BASE FOR THE ASSESSMENT OF LBP AND FUTURE RESEARCH DIRECTIONS

Guidelines published nationally and internationally recommend diagnostic triage (non-specific LBP, radicular syndrome, serious pathology), screening for serious pathology using red flags, screening of psychosocial risk factors, physical examination for neurologic screening, and the avoidance of routine imaging for non-specific LBP[11].

Valid and reliable assessment procedures are required to accurately understand the clinical presentation of pain. Recent Cochrane diagnostic test accuracy reviews have reported that the many red flags reported in clinical guidelines display low individual diagnostic accuracy[5,6]. However, a combination of red flags such as significant trauma, older age, corticosteroid use and the presence of contusion improve the diagnostic accuracy of vertebral fractures[5]. For the identification of spinal cancer, a history of cancer was the only useful red flag meaningfully increasing the likelihood of cancer[6]. Raison *et al*[12] reported that bowel and bladder dysfunction and saddle sensory disturbance where significant red flags but only marginally raise clinical suspicion of spinal cord or cauda equina compression.

A systematic review of literature by Shultz *et al*[13] displayed how history items such as age > 50, lower extremity pain or numbness, symptoms relieved with sitting/bending over and symptoms exacerbated with standing/walking suggests lumbar spinal stenosis in patients with LBP and non-specific lower extremity symptoms. Furthermore, a limited amount of literature for the diagnosis of nerve root compression/radiculopathy suggests that, dermatomal distribution/radiation was the history component with the largest diagnostic odds ratio followed by history of nerve injury, more pain on coughing, sneezing or straining, leg pain, subjective muscle weakness, subjective sensory loss, and disturbed urinary passage[13]. Regarding the diagnosis of lumbar disc herniation, a limited amount of literature suggests previous non-spinal surgery, education level and progressive sciatic pain to be significant history components[13]. Kasai *et al*[14] reported symptoms exacerbated by specific movements such as standing up and rolling over and the timing of symptoms such as morning pain could assist clinicians in diagnosing structural lumbar segmental instability. When no anatomical abnormality is suggested in the patient's history, patients with pain or aggravating/easing factors disproportionate to injury, along with psychosocial symptoms were very likely to be diagnosed with central sensitization. Similarly, patients with localized or intermittent pain were more likely to be diagnosed with nociceptive LBP[13]. The future research direction for the value of patient history will focus on clustering items to improve diagnostic accuracy.

The physical examination aims to confirm or rule out serious pathological condition or neurological compromise and classify body function impairments and activity limitations. Systematic literature reviews suggest that neurological examination including muscle weakness, muscle wasting, impaired reflexes and sensory deficits display poor pooled diagnostic accuracy values with low individual sensitivity and moderate specificity for surgically and radiologically confirmed disc herniation and the identification of affected segmental level[15,16]. Mechanical diagnostic tests such as forward flexion, hyper-extension test, and slump test have slightly better diagnostic accuracy and combining positive test results increased the specificity of physical tests[15]. The straight leg raising (SLR) test has high sensitivity and widely varying specificity while the crossed SLR showed high specificity with low sensitivity[15].

A systematic review by Hancock *et al*[17] reported that high intensity zone, endplate changes and disc degeneration assessed on magnetic resonance imaging are informative for the disc being the source of LBP. The only clinical feature found to increase the likelihood of the disc as the source of pain was the centralization phenomena. Manual tests of the sacroiliac joint when use in combination were informative but none of the tests for facet joint pain were found to be informative to distinguish the source of LBP. A systematic review by Alqarni *et al*[18] showed that high specificity and moderate to high sensitivity for lumbar spinous process palpation test for the diagnostic test for lumbar spondylolisthesis. Another systematic review by Alqarni *et al*[19] showed the passive lumbar extension test may be useful in orthopaedic clinical practice to diagnose structural lumbar segmental instability.

Studies investigating the reliability of mechanical LBP provocation test show varying results and methodological qualities. Low reliability is often reported in palpation-based assessment but improves to moderate reliability

when based on symptom response[20]. Furthermore, timed muscle endurance tests and symptom response with repeated movements have high reliability[20]. The reliability of the SLR procedures are considered good in most studies[21]. Carlsson and Rasmussen-Barr[22] in a systematic review of reliability of functional and active movement control tests to identify movement dysfunction in LBP showed that prone knee bend and one leg stance have moderate and good reliability across studies with low risk of bias.

Future research directions recommended in the literature focus on the clustering of diagnostic tests to improve the diagnostic accuracy for identifying specific diagnostic subgroups. This research direction is closely aligned with the process of clinical decision making[23].

## EVIDENCE BASE FOR PRIMARY HEALTH CARE INTERVENTIONS FOR LBP AND FUTURE RESEARCH DIRECTIONS

Therapeutic recommendations from guidelines published nationally and internationally discourage the use of bed rest and therapeutic ultrasound as well as the solitary use of electrotherapy[11]. Early and gradual return to normal functioning and activities, the time-contingent use of paracetamol progressing to non-steroidal anti-inflammatories, and the assessment of psychosocial risk factors for chronicity are recommended[11] based on a low number of randomized controlled trials (RCTs) with overall low methodological quality showing significant analgesic and/or functional effects[24-27]. As LBP persists, the guidelines recommend therapies such as supervised exercise, manual therapy, acupuncture, cognitive behavioral therapy and multidisciplinary treatments[11] based on a low number of RCTs with overall low-moderate methodological quality showing significant analgesic and/or functional effects[24-27].

Research investigating the effectiveness of conservative interventions for LBP have often reported small to moderate effect sizes in the short term with no longer-term effect on LBP trajectories for patients[24-27]. These studies may however be confounded due to heterogeneous pooling of patients and treatment modalities where average treatment effect masks patient's responding with large effect or little or no effect[28]. This has led to an increased research focus on stratified care which targets treatment to patient subgroups based on key characteristics such as their prognostic risk profile for persistent LBP, likely response to specific treatment based on clinical prediction models (CPRs) or suspected underlying causal mechanisms[29].

The STarT Back approach stratifies patients based on a multi-domain prognostic model to determine patients at low, medium and high risk of persistent back pain. Patients at medium and high risk are referred for more extensive treatment while those at low risk can be reassured and offered minimal treatment. The model performed well in a validation study and impact analysis and is current undergoing broader external validation[29].

Another option is to take aspects of the patient history, physical examination and clinical test findings to match the patient to treatment based on the prediction of responsiveness to a specific treatment. Currently 13 CPRs for LBP have been developed from clustering of diagnostic clinical tests[30]. Most of these CPR for LBP are in their initial development phase with only 1 tool for identifying lumbar spinal stenosis and 2 tools for identifying inflammatory back pain having undergone validation and no studies have yet undergone impact analysis[30]. Furthermore 30 prognostic LBP CPRs have been developed with 3 having undergone validation including the Cassandra rule for predicting long-term significant functional limitations and the five-item and two-item Flynn manipulation CPRs for predicting a favorable functional prognosis in patients being treated with lumbopelvic manipulation[31].

Targeted treatment can also be based on underlying mechanisms of the patient's LBP. For example, mechanism-based classifications of pain aim to define if underlying nociceptive, neuropathic, central sensitization, autonomic/motor, or affective neurophysiological mechanisms are driving the LBP[4]. Other classifications include the Pathoanatomic Based Classification approach and the Mechanical Diagnosis and Treatment approach. These models have nonetheless been criticized for aspects of poor validity and reliability, not covering all dimensions of the biopsychosocial nature of LBP and not adequately being tested in RCTs[29,32]. The Classification based Cognitive Functional Therapy approach integrates pathoanatomical, neurophysiological, psychosocial, physical and lifestyle domains. It has been validated in a RCT but has not undergone impact analysis or broader external validation[33]. The approach requires effective communication, education of body relaxation strategies, the normalization of functional movement patterns and discouragement of pain behaviors and utilization of mindfulness and motivational principles[29].

Fersum *et al*[32] reported in their systematic review and meta-analysis that a statistical significant difference exists in favor of the classification-based intervention for reductions in LBP and disability in the short and long-term with moderate effect size reported in the short term. However, only 7.4% of published RCT studies had performed sub-classification beyond applying general inclusion and exclusion criteria and matched interventions[32]. Fairbank *et al*[34] suggested that future efforts in developing classification systems should focus on one that helps to direct both surgical and nonsurgical treatments.

## EVIDENCE BASE FOR SECONDARY/TERTIARY HEALTH CARE INTERVENTIONS FOR LBP AND FUTURE RESEARCH DIRECTIONS

While primary health care is the first step in the mana-

gement of LBP, in the case of persistent pain despite primary health care intervention and in the presence of a clear pathoanatomic pain mechanism, secondary health care in the form of surgical intervention may be indicated. With regards to isthmic spondylolisthesis, one study with a high risk of bias has indicated that surgery leads to better improvement in pain and overall clinical outcome compared to conservative treatment, while the different surgical techniques show conflicting results[35]. Regarding degenerative spondylolisthesis, fusion results in better clinical outcomes than decompression, but there is a lack of evidence regarding if instrumented or non-instrumented fusion is optimal and there is a need for comparisons with conservative treatment[36]. For spinal stenosis, there are heterogeneous studies of low methodological quality suggesting that surgery result in better leg pain and disability outcomes compared conservative treatment[37]. Considering that the prevalence of lumbar spinal stenosis with neurogenic claudication is expected to rise with an aging population, large high-quality trials comparing surgery and conservative treatment are warranted[37].

A recent systematic review and meta-analysis suggests that there is strong evidence that lumbar fusion surgery is not more effective than conservative treatment in reducing disability because of chronic LBP[38]. In a review of systematic reviews and RCTs, Jacobs *et al*[36] reported that for discogenic LBP, surgery is no more effective than high-intensity conservative interventions for improvements in pain scores or function. Similarly disc replacement results in equal success rates as surgical fusion does[36]. With regards to disc herniation with radiculopathy, surgery leads to short-term benefits for leg pain and to a lesser extent for LBP. Despite this, no short-term and long term effects have been observed for functional outcomes measures. Furthermore, the different surgical techniques show no differences in outcomes. There is currently a lack of high quality RCTs comparing conservative or surgical treatment for disc herniation with or without sciatica[36].

There are differing views about how a patient should prepare for and afterwards undergo rehabilitation for lumbar spinal surgery. The evidence base is evolving as are the differing opinions. In the past, surgeons have commonly restricted the amount of active rehabilitation after surgery in the belief that it may prevent complications during healing. Usual care has therefore often consisted of limited advice to stay active postoperatively and has sometimes included brief general exercise programs. It has however become more apparent the importance to optimizing pre- and post-operative care in aid to improve patient outcomes.

A recent systematic review and meta-analysis by Oosterhuis *et al*[39] summarized 22 clinical trials investigating the effectiveness of rehabilitation after first-time lumbar discectomy surgery. The results suggest that exercise programs conducted four to six weeks post-operatively result in less pain and disability with small to medium effect sizes compared to usual care. Furthermore, rapid reduction in pain and disability occurred in high intensity exercise programs compared to low intensity programs. Supervised or home exercise programs did not show significant differences for pain relief or disability. There were no indications that re-operation rate increased as a result of active rehabilitation programs after first-time lumbar disc surgery[39]. The study's active rehabilitation programs consisted of exercise therapy, strength and mobility training, physiotherapy and multidisciplinary programs. More specifically, these included back schools, ergonomics education, motor control modification, resumption of activities of daily living including work and physical activity and enhancement of pain coping strategies delivered by individual sessions, group training or education or a combination of these. The quality of evidence was concluded to be low as more than half of the studies had high risk of bias and heterogeneity in rehabilitation programs warranting the need for more research with methodological rigor and the stratification of rehabilitation content[39]. Findings from a recently published RCTs from Ozkara *et al*[40] support the conclusion drawn by Oosterhuis *et al*[39]. Furthermore in a RCT conducted by Louw *et al*[41], preoperative neuroscience education for lumbar radiculopathy resulted in significantly better patient-rated preparation for lumbar discectomy surgery, fulfillment of postoperative expectations as well as less health care utilization compared to usual preoperative education provided by surgeons and staff.

Another systematic review and meta-analysis has investigated the effectiveness of rehabilitation after spinal stenosis surgery from 3 existing RCTs[42]. The study's active rehabilitation programs focused on functional outcomes and used group or therapist-led exercise or educational materials encouraging activity starting between 6 and 12 wk after surgery. The review highlighted that active rehabilitation is more effective than usual care for improving functional status and LBP both in the short and long-term. Furthermore long term improvements were seen for the reduction of leg pain. The review as a whole concluded that despite the studies having low risk of bias, the small number of relevant studies rendered the quality of evidence as very low. Additional research including stratification of rehabilitation content is warranted[42].

With regards to rehabilitation after lumbar spinal fusion, several RCT's have highlighted that the integration of active rehabilitation and cognitive behavioral programs improve patient functional and pain outcomes significantly more than usual care[43-45]. Nielsen *et al*[46] conducted an RCT taking a structured pre-habilitation and early rehabilitation program compared to standard care. The structured pre-habilitation and early rehabilitation program consisted of muscle strengthening exercise for the back and abdomen as well as cardiovascular conditioning, analgesics and a nutritional program. The integrated program of pre-habilitation and early rehabilitation improved the outcome and shortened

the hospital stay, without more complications, pain or dissatisfaction. Only one existing study has reported prospective outcomes of a structured rehabilitation program after total disc replacement (TDR). Canbulat *et al*[47] reported good outcomes with regards to early pain relief and return to activities when combining careful patient selection, surgical technique, and a structured rehabilitation program. Furthermore, a large retrospective study has highlighted that 4 or more sessions of clinic-based physiotherapy produces better functional disability, pain and quality of life outcomes compared with self-mediated rehabilitation after TDR[48]. In conclusion, more research is need using a stratified biopsychosocial approach to pre-habilitation and rehabilitation of patients undergoing lumbar spine surgery.

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EDITORIAL

# New regulations for medical devices: Rationale, advances and impact on research and patient care

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## Abstract

A series of events relating to inferior medical devices has brought about changes in the legal requirements regarding quality control on the part of regulators. Apart from clinical studies, register and routine data will play an essential role in this context. To ensure adequate use of these data, adapted methodologies are required as register data in fact represent a new scientific entity. For the interpretation of register and routine data several limitations of published data should be taken into account. In many cases essential parameters of study cohorts - such as age, comorbidities, the patients' risk profiles or the hospital profile - are not presented. Required data and evaluation procedures differ significantly, for example, between hip and spine implants. A "one fits for all" methodology is quite unlikely to exist and vigorous efforts will be required to develop suitable standards in the next future. The new legislation will affect all high-risk products, besides joint implants also contact lenses, cardiac pacemakers or stents, for example, the new regulations can markedly enhance product quality monitoring. Register data and clinical studies should not be considered as competitors, they complement each other when used responsibly. In the future follow-up studies should increasingly focus on specific questions, while global follow-up investigations regarding product complication rates and surgical methods will increasingly be covered by registers.

**Key words:** Arthroplasty; Outcome; Research; Medical device; Regulation

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**Core tip:** In the next few years new worldwide regulations as well as the availability of register data will

lead to a shift in scientific focuses. The interpretation of register and routine data will be associated with new methodological challenges. Monocenter follow-up studies will become less attractive. Publications based on large data sets from registers will continue to gain influence and cover general issues; clinical studies should focus on specific questions.

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## INTRODUCTION

Arthroplasty is one of the most successful interventions in terms of gain in quality of life[1]. Nevertheless we must acknowledge the fact that about one in ten patients have to undergo revision surgery in the course of their life[2]. Increasing age and the patients' growing confidence in the success of the operation are leading to rising numbers of cases. Moreover, patients are treated at an ever younger age, and even older patients increase their physical activity - and thus the strain on the implant. As a consequence, a marked future rise in revision surgeries has to be expected[3].

Incidents with inferior products occurred at regular intervals in the past, with a significant number of patients harmed and great cost incurred by the healthcare system due to the necessity of revision surgeries. ASR™ and other metal-on-metal large diameter head implants, 3M™ hip system or cemented titanium stems are only a few examples[4,5]. These problems are by no means restricted to joint implants only, but affect all groups of high-risk products, such as osteosynthesis devices, breast implants, contact lenses or cardiology products[6-9]. It should therefore not come as a surprise that regulatory bodies like Food and Drug Administration or European Union Commission have taken initiatives to improve the situation as a whole, provide a higher level of safety to patients and physicians, and apart from personal suffering also reduce expenses in healthcare.

The experience of the past few years has shown that technical assessment, as well as the standard practice to evaluate outcome quality and potential risks of medical devices by means of sample-based clinical studies are insufficient[10-12]. This is mainly due to some basic-medical device-specific-conditions, as well as to general structural weaknesses in the scientific system and the current evaluation procedures.

### *Limitations of the present system*

Any of the current procedures is based on a standardized rating system for clinical evidence and studies with propspective randomized controlled Trials (RCT) considered as best study design. These standards primarily take account of the circumstances that apply to pharmaceuticals. White tablets in anonymous boxes can easily be used in controlled and randomized circumstances; biological half-life allows a good estimate of the period of examination during which side effects have to be expected; persons collecting data can easily be blinded.

When it comes to implanted medical devices, this scheme reaches its limits. It is difficult to randomize surgical procedures, in many cases impossible due to ethical reasons. Placebo groups are unethical in general. Blinding of the physician who makes the decision and is responsible for documenting the study endpoint is hardly possible. For the standard endpoint Revision Rate this would, for instance, mean that the surgeon who decides on revision surgery and performs the intervention would neither be granted access to patient records nor to X-rays.

These limitations might be one reason fort he low numbers of RCT's in orthopaedics. Since it is virtually impossible to estimate the time at which a complication occurs, the times for follow-up examinations and the duration of the study can hardly be determined prospectively. For example, if the lifespan of the battery of a pacemaker is three years, the problem would not be realized in a one-year study; at 5 years follow-up two years would have passed until measures can be taken - with patients being treated with a suboptimal product in the meantime. The logical approach of regular concomitant check-ups carries the risk of bias due to a break of the blinding and impact on the assessment of findings by discussing the evaluations performed; the methodological benefits of prospective study design would seriously be put into question.

Regardless of these limitations a systematic analysis of published results in regular clinical studies as compared to register data has revealed profound structural weaknesses in the current science system. About half of the implants examined in this worldwide meta-analysis of clinical studies showed statistically significant deviations of over 300% (as a measure of relevance in which deviations might also be explained by other factors, such as patient selection or the surgeon's expertise) compared with national register data as a measure for average patient care. Especially studies from the United States, as well as studies authored by implant developers were conspicuously often affected by implausibly good results. Marked differences were also found as to what was published in journals, for example, that on average 55% of cases published in orthopedic United States journals stem from implant developers, compared to only 7.5% in European journals[13]. We must therefore accept that the present standards in scientific activities are susceptible to stakeholder influence, with a substantial impact on the opinion of orthopedic literature.

In principle the current standard of assessment gives very limited consideration to clinical studies. The primary objective of this assessment scheme is to restrict methodological shortcomings of sample-based studies. However, the concept neither gives full consideration

to the complete registration of all cases, as is largely achieved in good registers, nor does it allow for the specific requirements outlined above. Thus, a prospective randomized study of 50 patients would have to be classified as superior to a register evaluation of 50000 cases. Owing to the high standard in patient care, the endpoints of orthopedic studies, such as revision rate, are relatively rare. L.I. Havelin, one of the major co-founders of the Norwegian Arthroplasty Register, proved in his PhD thesis that in a conventional follow-up study nearly 15000 cases would be needed to determine a difference of 1 percentage point in the complication rate after 10 years. The relatively big effect of 2 percentage points would still require about 3000 patients. Therefore, the vast majority of published studies have to be considered as statistically underpowered, even if they are impeccable from a methodological point of view. In the 2010 comparative analysis of published clinical studies worldwide and the restricted number of high-quality national registers 80% of all cases available came from registers, only 20% from clinical studies[13]. Now, five years later, the ratio has shifted to 90:10 percent. Considering that the National Joint Registry of England, Wales and Northern Ireland records more than 200000 cases per year, it is reasonable to assume that this data source will become increasingly important in the future.

### *Advances in future regulations and new challenges*

In addition to a comprehensive presentation of all outcome quality data available, future legislation will also require a performance estimate within the scope of average patient care. This is supposed to address the problems associated with the fact that clinical studies are often conducted in centers of excellence, which are not representative for average use.

Improved monitoring shall include the product's entire lifetime, which can de facto only be covered by registers. Indicators for measuring embrace the whole treatment chain. Revision rate, the most important indicator for arthroplasty, in addition to product quality for example also includes the surgeon's quality, the patient's risk profile or general conditions of a healthcare system. Attribution of inferior outcome to a causer will be an essential factor as it defines at which stakeholder improvement measures can be launched. It is expected that this point will be an issue of controversial debate, particularly since responsibilities will be shared in many cases and serious legal and financial consequences may be involved. In the necessary decision-making process previous experience from register practice so far will be only of limited use. In past years and decades the interpretation of scientific data was largely a preserve of physicians. The data were published at congresses or in journal articles; that way critical debate was initiated within the expert audience, and physicians as the main decision-makers were expected to draw the consequences. Under these circumstances it makes sense to take action as early as a relevant problem is suspected. Regulators, authorities or manufacturers, however, are bound to make clear and unambiguous decisions, such as recalling a product from the market - or not. This requires a higher level of reliability with regard to conclusions than is necessary for the discussion among experts. To ensure that the future procedures can actually meet the objectives of safety improvement, a number of issues have to be dealt with.

### *Issues to be addressed*

Registers in principle are a new scientific entity which imposes special requirements on data collection and evaluation. One could compare the published annual reports, in some cases also journal publications, to clinical studies without "Materials and Methods". The patient cohorts included often are not or only insufficiently described, which may also be explained by the fact that the evaluations are chiefly addressed to physicians and other stakeholders of the respective country - who are usually familiar with the local circumstances. As the results are primarily intended for implementation in this particular area, the circumstances represent a constant and are therefore less important than for those readers who would like to apply the findings to other countries.

Even within the European Union the results of interventions show relevant differences in the population. Life expectancy, for instance, is about 10 years lower in some countries, such as Romania, than it is in Central European countries, or compared to Australia, for example, since the "positive outcome" of arthroplasty interventions effectively is the patient's death for another reason without the implant being revised, this is more probable for a 70-year-old Romanian than for a German, British or Australian of the same age. Therefore, registered differences in revision rate cannot be automatically interpreted as differences in the quality of treatment. The definition of relevant parameters for the final outcome and a structured description of the respective dataset would be useful to enable the reader to check whether the conclusions of a foreign register can be transferred to his or her own conditions.

Furthermore, the effects of the individual parameters should be quantified, which would be possible by comparative analyses of existing register datasets. The ultimate aim should be the standardization of data collection and evaluation procedures, at least when data from different registers are aggregated.

This can only be realized through international, if possible world-wide cooperation of registers, regulators, as well as the other stakeholders involved. Moreover, it would make sense to include the users of the data such as physicians and - beyond the narrow circle of register experts - product manufacturers or patients' mandatories. Open, transparent and democratic processes are of vital importance to ensure that the solutions to be elaborated receive social acceptance. As the results will have great influence on far-reaching decisions in patient care, careful and critical evaluation practice is a necessity. Risk adjustment regarding individual

factors and confounders is essential in the analysis of aggregated international data.

When going through foreign register data one should critically examine whether the results and conclusions could be affected by confounders and whether the basic data are representative for one's own area.

Future legislation is supposed to apply to all high-risk products. However, the pathologies, circumstances and aims these will be used for will vary greatly. Apart from joint implants, the range of products concerned also includes all permanently implanted orthopaedic devices, contact lenses, pacemakers, artificial cardiac valves or stents.

This inhomogeneity certainly has an impact on the evaluation and interpretation of the data, as well as on the conclusions drawn. Arthroplasty has acquired a leading position with regard to registers, not least because of favourable circumstances. The demand that no revision surgery should be required in the course of a patient's life after arthroplasty implantation is the basis for quality measurement. Any serious problem of or around the implant usually leads to revision surgery - which by definition is the "undesirable side effect" of the intervention. The procedure is performed in a hospital; comprehensive documentation is available for evaluations. Similar circumstances are true for a whole series of other medical devices, such as contact lenses, breast implants or pacemakers, but not for all. For a number of products, such as cardiac stents, mortality is the primary endpoint - and death may, but does not have to be associated with the use of a certain product. The removal of osteosynthesis devices or extension of a spinal fusion is not necessarily an undesired consequence of a primary intervention of insufficient quality. In the case of some products, for example, in shoulder and ankle arthroplasty, there are numerous patients who, in spite of unsatisfactory outcome, do not receive revision surgery. Thus, the endpoint of revision rate is meaningful only to a limited extent. In the future it will therefore be necessary to develop optimal solutions for every situation, "one fits for all" will hardly work.

### *Effects on patienten care and science*

The possibilities offered by the growing penetration of information technology in our working envirement IT will lead to a rapid increase in routine data available. These provide a much better reflection of the reality of patient care than many clinical studies ever could since they are based on clearly defined patients and carried out by experienced surgeons under the favorable circumstances of centers of excellence. However, as medicine is anything but standardized - and presumably can hardly be standardized owing to the variability of patients and medical care - the transferability of results remains a relevant problem inherent to the system. Big data will become increasingly important in all our efforts to improve the quality of our services. Just like in other areas of electronic data growing quantity does not automatically mean better quality. However, if dealt with and used critically, they open up new possibilities. In the process, certain study designs may become less important, such as simple follow-up studies with minor cohorts of a few hundred patients. The knowledge gained will hardly be able to compare favorably with register data and the usually considerably larger numbers of cases. Register evaluations, on the other hand, can only convey a relatively rough outline; the examination of detailed questions or treatment options will remain a domain of clinical studies. The cooperation of these two schientific tools can create added value, for example, when register data are used to adjust control groups more precisely. As many conventional follow-up studies are at present conducted for the purpose of the post-marketing clinical follow-up of products, it is likely that it will be less economic for implant manufacturers in the future to keep supporting this tool with the resources currently available. It is to be anticipated that budgets will be reallocated to registers on the one hand and clearly focussed clinical studies on the other hand in order to meet the requirements on the part of authorities and regulators. Most likely this will affect the way of implant development and acquisition of clinical evidence. Registries open opportunities for improvement by continuous feedback and outcome monitoring for manufacturers and implant designers. To assess detailed issues experimental, biomechanical and clinical studies will be essential, in premarket test phases as well as innovation circles.

## CONCLUSION

Amended legislation in the quality assurance and monitoring of medical devices will allow for a marked improvement in patient safety and the quality of medical care. However, a number of methodological fundamentals for scientific assessment are still to be elaborated. While routine and register data are an increasingly important source of information, they will by no means supersede clinical studies but rather complement them. The time frames of scientific studies in orthopedics are often long; one should consider to make the necessary adjustments to the future situation now.

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EDITORIAL

# Entrapment of middle cluneal nerves as an unknown cause of low back pain

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## Abstract

Entrapment of middle cluneal nerves induces low back pain and leg symptoms. The middle cluneal nerves can become spontaneously entrapped where this nerve pass under the long posterior sacroiliac ligament. A case of severe low back pain, which was completely treated by release of the middle cluneal nerve, was presented. Entrapment of middle cluneal nerves is possibly underdiagnosed cause of low-back and/or leg symptoms. Spinal surgeons should be aware of this clinical entity and avoid unnecessary spinal surgeries and sacroiliac fusion. This paper is to draw attention by pain clinicians in this unrecognized etiology.

**Key words:** Entrapment neuropathy; Superior cluneal nerve; Middle cluneal nerve; Sacroiliac joint; Low back pain; Neuropathic pain

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**Core tip:** A case of severe low back pain, which was completely treated by release of the middle cluneal nerve, was presented. Clunealgia is underdiagnosed cause of low back pain and leg pain. The middle cluneal nerve may be entrapped where this nerve pass under or through the long posterior sacroiliac ligament.

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## INTRODUCTION

Recently, clunealgia has become known as an under-diagnosed cause for chronic low back pain (LBP) or leg pain[1-5]. Trescot[2] stated that cluneal neuralgia is more commonly the result of an entrapped nerve rather than a nerve injury resulting from iliac crest bone harvest. Kuniya *et al*[3] reported that patients with superior cluneal nerve (SCN) entrapment occurs where pierce fascial attachment at posterior iliac crest. SCN disorders comprised 12% of all patients presenting with a chief

complaint of LBP and/or leg symptoms in their clinic and approximately 50% of SCN disorder patients had leg pain and/or tingling.

The concept of a relationship between the cluneal nerve and LBP is not new. A relationship between the cluneal nerve and LBP was sporadically reported several decades ago[6,7]. The first detailed description was made by Strong *et al*[7] in 1957. Deafferentation of the SCN and/or middle cluneal nerve (MCN) was attempted in 30 patients because these nerves were considered to cause LBP with or without referred leg pain. Of 30 patients, five had referred pain in their leg in the S1 and/or S2 area and had deafferentation of the MCN with favorable outcomes.

Maigne *et al*[8] and Lu *et al*[4] performed cadaveric dissections to study anatomy of the SCN and concluded that that the medial branch of the SCN consistently passed through an osteofibrous tunnel and might be spontaneously entrapped in the tunnel. Following these anatomical studies, several surgeons reported successful surgical outcomes of SCN release[3,5,9]. However, surgical reports of release are limited to SCN entrapment. Until now, MCN entrapment has not yet been reported in English literature. This paper is to firstly present a case of MCN entrapment and to draw attention by pain clinicians in MCN entrapment.

## CASE REPORT

In April 2013, a 48-year-old woman presented complaining of LBP and buttock pain radiating to both legs that had gradually developed over 10 years. L4-5 discectomy performed at another hospital two years before resulted in no improvement. The pain was continuous and severe even with long-term daily use of tramadol 225 mg/acetaminophen 1950 mg, pregabalin 50 mg and loxoprofen sodium 180 mg. The visual analog scale (VAS) score was 67 mm and the Roland-Morris Disability Questionnaire (RDQ) score was 18. A neurologic examination revealed no sensory or motor disturbance in her legs. Lumbar motion was greatly limited in all directions because of pain (Appendix, video 1). The finger floor distance in flexion was 50 cm. Palpation of the superior SCN tender point, located 7 cm laterally to the midline on the bilateral iliac crest[7], replicated the postero-lateral aspect of calf pain. She also had significant tender points approximately 1.5 cm caudal to the palpable margin of the bilateral posterior superior iliac spine, by the lateral sides of the long posterior sacroiliac ligament (LPSL). These loci were along the running course of the MCN as described in an anatomical report by Tubbs *et al*[10]. Palpation of MCN tender points provoked mid-posterior thigh pain. Repetitive infiltration of a local anesthetic, Lidocaine, into each tender point consistently resulted in clear improvement of symptoms for three hours.

The patient was informed that release was previously performed exclusively for SCN entrapment and had never been applied for MCN entrapment. She gave their informed consent to undergo surgical decompression. In May 2013, microscopic SCN and MCN releases were attempted. Surgeries were approved by the Institutional Ethics Committee of our institution. Surgery was performed bilaterally under general anesthesia with the patient in the prone position. An oblique 10 cm skin incision was made over the iliac crests. Being careful not to injure nerve branches passing through subcutaneous tissues, the superficial layer of the thoracolumbar fascia was opened. Two branches of the SCN were identified within 5 cm above the iliac crest and were seen to emerge from the lateral margin of the deep layer of the thoracolumbar fascia. These SCN branches were traced in a caudal direction until they passed over the iliac crest. In agreement with a recent anatomical study, the two medial branches of the SCN where they pierce the thoracolumbar fascia over the iliac crest were found to be entrapped in adhesions. A thin branch of the MCN perforating the thoracolumbar fascia was identified just medial to the posterior superior iliac spines. Although obvious entrapment was not observed, the perforating orifices were opened.

Within one week following surgery, the patient reported that her pain had completely disappeared around the upper iliac crests, but remained around the LPSL on both sides. Palpation on the LPSL consistently induced LBP and leg tingling radiating from the buttocks to the calves on both sides. Injections around the LPSL were repeated every month. Each time, the patient reported reappearance of leg tingling during the block procedure and, soon after, complete improvement in LBP and leg tingling that continued for three days. Consequently, blocks were repeated six times over six months without substantial permanent change in LBP. The VAS score was 50 mm at six months after surgery. Near-full range of flexion was obtained with no pain reappearance, but lumbar extension was still severely limited.

In an attempt to eliminate remaining pain, in December 2013, revision surgery was done. Previous operative incisions were reopened. After gluteal muscle splitting approach, the bilateral MCNs were explored where the nerves penetrate the LPSL (Figure 1). Proximally, the nerves possibly arose from the S2 foramen. The MCNs were decompressed by excising the LPSL where the nerve penetrates the ligament. After revision, pain dramatically improved, precluding need for any medication. The patient had no limitation in lumbar motion. The VAS score at eight months after revision was 0 mm and the RDQ score was 1.

## DISCUSSION

The MCN is composed of sensory branches of the dorsal rami of S1 to S3 foramina and travels below the PSIS in an approximately horizontal course to supply the skin overlying the posteromedial area of the buttock[10-12]. The evidence that predominantly the S1 and S2 lateral branches may explain why MCN disorder could cause leg symptoms in posterior thigh to calf.

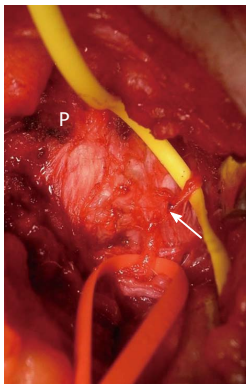


**Figure 1 Photo taken during the surgical release of a left-side middle cluneal nerve.** Medially to the posterior superior iliac crest (P), the MCN is identified passing under the superficial layer of the long posterior sacroiliac ligament. The nerve is seen to be entrapped under the deeper layer of the long posterior sacroiliac ligament where it penetrates the ligament (arrow). The yellow and red tapes have been used to lift the proximal and distal portions of MCN branch, respectively. MCN: Middle cluneal nerve.

Tubbs *et al*[10] studied anatomy running course of MCN and concluded that the MCN would be less likely to become entrapped because MCN travels superficial to the LPSL. On the other hand, anatomical studies by Horwitz[13], Grob *et al*[12], and McGrath *et al*[14] showed that the primary and secondary loops of the posterior sacral nerve plexus passed through or underneath the LPSL. They suggested entrapment of the penetrating nerves within or under the ligament is a potential cause for LBP and peripartum pelvic pain.

A diagnosis of SCN/MCN entrapment was made by palpation of the iliac crest or LPSL resulting in marked tenderness and provocation of symptoms, and by pain relief after local anesthetic injection. The SCN tender point was on the posterior iliac crest approximately 70 mm from the midline and 45 mm from the PSIS[3]. The MCN tender point was on the LPSL within 40 mm caudal to the PSIS (Figure 2).

Pain due to MCN entrapment may be treated as sacroiliac joint pain. Although sacroiliac joint pain remains a controversial subject, it is thought to cause 15% to 30% of LBP and is often associated with buttock to lower extremity symptoms[15]. There are no medical history or physical examination findings consistently capable of identifying sacroiliac joint pain[16]. The physical examination tests, such as Patrick's test or Gaenslen's test, have weak predictive value[15]. Radiological imaging contributes little to diagnosis[15]. The current gold standard for the diagnosis is fluoroscopically guided sacroiliac joint blocks[15]. Fortin *et al*[17] analyzed contrast extravasation patterns during 76 sacroiliac joint arthrograms by using computerized tomography and found dorsal leakage around LPSL in 18 cases (24%) and dorsal leakage into the S1 foramen in 6 (8%) The LPSL is a significant posterior ligamentous structure, resisting shearing of the sacroiliac joint and is a potential pain generator[14,18]. Murakami *et al*[19] compared the effect of injections into the intraarticular space and periarticular region around

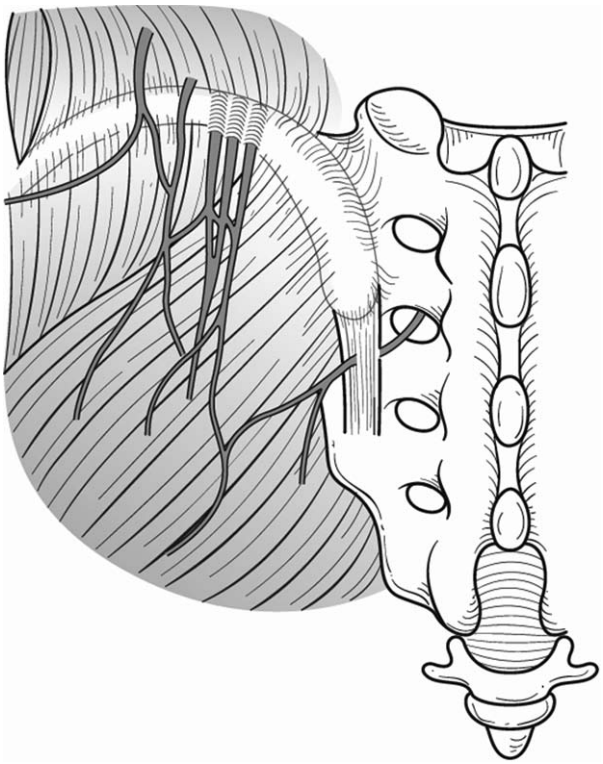

**Figure 2 Schematic illustration of typical running courses and entrapment of superior and middle cluneal nerves.** Multiple branches of the superior cluneal nerve may be entrapped where they pierce the thoracolumbar fascia over the iliac crest. Middle cluneal nerve may be entrapped where this nerve pass under or through the long posterior sacroiliac ligament.

the LPSL in patients with sacroiliac joint pain. The injection around the LPSL was effective in all 25 patients, whereas the intraarticular injection was effective in only nine out of 25 patients (36%). Furthermore, all 16 patients without pain relief after the intraarticular injection reported almost complete pain relief after injection around the LPSL. Fortin *et al*[16] stated that sacroiliac joint patients could localize their pain with one finger and the area pointed to was immediately inferomedial to the posterior superior iliac spine within 1 cm. Murakami *et al*[20] observed a positive effect with periarticular sacroiliac joint block in 18 patients out of 25 patients who indicated the main site of pain within 2 cm of the posterior superior iliac spine. These results suggest that sacroiliac joint pain can originate from the LPSL[20].

LBP is one of the most common problems that most people suffer at some point in their life. There are many sources of LBP. In most LBP patients, the exact cause of LBP is not clear. Thus, one of the most difficult tasks with LBP is to identify the actual pain generator. Large epidemiological studies show that 20% to 37% of patients with back pain suffer from a neuropathic pain component[21]. So far, neuropathic pain is considered to be caused by lesions of nociceptive sprouts within the degenerated disc, mechanical compression of the nerve root, or by action of inflammatory mediators originating from the degenerative disc[22]. SCN/ MCN entrapment must not be forgotten as cause of neuropathic LBP.

## CONCLUSION

MCN entrapment is underdiagnosed cause of low back pain and leg pain. For a structure to be considered as a potential source of pain, pain must be provoked by palpation or relieved by local anesthetic injection of the tender point around LPSL. Knowledge of this clinical entity would avoid unnecessary sacroiliac joint fusion and spinal surgeries.

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REVIEW

# Major osteoporotic fragility fractures: Risk factor updates and societal impact

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## Abstract

Osteoporosis is a silent disease without any evidence of disease until a fracture occurs. Approximately 200 million people in the world are affected by osteoporosis and 8.9 million fractures occur each year worldwide. Fractures of the hip are a major public health burden, by means of both social cost and health condition of the elderly because these fractures are one of the main causes of morbidity, impairment, decreased quality of life and mortality in women and men. The aim of this review is to analyze the most important factors related to the enormous impact of osteoporotic fractures on population. Among the most common risk factors, low body mass index; history of fragility fracture, environmental risk, early menopause, smoking, lack of vitamin D, endocrine disorders (for example insulin-dependent diabetes mellitus), use of glucocorticoids, excessive alcohol intake, immobility and others represented the main clinical risk factors associated with augmented risk of fragility fracture. The increasing trend of osteoporosis is accompanied by an underutilization of the available preventive strategies and only a small number of patients at high fracture risk are recognized and successively referred for therapy. This report provides analytic evidences to assess the best practices in osteoporosis management and indications for the adoption of a correct healthcare strategy to significantly reduce the osteoporosis burden. Early diagnosis is the key to resize the impact of osteoporosis on healthcare system. In this context, attention must be focused on the identification of high fracture risk among osteoporotic patients. It is necessary to increase national awareness campaigns across countries in order to reduce the osteoporotic fractures incidence.

**Key words:** Fracture prevention; Fracture risk; Fragility fracture; Osteoporosis; Hip fracture

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**Core tip:** The osteoporosis burden is growing and 9 million fractures occur each year worldwide. Unfortunately, because of the underutilization of available preventive strategies, only a minority of women and men at high fracture risk are identified and successively referred for treatment. The aim of this review is to analyze the most important factors related to the enormous impact of osteoporotic fractures on population. Because early diagnosis is the key to reduce the impact of osteoporosis on healthcare system, attention must be focused on the identification of high fracture risk among osteoporotic patients.

Pisani P, Renna MD, Conversano F, Casciaro E, Di Paola M, Quarta E, Muratore M, Casciaro S. Major osteoporotic fragility fractures: Risk factor updates and societal impact. *World J Orthop* 2016; 7(3): 171-181 Available from: URL: http://www.wjgnet.com/2218-5836/full/v7/i3/171.htm DOI: http://dx.doi.org/10.5312/wjo.v7.i3.171

## INTRODUCTION

Osteoporosis has been defined as a systemic disease which affects the skeleton and is characterized by low bone mass, deterioration of microarchitecture of bone tissue and bone fragility increase with consequent susceptibility to fracture[1].

This bone pathology can be classified in primary or secondary forms. Primary osteoporosis is characterized by a progressive mineral bone lost as a function of people aging and it is influenced by changes of sex hormone. Instead, different pathologies as well as the use of specific medications, which affect skeletal health, can induce secondary osteoporosis. Primary form of osteoporosis comprises postmenopausal or senile disease (type Ⅰ or type Ⅱ respectively)[2]. Type Ⅰ osteoporosis takes place in a subgroup of postmenopausal women, usually aged from 50 to 65 years, due to estrogen deficiency and consequent trabecular bone resorption. In this set of women fracture pattern mainly involves the spine and wrist. There is no evidence that postmenopausal bone loss itself causes any symptoms, and therefore, progressive bone loss has been called "the silent epidemic" or "silent thief". The morbidity arises from the type of fracture sustained[3]. In senile osteoporosis, there is a balanced loss of both cortical and cancellous portions of bone tissue. Fractures of the hip, proximal humerus, tibia, and pelvis represent characteristic fractures of type Ⅱ osteoporosis[4].

Although osteoporosis has long been considered a disease of women, an increase in age-related fractures has been observed also in men[5]. Nowadays, the number of males with osteoporosis is unknown, probably because of the infrequency of screening and controversies in bone mineral density (BMD) testing standards in men. Approximately the 50% of women and the 25% of men aged 50 and older will have an osteoporotic fracture in the lifetime[6]. Although many national and international organizations indicate to realize osteoporosis screening and treatment for men in their clinical guidelines, male osteoporosis remains recurrently not diagnosed and not treated[7,8].

The high socio-economic impact of osteoporosis is due to increased incidence of the disease, mortality and fracture-related costs. The occurrence of osteoporotic fractures is growing in several world areas as a consequence of the increased longevity of the population. Indeed, the number of hip fracture worldwide has reached 1.7 million by 1990[9,10]. In 2050, hip fractures could exceed 21 million[10,11]. In this context, attention must be focused on the identification of high fracture risk patients[12]. There is, therefore, the strong need to assess the best preventive methods and therapeutic approaches to contrast fracture widening accross populations. A large number of techniques can be used to assess the risk of fracture. In general, they fall into two major categories: Assessment of clinical risk factors (CRFs) and physical measurement of skeletal mass. Nowadays, the assessment of osteoporosis is based on bone density evaluation, and there are no satisfying clinical approaches, independent of BMD, for bone quality estimation[3].

The aim of this review is to analyze the main factors causing the huge impact of osteoporosis on the population, and to stress the importance of risk factors recognition and early identification of fracture risk in order to discriminate frail patients from non-frail patients. Currently, only a small number of high fracture risk patients are recognized and successively referred for therapy. In this context, the present report provides analytic evidences to assess the best practices in osteoporosis management as well as the indications for the adoption of a correct healthcare approach to decrease the socio-economic burden of osteoporosis.

## FRACTURE RISK ASSESSMENT

### *Assessment of CRFs*

A list of risk factors has been determined (Table 1) both for women and men. In several instances, exist a clear relationship between these risk factors and low bone density or other causes of osteoporotic fractures.

In recent years, there have been a number of advances, principally in BMD measurement, osteoporosis diagnosis, fracture risk evaluation, the development of interventions that decrease risk of fractures and the creation of practice guidelines. Recently, a set of meta-analyses have been carried out to recognize CRFs to use in case finding strategies with or without the use of BMD. These are summarized below together with risk factors for falling because the majority of osteoporosis-related fractures derive from falls[13].

An important risk factor for hip fracture is low body mass index (BMI). Thus, the risk is nearly two-fold

**Table 1 Clinical risk factors associated with increased risk of fragility fracture**

| Risk factors associated with low BMD and fracture | Risk factors for falls |
|---|---|
| For woman as for men | |
| [1]Increased age | Age |
| [1]Low BMI | Environmental risk |
| [1]Hystory of fragility fractures | Previous falls |
| [1]Previous fragility fractures | Dehydratation |
| [1]Parental hystory of fragility fractures | Depression |
| Recent falls | Poor vision |
| [1]Premature menopause | Sarcopenia |
| [1]Untrated hypogonadism | Urgent urinary incontinence |
| Poor neuromuscular function | Malnutrition |
| [1]Prolonged immobilization and inactivity | Neurological risk factors |
| [1]Alcohol intake | |
| [1]Current smoking | |
| [1]Glucocorticoids treatment (≥ 5 mg preadnisolone daily for 3 mo or more) | |
| [1]Type I diabetes (and other endocrine disorders) | |
| Vitamin D insufficiency | |
| [1]Rheumatoid arthritis (and other rheumatologic diseases) | |
| Aromatase inhibitor for breast cancer treatment | |
| Chemioterapy for breast cancer | |
| [1]Thyroid disorders | |
| Cronic obstructive pulmonary disease | |
| Anorexia nervosa (and other hypogonadal states) | |
| Depressed mood | |
| Tricyclic antidepressant use | |
| Stroke | |
| IBD and other gastrointestinal disorders | |
| Organ transplantation | |
| Hematologic disorders | |
| Neurological and muscoloskeletal risks | |

Adapted from Cosman *et al*[13] with modification. [1]CRFs for fracture risk assessment from tool FRAX®. BMD: Bone mineral density; CRFs: Clinical risk factors; IBD: Inflammatory bowel diseases; BMI: Body mass index.

increased for individuals with a BMI of 25 kg/m$^2$ *vs* 20 kg/m$^2$[14-17]. Numerous studies show that a history of fragility fracture represent an important risk factor for further fracture independently of BMD[1,18,19]. It was shown that the risk of fracture is around doubled in the presence of a prior fracture[1,20].

Early menopause (before age 45 years), both natural and surgically induced, leads to an increased risk of mortality and fragility fractures[21] because these women are exposed to a hypogonadal state for a longer time[3].

Similarly, many abnormalities of menstrual function as well as late menarche and primary or secondary amenorrhea might also contribute to low BMD and therefore also increase the risk of osteoporosis[3,22,23]. Hypogonadism also occurs in a small proportion of men and might led to bone loss[24] and fractures[25]. Postmenopausal women are capable of producing adrenal steroids, of which androstenedione is converted to estrogens in adipose tissue. This might explain why thin women are at greater risk than their heavier counterparts, and possibly because smoking, which decreases appetite and body fat, is a risk factor[3]. There might be, however, additional factors related to smoking, and there is some evidence that smoking might accelerate the peripheral metabolism of exogenously administered estrogen[26]. Moreover, because female cigarette smokers are thinner than non-smokers, they have an earlier natural menopause[3].

On one hand crucial role for estrogen in bone loss is indicated by the increasing resorption of bone at menopause[5,27,28]; on the other hand, in men, although total serum testosterone and estrogen levels not vary with increasing age, the bioavailability fractions decrease progressively to 30%-50% of the young adults average after 80 years of age[5,29].

Lack of vitamin D is another risk factor. It is well known that vitamin D, calcium and protein insufficiency is highly frequent in the elderly. Vitamin D deficiency in adults can aggravate osteopenia and osteoporosis, and causes osteomalacia and muscle weakness, increasing the risk of fracture. Vitamin D can be obtained from diet or exposure to sunlight. Solar ultraviolet B radiation (wavelength, 290-315 nm) can convert 7-dehydrocholesterol to previtamin D3 and consequently to vitamin D3 by penetrating the skin. Vitamin D deficiency and bone fragility are also common in some countries such as Iran, where conservative cultural codes encourage body coverage and so limit sun exposure[30].

In addition to vitamin D insufficiency, hyperthyroidism and secondary hyperparathyroidism also take part in particular to age-related cortical bone loss in the elderly[31]. Other probable pathogenetic aspects comprise reduced serum levels of insulin-like growth factors[32]. Age-related bone loss and reduced bone strength (due to the imbalance between the activities of osteoblasts and

the osteoclasts) are believed to start in both men and women from the beginning of the 5th decade until the end of life[33]. It is also possible that some early factors (*i.e.*, perinatal nutrition) have affected the successive late-life risk of fractures in adults[8,34,35].

Bone loss is due to many disorders, such as insulin-dependent diabetes mellitus and Cushing's disease. Myelomatosis might be present with osteoporotic crush. Rarer causes of osteoporosis include osteogenesis imperfecta, malabsorption, chronic renal failure and some drugs. However, all these disorders are comparatively rare and have relatively little impact upon any general screening strategy[3].

Other secondary causes of osteoporosis are linked with an increase in fracture risk (*e.g.*, inflammatory bowel disease, endocrine disorders), but it is unclear if these are dependent on other risk factors. For example, the use of glucocorticoids is an important cause of osteoporosis and fractures according to the research groups of Kanis *et al*[1] and van Staa *et al*[36]. In contrast, rheumatoid arthritis determines a fracture risk independently of BMD and the use of glucocorticoids[37].

Immobility is also an important cause of bone loss. A woman immobilized for 1 mo can lose more bone than she would normally lose in 1 or 2 years of the osteoporotic process[3].

A family history of osteoporosis might be important and there is some evidence for a genetic component to peak bone mass[38]. Drugs such as corticosteroids and thyroid replacement treatments increase the risk of osteoporosis, as does excessive alcohol consumption[3]. These risk factors have a dose-dependent effect: The higher the exposure to these substances, the greater the risk (*i.e.*, daily intake of about 3 units)[1,17].

### *Fracture risk assessment tool*

All postmenopausal women and men 50 years of age and older should be assessed for osteoporosis risk in order to establish the need for BMD measurement and/or vertebral imaging.

Low BMD alone is a poor predictor of fracture in men and women, indicating the need for tools that predict fracture risk independent of, or in addition to, BMD. The use of risk assessment tools that include clinically relevant risk factors to predict fracture risk are being increasingly incorporated into osteoporosis screening and treatment guidelines.

The World Health Organization (WHO) and the International Osteoporosis Foundation advice that fracture risk should be expressed as a short-term absolute risk. The absolute risk of fracture is relative to age and life expectancy as well as the current relative risk, *i.e.*, the probability over a 10-year interval[1,39]. The period of 10 years comprises the probable duration of treatment and the benefits that might persist once treatment is suspended.

Algorithm that combines the influence of CRFs on fracture risk, integrating or not data on BMD, is FRAX®[40,41] which takes into account the risk factors previously described in Table 1.

The FRAX tool (www.shef.ac.uk/FRAX) calculates alternatively the 10-year probability of hip or major osteoporotic fracture (hip, spine, hip, humerus or forearm fracture). Probabilities can be calculated for the different countries[40,41]. In all national treatment guidelines some case-finding approach is proposed for patient recognition. However, they differ on the basis of recognized risk factors, BMD and fracture risk assessment. Moreover, recommendations in national guidelines are not always implemented.

According to the Italian guidelines for osteoporosis treatment, postmenopausal women, men, and individuals taking glucocorticoids are included in the program of prevention, screening and diagnosis. Bone densitometry is suggested for all women aged 65 years and over, but, for men and younger postmenopausal women, only for those with CRFs. The guidelines recognize FRAX as a tool for estimating fracture probability and propose that pharmacological treatment should be indicated for people with "rather high" fracture risk but do not identify intervention thresholds[40].

### *Assessment of fracture risk: Available imaging methods*

Osteoporosis causes loss of bone mass and deterioration of bone microarchitecture with a consequent reduction in bone stiffness and strength, thus resulting in an increased risk of fragility fractures.

Early diagnosis is essential for timely treatment and for identification of patients who are at a higher risk of fractures. Currently, osteoporosis diagnosis and fracture risk assessment are based on the quantitative BMD evaluation realized by the gold standard dual-energy X-ray absorptiometry (DXA). However, BMD assessment (which is a measure of bone mass) only partially provides information about bone strength. Indeed, on one hand BMD is a measure of bone mass, and on the other hand, bone fragility is dependent also on its microarchitecture quality which is determined by all the features (microarchitecture, microdamage and remodeling rates in bone) that influence a bone's ability to resist fracture. The decay of trabecular bone microarchitecture has been acknowledged, among the features, as a major contributor to bone fragility[42].

Because DXA is a two-dimensional technique, it does have intrinsic limitations; it cannot aid in discriminating cortical from cancellous bone and cannot aid in distinguishing changes due to bone geometry from those due entirely to increased bone density.

There are several recently developed approaches that can provide complementary information for assessing fracture risks in addition to BMD. One of them is the quantitative computed tomography (QCT) which has been developed to assess bone loss[43]. In QCT trabecular bone can be examined separately from cortical portion of bone and a true value for mineral density is given, unlike other techniques[3,44].

In addition, currently, the microarchitecture of cancellous bone can be evaluated *in vivo* by high-resolution peripheral QCT techniques. However, such imaging techniques remain a high-end research tool rather than a diagnostic tool for clinical applications[42].

Other imaging techniques have been developed in order to improve the correct osteoporosis diagnosis, because the accurate diagnosis of osteoporosis leads to a better management in terms of prevention and appropriate pharmacologic or surgical treatment.

It has been demonstrated that BMD evaluations on reference anatomical sites, spine and proximal femur standardly evaluated by DXA examinations, are the most reliable available tool to predict the risk of osteoporotic fractures.

Unfortunately, DXA has precise limitations (*i.e.*, bulky device, high cost, limited accessibility and use of ionizing radiation) that impede its application for population screenings and primary care diagnosis.

These limits have resulted in the development of an increasing number of radiation-free United States-based technologies as screening tools for early osteoporosis diagnosis and fracture prevention[45-48].

However, the actual clinical utility of United States devices for osteoporosis diagnosis is quite limited since they are referred only to peripheral sites (*i.e.*, calcaneus, radius, tibia, *etc.*).

To overcome this limitation, a novel ultrasound approach has recently been developed to evaluate bone status and fragility fracture risk[49,50]. In this context, this new ultrasonic method is the first tool for bone characterization and microarchitecture assessment that enables the scanning of central axial reference sites (lumbar vertebrae and proximal femur) through an innovative approach without the use of ionizing radiations.

Unfortunately, in many countries, even patients at high risk of fractures might not be able to obtain therapy because effectual medicines are not reimbursed by government health insurance plans[10]. Moreover, worldwide osteoporosis is under-diagnosed, under-recognized and undertreated, and only a small number of patients with fractures receives proper investigation and therapy.

In 1994, a statement on the evaluation of fracture risk and its usage in screening for postmenopausal osteoporosis has been published by the WHO. In this report diagnostic criteria for BMD measurement have been provided and osteoporosis has been described as a recognized and well-defined disease that affected more than 75 million people in the world[3]. Based on WHO recommendations, national guidelines have been developed for osteoporosis management focusing mainly on the prevention of fractures in postmenopausal women.

In recent years, integrated programs to improve the management of osteoporosis are under development in some countries. Among the various aspects considered in these programs, those of particular relevance are related to education, improved screening and treatment efficacy monitoring. Indeed, many studies show that these programs reduce the risk of hip fractures compared to standard management[40]. Then, osteoporotic fractures are preventable by implementation of programs to assess and treat high risk individuals.

### *Geographical factors*

Substantial difference has been shown in hip fracture incidence rates around the world due to environmental factors and lifestyle or cultural differences[8,51]. Generally the incidence of hip fracture increases with age. Moreover, the incidence rate differs across different regions or ethnic groups[30]. In Scandinavia and in North America, age-adjusted rates seem to be highest with almost seven-fold lower rates in Southern Europe[51,52]. The incidence of hip fracture is also lower in Asia, Latin America and Africa[53,54], particularly in rural areas[55-57].

In fact, bone mass is lower in Norwegian and Swedish with respect to other European people[58]. Whereas, Chinese, Japanese, South Koreans and black Africans show significantly lower bone mineral content (BMC) with respect to Western Caucasian populations[59-61]. One probable reason for this evidence is the difference between studies leading to different levels of underreporting[30]. Furthermore, compared to Caucasian, African Americans have a higher BMC, but likewise a lower prevalence of osteoporosis[30]. The lower hip fracture incidence rates among Asians and blacks can be due to also to their shorter hip axis length[62]. The genetic background of populations in the studied regions is an important factor to explain global variations in hip fractures. For example, the hip fracture incidence rates in Ontario are similar to those in the United Kingdom because older cohorts in Ontario are of English ancestry[63], Likewise, incidence rates are similar in Mexico and Spain; in fact, this two population group share the same genetic background[64]. Rates in Argentina are close to those from other predominantly populations because the ethnic background in Argentina is largely Caucasian. Furthermore, many Scandinavian cities where immigration is increasing have lower hip fracture rates than those with uniformly Scandinavian populations[65].

The worldwide risk of hip fracture is variable more in women than in men. Women have a higher osteoporosis risk; in the United States the lifetime risk of a hip fracture from age 50 years onward has been estimated at 17% and only 6% for Caucasian women and men, respectively. Among Asian, black, and Hispanic population, women and men were about 50% and 40% less susceptible to fracture with respect to white women and white men, respectively[66]. The rates in men and women are similar in low risk populations, particularly those of Asian or African heritage[30].

The incidence rate of hip fractures depends also on the country's development. Where life expectancy at birth is low and the population is very young, as well as in African countries, the hip fracture incidence rates are the lowest[67,68]. However, the low incidence might be an artifact due to incomplete case ascertainment or national

health database unavailability in developing countries.

The improvement of health care and the augmented life expectancy due to industrialization and urbanization have led to an increased incidence of hip fracture[30]. In fact, the rapid modernization and the consequent decline in routine load of physical activity induced an increased fracture incidence of the hip in Hong Kong[69] and Beijing[70]. Moreover urban settings have higher incidence rates than rural ones (*i.e.*, Oslo, Norway )[56,71,72].

## PREVALENCE OF OSTEOPOROTIC FRACTURE

Between 1990 and 2000, osteoporosis caused a 25% worldwide increment in hip fractures. The peak for hip or other fracture types occurs for both women and men aged 75-79 years and 50-59 years, respectively[73]. The annual number of hip fractures will grow significantly with the sustained ageing of the people. It is estimated that this demographic trend could induce a global increment of hip fractures from about 2 million in 1990 to a projected 6 million in 2050[9,10]. However, the future worldwide load of age-related fractures (hip and others) should be predicted by analyzing the variations in fracture incidence rates adjusted for demographic changes in the global population. Assuming a 1% annual rise in incidence adjusted for age, hip fractures in 2050 could exceed 8 million; if rates stabilized in Europe and North America but rose by 3% per year in the rest of the world, the total could account for more than 21 million[10,11] (Figure 1).

By 2050, the global incidence of hip fracture is expected to increase more than 300% and 240% in men and in women, respectively[11]. In women aged 45 years or more, the number of days spent in the hospital due to osteoporosis are greater than those due to other pathologies, such as breast cancer, diabetes, and myocardial infarction[74]. In Switzerland hospital bed days related to osteoporotic fracture are higher than those related to stroke and other cardiac disease[75]. In England, a fifth of all orthopedic beds are dedicated to hip fractures[10] and the cost related to osteoporotic fractures treatment in postmenopausal women has been estimated to reach about 2 billion dollars or more by 2020[76]. In Spain, there are around 2 million osteoporotic women (about 30% of them are aged 50 years or more): Each year 25000 fractures arise and cause, consequently, direct costs of about €120 million and indirect costs of about €400 million[77]. In Italy, approximately 4 million of women and 800 thousand men are thought to be affected by osteoporosis. In 1998, the European Commission estimated an incidence rise of hip fractures from 117000 to 240000 in the year 2000 in Germany[78]. However, the highest risk of hip fractures are shown in Northern Europe and the United States[79]. In Swedish male population the number of hospital bed days related to osteoporotic fractures are higher than those related to prostate cancer[80]. In Denmark, in population group aged 50 years or more, about 40% of women and 20% of men are osteoporotic[81]. In Finland, hip fractures total number augmented by 70% within a 10-year period (1992-2002)[82].

In the United States, among people aged 50 years or more, there were approximately 12 million cases of osteoporosis in 2010; this data are estimated to increase up to 14 million cases of disease by 2020[83], inducing the number of hip fractures to triple by 2040[84]. In Canada, osteoporosis affects 1.4 million postmenopausal women and the elderly. Almost 30000 hip fractures occur each year, and approximately 80% of these fractures are related to osteoporosis[85]. By the year 2030, the cases of hip fractures is estimated to quadruple[86].

In Australia, osteoporosis affects 2.2 million people (approximately 11% of men and 27% of women aged 60 years or more), causing 20000 hip fractures per year (growing by 40% every ten years), with total disease-related costs of $7.4 billion per year ($1.9 billion of direct costs)[87].

It is expected that approximately half of all osteoporotic hip fractures will take place in Asia by the year 2050[11]. Osteoporosis affects almost 70 million Chinese aged 50 years or more causing 687000 hip fractures each year[88]. In Japan, hip fractures total number was 153000 in 2010 and is projected to be 238000 in 2030[89].

### *Economic burden*

In Europe, the total osteoporosis economic burden was estimated at €30.7 billion in 2010. The increment of direct costs is expected to be due to changes in demography to 76.7 billion in 2050[73]. In the United States, the medical cost of osteoporosis and related fractures is estimated at $20 billion per year[10], and can be predicted to be at $50 in 2050 due to the annual increase in incidence of osteoporotic fractures adjusted for age. China spent approximately $1.5 billion treating hip fracture in 2006. It is projected that this will grow to $12.5 billion in 2020 and to more than $264.7 billion by 2050[90] (Figure 2).

The WHO considers osteoporosis to be second only to cardiovascular diseases as a crucial health problem[74]. The disability caused by osteoporosis is comparable or even greater than that produced by cancers and by different chronic non-transmissible pathologies, as reported by Johnell and Kanis[73] in 2006. Furthermore, the total costs per year of osteoporosis exceeds those for a variety of brain disorders[91] (Figure 3).

Currently in Europe, the annual expenditure for osteoporosis corresponds about to 3.5% of the total spent on health care[40]. However, osteoporosis total cost in a country is difficult to estimate because it depends on various factors, such as fracture risk related to age, size of population, acute hospital care, cost per fracture, long-term care at home, needs of nursing home care after hip fracture occurrence, medications, rehabilitation, treatment and loss of working days. Sometimes estimated costs are based on many assumptions that are

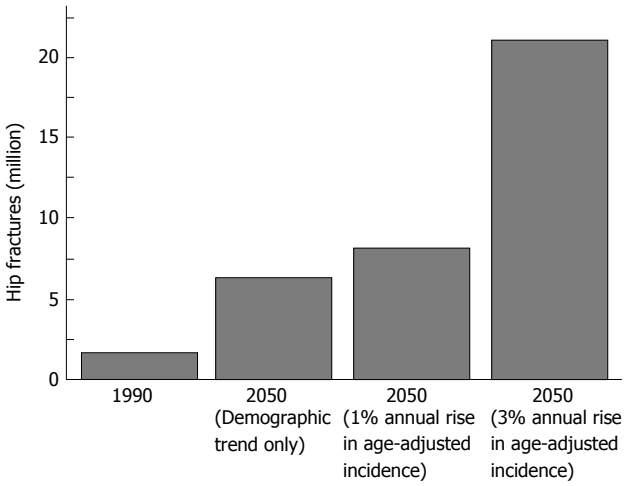


**Figure 1 Hip fractures expected impact.** Incidence of hip fractures worldwide adjusted for demographic changes.

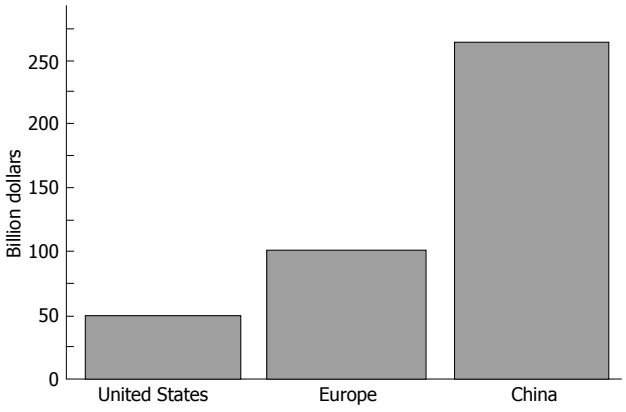


**Figure 2 Economic burden.** Expected costs in 2050 based on changes in demography.

difficult to test. Moreover, not all costs related to fracture come from a country's healthcare budget (*e.g.*, long-term care, community care).

Generally, a greater part of costs is related to incident fractures, whereas pharmacological treatment only represents less than 5% of total costs. The monetary burden depends mainly on the fracture risk; in fact, the cost per fracture increases with age (the 70% of the total costs are related to people aged more than 70 years). Also, fractures occurred in women represent the main part of the total cost[40].

Hip fractures account for more than half of the cost, whereas that of vertebral fractures is underestimated because of the difficulties of studying them. Only few people with clinical vertebral fractures become hospitalized[92] and, therefore, these cases are more complex to include in observational studies[93].

### *Outcome of osteoporotic fracture*

Osteoporosis load is referred not only to fractures, costs, mortality, morbidity, but also to quality-adjusted life years (QALYs) lost.

Generally osteoporotic fractures caused more deaths

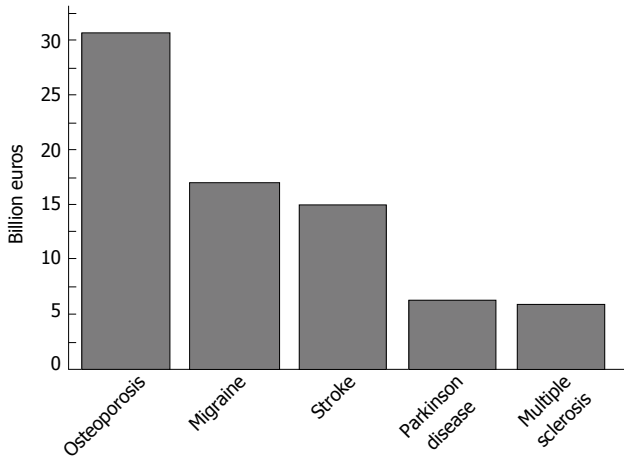


**Figure 3 Total cost of osteoporosis *vs* brain disorders.**

and morbidity than cancer (except lung cancer). In particular, fracture of the hip is responsible for more deaths than suicide and transportation accidents[40].

The fractures effect on survival is related to the fracture type[94]. Hip fractures are the most dangerous, since approximately 10%-20% women with hip fractures die than expected for age within the first year. Moreover, the mortality is greater for men, and the death risk is greatest immediately after the fracture and decreases over time[10], even if it seems that mortality rates after fracture of hip have remained constant over the past 20 years[95]. Very often osteoporosis related fractures cause loss of physical functioning including loss of mobility and self-care. Approximately 7% of women become dependent on others to assist with the basic activities of daily living, and an additional 8% require nursing home care. The main long-term damage is in the capability to walk; half of patients able to walk before fracture cannot do so autonomously afterwards. Furthermore, up to a third of individuals who have a fracture of the hip can become totally dependent[96].

The principal vertebral fractures consequences are height loss, kyphosis, and back pain. Compression fractures cause acute symptoms[97] but many fractures seem to occur without pain. Women with vertebral deformities are substantially more likely to have chronic back pain as well as future fractures. Vertebral fractures, however, affect not only physical function but also physical aspect, and humor[10].

Osteoporosis load can also be quantified by loss of quality of life (QoL). Loss of QoL reflects the disutility or loss in utility due to both the pathology and increased mortality. The utility loss caused by fracture depend on the site of fracture; in fact, fractures of the axial anatomic sites (hip and vertebrae) induce more disutility with respect to forearm fractures. The loss of utility is similar for the both sexes[98]. During the first year after fracture of hip, vertebrae and wrist a person's utility (relative to the age-specific utility) has been estimated to be 0.70, 0.59 and 0.96, respectively. On the other hand, in the subsequent years quality of life was assumed to be 80% of that of a healthy individual[99].

Combining mortality and loss of QoL, it is possible to evaluate the annual number of lost QALYs due to fractures. It is estimated that Germany has the highest number of lost QALYs due to its high fracture incidence and its great population. The estimation of QALYs lost due to fracture-related deaths was done considering an averaged interval time of four months between fracture and death[82]. Mortality during the first year after fractures represents approximately 1% and 3% of the total QALY-loss in women and men, respectively. A great part of the QALYs lost derives from the long-term disability after fractures due to osteoporosis. This component is larger in women, because men have a higher absolute mortality after fracture.

## CONCLUSION

Osteoporosis incidence is rising in many countries. Osteoporotic fractures are a crucial public health concern and represent one of the main and frequent cause of disability and medical costs worldwide. Therefore, early diagnosis of patients with high risk of osteoporotic fractures is essential. Fortunately osteoporotic fractures are preventable. The comprehension of the main factors causing this "silent disease" could help the prediction of fractures in high-risk individuals worldwide. Early diagnosis of a larger range of the population is the key to resizing the impact of osteoporosis on the health-care system. With this, it is necessary to encourage the widespread use of quick, cheap, non-invasive screening techniques and to increase national awareness campaigns promoting a healthy lifestyle across countries.

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MINIREVIEWS

# Injuries in jumpers - are there any patterns?

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## Abstract

Suicide as a cause of death, affects every health system, and is a particular problem in heavily urbanised states and low and middle income countries (which account for 75% of suicide deaths). The World Health Organisation records that 800000 commit suicide each year, representing 1.4% of annual global deaths, and that suicide was the second leading cause of death in 15-29 year-olds across the world in 2012. In the United Kingdom, jumping from height accounts for 3%-5% of the 140000 suicide attempts annually is similar incidence to the rest of Europe. The Medline and EMBASE were interrogated for studies examining suicide caused by jumping from height. Manual screening of titles and abstracts was used to identify relevant works before data was extracted and systematically reviewed to identify the characteristics of a patient who jumps from height to commit suicide, delineate their patterns of injury and explore techniques that could be used to limit its occurrence. Emergency departments receiving patients who jump from a height need to have an understanding of the potential pathology that is likely to be encountered in order to deliver multidisciplinary, efficient and timely care in order that the impact of this devastating physical, psychological and social problem could modified to the benefit of the patients involved.

**Key words:** Polytrauma; Suicide; Fracture

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**Core tip:** This paper examines the incidence of injuries following a deliberate fall from height, and argues that there are predictable patterns of injury following this mechanism.

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## INTRODUCTION

Suicide, as a cause of death, affects every global health system, and is a particular problem in low and middle income countries (which account for 75% of suicide deaths) and in heavily urbanised states[1-5]. More than

800000 commit suicide each year. The World Health Organisation records that 1.4% of annual global deaths are caused by suicide, and that suicide was the second leading cause of death in 15-29 year-olds across the world in 2012[1,6-9].

Jumping from height accounts for 3%-15% of the 140000 suicide attempts in the United Kingdom each year, a similar incidence to the rest of Europe but lower than the 26% incidence found in California[7,9-15]. Jumping requires no equipment and is easily carried out with little planning, and is likely to be fatal with 55% of patients dying either at the scene within an emergency department[16-18].

Emergency departments that receive patients who jump from a height need to have an understanding of the potential pathology that is likely to be encountered in order to deliver organised and timely care to these patients. The management of these patients requires a multidisciplinary approach and involves the consumption of significant resource[19]. When it is considered that patients are most often of working age in low to middle income countries, this becomes particularly relevant as the social and economic consequences as suboptimal management of a patient can be devastating to a family unit.

By identifying the characteristics of a patient who jumps from height for suicidal purposes, delineating their patterns of injury and exploring measures that could be used to limited the incidence of deliberate falls, the impact of this devastating physical, psychological and social problem could modified to the benefit of the patients involved.

## RESEARCH METHODS

Using the OVID portal (Wolters Kluwer, Alphen aan den Rijn, the Netherlands), both Medline (1950-Present) and EMBASE (1980 to 2015 week 16) were searched for studies examining the subject. The search was conducted using the term suicide (mapped to MeSH headings) in combination with synonyms for jump (jump, leap, fall, autokabales). Abstracts identified were then screened manually for relevance and data extracted.

## THE JUMPER AND THE JUMP

### *The jumper*

Suicide is a desperate conclusion to a psychological problem, one that may have been diagnosed prior to the attempt or may have yet to be found. Several attempts have been made to describe the characteristics of a patient who attempts suicide by jumping from a high place. Gore-Jones *et al*[11] and others have described the jumping patient as a 31-year-old single person with a diagnosis of a psychotic illness or borderline personality disorder, of which 60% will have had contact with mental health services[20]. Work from our own unit in the United Kingdom shows that in a series of 41 patients a Caucasian male aged 25-30 years is the most common patient to present with this mechanism, a picture also seen in the United States[20,21]. Other work has shown conflicting descriptors of patients. Chia and several European studies show that jumpers were usually female, young and single whereas many other reports show that jumping is more common in males[7,9,13,17,20,22-25].

Other demographics of the patient group have been identified. Whilst eighty percent of patients show features that the act was impulsive, three in every four patients have made previous suicide attempts[11]. Furthermore, Choi *et al*[16] showed that patients who jumped had a lower final grade of education, showing that severe injury following an attempt was associated with having attained a high school diploma rather than a university degree, perhaps indicating the social-economic situation in which the patient finds themselves at the time of their attempt.

Small *et al*[26] showed that inpatient suicide was a unique problem. The group showed that youth and social isolation in common with prolonged admission, a history of assaults and previous suicide attempts were particularly associated with jumping. Work in the inpatient population in the United Kingdom showed that jumping was likely to be the most common method of suicide for inpatients, as their access to alternative methods was likely to be restricted by virtue of sectioning or other controls in their environment[14].

The presence of a psychotic illness in patients who jump is agreed on in all series' that examine the phenomenon. Psychosis may be diagnosed either before or after the attempt, but is typically made in association with the presentation. Estimates of pre-existing psychiatric illness, most commonly schizophrenia (which is more severe than that suffered by those who employ other methods of suicide) range from 10%-97%[3,4,11,19,21,22,24,26-37]. Nielssen *et al*[29] examined a cohort of survivors of deliberate jumps from height and noted that only 44% of the cohort had a diagnosis of psychotic illness, of which 44% had received no previous treatment, suggesting that they were in their first episode of psychosis. Further exploration of the psychological state of these patients showed that 20% had a robust diagnosis of delusional psychosis, suggesting that the first episode of psychosis is a significant risk factor for suicide attempt[29].

Although schizophrenia is the most often quoted psychotic diagnosis given to this cohort of patients, others diagnoses do feature. Stanford *et al*[35] found a diagnosis of personality disorder in 49%, depression in 25% and mood disorder in 18%. Kennedy *et al*[22] showed depression in 27% of patients, and Kontaxakis *et al*[24] showed affective psychosis-depressive type in several of their 46 patients. In contrast, our own cohort showed an absence of documented psychiatric disease either pre-existing or newly diagnosed during inpatient stay in 44% of patients; however depression features in 23% and psychosis in 13% of cases[21]. Organic illness is found within the cohort more than one might expect given the young age of patients. Wong *et al*[4] showed that 44% of patients had physical illness, while others list

"serious somatic illness" as a comorbidity[24]. Substance abuse also features in patient backgrounds with Bostman quoting 15% of Finnish patients suffering alcoholism at the time of their jump[19,21,23,35].

The frequency of previous suicide attempt ranges from 23% to 75%[11,22,38]. Alongside this, the methods of suicide do seem to change following a failed attempt. Paraschakis found that most patients who failed to commit suicide with self-poisoning, self-inflicted wrist laceration or jumping switched method to jumping on their subsequent attempts[38]. Stanford reports a cohort of 55 patients with an 84% follow-up at a mean of 8 years, four had gone on to successful suicide[35].

### *The jump*

Unfortunately, 55% of deliberate falls cause death, a figure influenced by the height of the jump and the physical and psychological comorbidities[16,17,39,40]. Dickinson *et al*[17] examined a cohort of 117 patients attended by the London's Helicopter Air Ambulance Service who had fallen from height either accidentally or deliberately, and found that those who jumped rather than fell were more likely to die and that if head and chest injuries occurred, the height fall required for 50% of patients to die was found to be 11 m. If these injuries did not occur, the height fall required for 50% of patients to die increased to 22 m[17]. Further study by Türk *et al*[39] showed that suicidal falls occurred from a mean height of 23 m compared to 11 m for accidental falls, and that 79% of suicidal jumps were from a height greater than 16 m, whereas Copeland showed most suicidal falls were from 7 storeys (21 m) or higher[23].

Deliberate jumps occur from a range of structures, including residential buildings in 63%-83% of cases, bridges and hotels[4,14,25,32,36,40-44]. The prevention of suicide from bridges by the installation of barriers or other protections reduces the incidence of suicide from that site, an effect seen in both Europe and the United States[8,9,14,25,36,42,43,45].

The surface that the patient lands on influences both injuries and survival. Whilst jumping from buildings is likely to end with a solid surface, jumping from a bridge could lead to landing on water. Gill[46] showed that 77 suicides involving a jump into water showed few external signs of injury, suggesting drowning as the mode of death. Simonsen examined 10 cases of suicide with a water landing, and of the 10, drowning was the cause of death in six cases. Injuries, which were restricted to the thorax and spine, due to the fall caused death in four cases[47].

## THE INJURIES

The injury severity score correlates to the height of the jump and position of the patient on landing. It is established that those patients who survive their jump have multiple, severe injuries that usually require extensive treatment and that jumpers usually sustain injuries to more than one body region[18,28,48,49]. Each region of the body has particular injuries associated with it following a jump, each of which may give a clue as to the attitude of the patient on landing and help to guide both investigation and treatment.

### *The spine*

The spine is the most commonly injured body region following a deliberate fall from height, an association that is magnified if sacral fractures are included into this category[11,21,35,37,50-53]. Each group who have examined these injuries has identified a different spinal level as being most vulnerable. It seems that the most mobile spinal segments are particularly at risk particularly the thoracolumbar junction[28,35]. Wirbel *et al*[50] showed that of 36 patients with spinal injuries due to jumping, 33 had spinal injuries and Hahn *et al*[51] showed that 83% of jumpers had fractures of the thoracolumbar spine, usually at the thoracolumbar junction. Li *et al*[20] showed an incidence of 19% of neck injuries in their series, and Stanford *et al*[35] showed in his series of 55 patients with spinal cord injury as a result of jumping, 23 patients (42%) had a complete cord injury with C5 and L1 being the most commonly injured levels. Our own series shows that 15/41 patients sustained a thoracolumbar fracture (37%) and 5/41 patients a cervical spine injury[21].

### *The head*

It is reasonable to hypothesise that primary brain injury is responsible for a significant proportion of the 55% of early deaths due to suicide *via* jumping, supported by Richter *et al*[28] who showed that half of patients with a head injury fell or jumped from a single storey died[16]. Abel *et al*[41] showed that 30% of patients seen at their unit sustained craniofacial injuries, a figure in approximate agreement with Richter *et al*[28] (27%) and our own series (29%)[21]. However, Li *et al*[20] showing an incidence of head injury of 70% in their series of 124 lethal falls or jumps, suggesting the conclusion that the head injury is often fatal. Head injury is further explored by Dickinson *et al*[17] who showed that at a jump height of 11 m, 50% of those patients sustaining a head or chest injury die. Slightly contradictory to this, Türk *et al*[39] showed that patients jumping from heights between 11-25 m, head injuries were less common than when patients jumped from heights outside this range, and that 79% of suicides were from 16 m or higher.

### *The pelvis*

The only reports of pelvic fractures caused by a deliberate jump have been made by Roy-Camille *et al*[53]. They describe an H-shaped transverse sacral fracture with vertical elements through the foramina. H-shaped fractures are now synonymous with the "Jumpers Fracture" are rare, with only 1.2% of pelvic fractures treated in a European trauma centre within a 9-year period being of this type[52]. They are however significant injuries, requiring surgery in all displaced fractures, especially

with vertical shear fractures and associated L5 and S1 neurological damage[52,53].

Teh *et al*[48] found that their series of 57 jumpers showed a higher rate of pelvic injury in those who jumped from height when compared to fallers, and Richter *et al*[28] found a 30% incidence of pelvic fracture amongst 39 jumpers with the incidence of pelvic injury increased significantly once the height of the jump was above 7 m[48,51]. Within the cohort in our unit, pelvic fractures were found in 14/41 patients (34%), with jumpers fractures sustained in 4 of these, perhaps refuting a causal link between jumping and jumpers fractures[21,53]. Pelvic injuries due to jumping come with poorer long-term results when compared to other causes of pelvic fracture. It is evident that these patients have a lower health related quality of life score than other pelvic fracture patients, and that patients who are younger at the time of injury fare better when compared to more elderly[54].

### *The limbs*

The limbs are intuitively the most vulnerable to injury with any significant trauma and in jumping[50]. However, the degree to which they are injured and the pattern in which those injuries are found is not well described. Jumpers appear to sustain significantly more bilateral limb injuries than fallers which tend to be metaphyseal and epiphyseal[28,48,49]. Hahn *et al*[51] reported a limb fracture incidence to be 45% with calcaneal and ankle fracture to be the most common extremity injuries seen, with a respective incidence of 65% and 27%. Li *et al*[20] showed a 28% incidence of extremity fracture in jumpers, and Katz *et al*[37] showed that the lower limbs were the most common skeletal injury. These figures fall short of our own, where we found a 93% incidence of lower limb injury in our series of jump survivors[21]. No studies have yet published regarding the relative incidences of open and closed fractures in jumpers, although one would expect a tendency toward a higher incidence of open fractures in this group, due to the higher energy. Only two studies reporting on upper limb injuries. Our own work has shown an incidence of 8/41 upper limb injuries (most often open fractures), and Hahn *et al*[51] identified a 25% incidence of upper limb fracture in 39 jumpers[21].

### *The thorax and abdomen*

Injuries to the thorax are associated with death in the jumper[17]. Chest injuries occur in up to 66% of jumpers, with abdominal injuries occurring much less frequently, estimated at being present in 6% of cases[20,28,41]. Dickinson details how the presence of a chest injury was associated with a higher risk of death, and that in the absence of chest (and head) injuries reduced the risk[17].

Abdominal injuries are rarely reported with one study reporting an incidence of 48% of abdominal injuries in a series of 139 fatal falls and jumps[20]. This figure varies from other published and raw data both of which give figure of 6% or less[21,28]. It may be that abdominal injuries, similar to cervical spine and head injuries, are often fatal in the very early stages (through massive haemorrhage or visceral trauma) and so could be over-represented in the fatalities.

## PATTERNS OF INJURY

Few papers have commented on the patterns of injury sustained by jumpers. As is seen above, every region of the body is affected by the trauma, and the trauma can affect a patient of any background, gender or age, with their concomitant influences on presentation and survival. It is difficult to categorise the injuries sustained to a particular attitude of landing or height of jump.

Richter *et al*[28] has stated that no significant differences exist in the pattern of traumatic injuries caused by either accidental falling or deliberate jumping. Dickinson *et al*[17] showed that jumpers have a higher injury severity score and mortality than fallers and Abel *et al*[41] showed that 56% of patients who jump from bridges died from polytrauma rather than drowning or accompanying substance ingestion.

## CONCLUSION

By recognising the common injury patterns of suicide attempts from jumping, the treating clinician can target investigation and treatment to severe and easily missed injury, the Jumpers fracture being the most obvious example. Outcomes are difficult to report in this patient population, but they almost all require multidisciplinary management. Patients presenting after jumping from a height should undergo routine screening of their head, chest, abdomen, pelvis and spine, and it is of course mandatory to address the psychological issues which lead to the suicide attempt.

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ORIGINAL ARTICLE

Retrospective Study

# Outcomes of tenodesis of the long head of the biceps tendon more than three months after rupture

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## Abstract

**AIM:** To demonstrate that long head of the biceps tendon (LHBT) tenodesis is possible more than 3 mo after rupture.

**METHODS:** From September 2009 to January 2012 we performed tenodesis of the LHBT in 11 individuals (average age 56.9 years, range 42 to 73) more than 3 mo after rupture. All patients were evaluated by Disabilites of the Arm Shoulder and Hand (DASH) and Mayo outcome scores at an average follow-up of 19.1 mo. We similarly evaluated 5 patients (average age 58.2 years, range 45 to 64) over the same time treated within 3 mo of rupture with an average follow-up of 22.5 mo.

**RESULTS:** Tenodesis with an interference screw was possible in all patients more than 3 mo after rupture and 90% had good to excellent outcomes but two had recurrent rupture. All of those who had tenodesis less than 3 mo after rupture had good to excellent outcomes and none had recurrent rupture. No statistical difference was found for DASH and Mayo outcome scores between the two groups ($P$ <0.05).

**CONCLUSION:** Tenodesis of LHBT more than 3 mo following rupture had outcomes similar to tenodesis done within 3 mo of rupture but recurrent rupture

occurred in 20%.

**Key words:** Popeye deformity; Chronic rupture; Biceps tenodesis; Muscular spasm; Interference screw; Long head of biceps tendon

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**Core tip:** While some think long head of the biceps tendon (LHBT) tenodesis is not possible more than 3 mo after rupture, we have demonstrated that it is and will yeld to outcomes similar to tenodesis done within 3 mo. The LHBT tenodesis was achieved in all patients affected by chronic rupture.

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## INTRODUCTION

Rupture of the long head of the biceps tendon (LHBT) is common, accounting for 96% of all biceps brachii injuries[1] and is generally treated non-operatively. The LHBT is a flexor of the elbow and a supinator of the forearm and also it flexes and medially rotates the shoulder[2].

Studies that focused on results following chronic LHBT rupture[3-5] have found disabilities could include persistent muscle pain, biceps spasm, strength loss and popeye deformity. The loss of strength has been reported at the elbow, not the shoulder, and is not insignificant. Soto-Hall and Stroot[6] reported a 20% loss of elbow flexion strength, Deutch *et al*[3] demonstrated a 23% loss of supination strength and a 28% loss of flexion strength at the elbow and Sturzenegger *et al*[5] found a strength deficiency of 16% in flexion and 12% in supination. The popeye deformity is a cosmetic abnormality resulting from distal displacement of the long head of the biceps muscle that in part, gives the appearance of the biceps muscle being bigger.

Despite the popeye deformity and loss of elbow strength, few patients have persistent pain and muscle spasm after LHBT rupture so most are satisfied with non-operative treatments. In the past, surgery has been almost exclusively reserved for active patients with acute rupture within 3 mo of rupture and persistent symptoms[7-9].

Acute tenodesis of LHBT rupture has yielded good to excellent results in most patients. Mariani *et al*[10] performed a tenodesis to the proximal humeral shaft within 12 wk of rupture and, after 13 years, only 7.4% of patients reported mild to moderate bicipital pain, 37% reported mild to moderate deformity at the biceps, 14.8% subjective weakness at the elbow and only 11.1% poor clinical outcome and arm disability. Gumina *et al*[11] performed a tenodesis of the LHBT to the coracoid process less than 10 d after rupture and good to excellent clinical outcomes in 78.6% of patients. Tangari *et al*[12] performed a tenodesis into the bicipital groove after an average of 3 d following rupture. By 5 mo, none reported abnormal cosmetic appearance of the biceps and all of them returned to their professional activity.

But some patients first seek treatment more than 3 mo after rupture and in some the diagnosis is missed. Also, it is often difficult to predict those that will have persistent symptoms with non-operative treatment and lastly, tenolysis of the LHBT can result in pain and biceps spasm that persist more than 3 mo after rupture.

Tenodesis more than 3 mo after LHBT rupture has been thought to be complicated by scarring and retraction of the biceps tendon that precludes success[13,14]. So, most surgeons do not offer surgery for individuals more than 3 mo after rupture. A case report of LHBT tenodesis 18 mo after rupture found return to full activity and no popeye deformity 6 mo later[15]. In a prior series of 11 symptomatic patients who were treated at least 3 mo after rupture while the LHBT was too short for the authors' preferred method of tenodesis in 6, 3 reported normal cosmetic appearance and patient subjective self-assessments of strength and pain were satisfactory in over 70%[14].

The purpose of this study is to report the surgical technique and objective clinical outcomes in a series of patients with LHBT tenodesis done more than 3 mo after rupture. First, we hypothesize that LHBT tenodesis done more than 3 mo after LHBT rupture can be done reliably with an interference screw technique. Second, we hypothesize that the outcomes will be similar to those within 3 mo of rupture.

## MATERIALS AND METHODS

From September 2009 to January 2012 tenodesis of LHBT rupture was performed in 16 patients by a single surgeon (PJM). Exclusion criteria were: (1) previous surgery on the affected shoulder; (2) osteoarthritis of the glenohumeral joint; and (3) age > 75 years. All patients complained of biceps pain, weakness and persistent spasm of the biceps muscle with resisted elbow flexion activities (Tables 1 and 2) and were informed and gave their consent to the procedure and participation in the study. While there was a "popeye" deformity of the biceps muscle following a traumatic event, such as heavy lifting, or a fall, or while playing hockey, none had surgery for cosmetic reasons alone. The patients were divided into two groups, chronic which was more than 3 mo after rupture and acute which was less than or equal to 3 mo. In the chronic group 11 patients, one female and ten males, underwent LHBT tenodesis more than 3 mo after rupture and the mean time from rupture to surgery was 30.1 (range: 3.5 to 240) mo (Table 3). Two patients reported they had LHBT rupture and associated disabilities for 20 years and "several years", respectively.

**Table 1 Pre-operative associated disabilities: Chronic group**

| Patient | Pain | Muscular spasm | Popeye deformity[1] |
|---|---|---|---|
| 1 | Moderate[3] | +[2] | + |
| 2 | Moderate[3] | +[2] | + |
| 3 | Moderate[3] | +[2] | + |
| 4 | Severe[3] | +[2] | + |
| 5 | Moderate[2] | +[2] | + |
| 6 | Moderate[3] | +[2] | + |
| 7 | Moderate[3] | +[3] | + |
| 8 | Moderate[3] | +[2] | + |
| 9 | Severe[3] | +[3] | + |
| 10 | Moderate[3]/severe[2] | +[2] | + |
| 11 | Moderate[3] | +[2] | + |

[1]Popeye biceps sign; [2]Intermittent during specific activities; [3]Persistent.

**Table 2 Pre-operative associated disabilities: Acute group**

| Patients | Pain | Muscular spasm | Popeye deformity[1] |
|---|---|---|---|
| 1 | Moderate[3] | +[2] | + |
| 2 | Moderate[3] | +[2] | + |
| 3 | Moderate[3] | +[2] | + |
| 4 | Moderate[3] | +[2] | + |
| 5 | Moderate[3] | +[2] | + |

[1]Popeye biceps sign; [2]Intermittent during specific activities; [3]Persistent.

All the patients in this group had failed to improve after a rehabilitation program. In the acute group were included 5 patients, all males, who underwent tenodesis 1.7 (1 to 2) mo after LHBT rupture (Table 4). All patients had a shoulder arthroscopy prior to the open biceps surgery.

The mean age at the time of the surgery was 56.9 (42 to 73) years in the chronic group and 58.2 (45 to 64) years in the acute group. Occupation was varied and included manual laborers, managers and retired individuals. In the chronic group, ten patients were right-handed and seven ruptured the right side. In the acute group, all patients were right-handed and three ruptured the right side.

Each patient had a deltopectoral incision about 6 cm in length and the superior 1 cm of the pectoralis tendon insertion onto the humerus is incised and the posterior pectoralis tendon was probed with a finger. This was where the proximal LHBT had often retracted and scarred and if it could be palpated, it is then hooked with the finger and brought into the wound and freed from the pectoralis tendon using sharp dissection. More often, the LHBT was difficult to palpate at the posterior pectoralis tendon and then a separate 4 cm incision was made at the superior aspect of the popeye muscle. After dissection through the subcutaneous tissue the myotendinous junction of the long head of the biceps muscle was palpated and the LHBT was palpated and freed with fingers in both incisions, most often from its scarred location posterior to the pectoralis. It was then brought out of the distal wound (Figure 1A) and the end of the tendon was resected with a scalpel. This separate incision at the superior aspect of the popeye muscle was used as prior attempts to find the LHBT with a deltopectoral incision alone often resulted in the LHBT being difficult to find or too short for interference screw fixation. In pilot study, indentifying the tendon distally and then using both incisions to dissect the scarred tendon from the posterior pectoralis tendon resulted in a robust and long tendon. Tenodesis was done with more tension in those greater than 3 mo after rupture than in those less than 3 mo; we tensioned the tenodesis with the elbow flexed 60 degrees (Figure 1B). We performed a suprapectoralis tenodesis with fixation at the bottom of the bicipital groove by re-routing the tendon from the distal incision to the proximal incision under the pectoralis tendon. Fixation in all patients was with a bioabsorbable interference screw (Figure 2, DePuy, Mitek, Inc, MA, USA). The normal appearance of the biceps muscle was restored.

After the procedure, the patient's arm is placed in a sling. A few days after surgery, the patient began pendulum exercises and elbow stiffness resolved within 2 wk of surgery. Active ROM was begun at 4 wk and strengthening was begun at 3 mo after the surgery.

The self-assessment of symptoms and function of the upper extremity were evaluated with the Disabilites of the Arm Shoulder and Hand (DASH) questionnaire which evaluates the disabilities of the arm, shoulder and hand with a score from 0 (no symptoms, full function) to 100 (most severe disability)[16]. For assessment of elbow function, the Mayo elbow performance score was administered which includes 45 points for pain, 20 for motion, 10 for stability and 25 for daily activities[17]. An overall score more than 90 means excellent, from 89 to 75 is good, from 75 to 60 is fair and less than 60 is poor.

### *Statistical analysis*

Statistical analysis was performed with the Mann-Whitney test to compare the DASH and Mayo scores between the two groups and with the Wilcoxon signed-rank test to compare the pre- and post-operative scores within the same group, significance was set at $P < 0.05$ (IBM-SPSS statistics). Lastly, a power analysis was performed with G*Power 3.1.5 version ($\alpha = 0.05$, $\beta = 0.80$).

## RESULTS

No infection, stiffness or other complications were found following LHBT tenodesis in any of the patients. At an average follow-up of 19.1 (range: 9 to 35) mo, 10 patients were available in the chronic group: 9 (90%) patients reported full recovery to daily work and sports activities, no biceps pain, no spasm and the strength was comparable with the opposite side (Table 5).

Two patients had a popeye deformity of the biceps (20%) but only one of them (10%) had a poor outcome with recurrent muscular spasm, mild to moderate persistent pain and weakness at the biceps.

At an average follow-up of 22.5 (12 to 31.5) mo, 5 patients were available in the acute group: All the

**Table 3 Patient demographics: Chronic group**

| Patient | Age (yr), sex, injured side | Rupture-to-surgery (mo) | Mechanism of rupture | Occupation |
|---|---|---|---|---|
| 1 | 59, M, R[1] | 4 | Lifting | Minister |
| 2 | 73, M, L[1] | 6 | Fall | Retired |
| 3 | 68, M, L[1] | Several years | Unknown | Retired |
| 4 | 56, F, L[1] | 4 | Lifting | Mental therapist |
| 5 | 48, M, R[1] | 6 | Fall | Police officer |
| 6 | 58, M, R[1] | 8 | Playing hokey | Teacher |
| 7 | 42, M, R[1] | 3.5 | Lifting | Electrician |
| 8 | 51, M, R[1] | 240 | Water skiing | Massage therapist |
| 9 | 61, M, R[1] | 12 | Lifting | Retired |
| 10 | 57, M, L[1] | 13 | Heavy lifting | Manager |
| 11 | 53, M, R[2] | 5 | Lifting | Carpenter |

[1]Right hand dominant; [2]Ambidextrous. M: Male; F: Female; L: Left; R: Right.

**Table 4 Patient demographics: Acute group**

| Patient | Age (yr), sex, injured side | Rupture-to-surgery (mo) | Mechanism of rupture | Occupation |
|---|---|---|---|---|
| 1 | 60, M, R[1] | 2 | Heavy lifting | Retired |
| 2 | 62, M, L[1] | 2 | Fall | Auto repair |
| 3 | 60, M, R[1] | 2 | Heavy lifting | Technologist |
| 4 | 64, M, R[1] | 1.5 | Lifting | Retired |
| 5 | 45, M, L[1] | 1 | Lifting | Welder |

[1]Right hand dominant. M: Male; L: Left; R: Right.

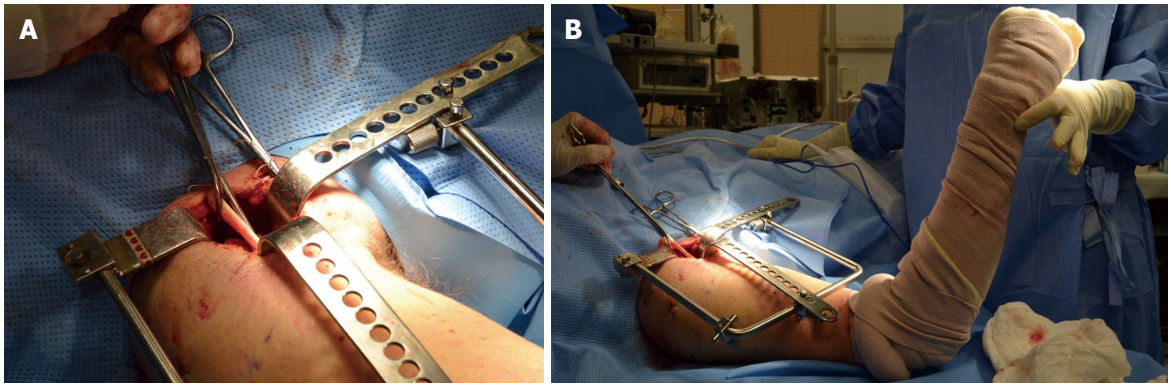


**Figure 1 Intraoperative image.** A: After incision of the proximal 1 cm insertion of the pectoralis tendon, the retracted and scarred long head of the biceps tendon is brought into the wound; B: Long head of the biceps tendon tenodesis is performed at 60° of elbow flexion.

patients reported full recovery to daily work and sports activities, no biceps pain, no spasm, strength was comparable to the opposite side (Table 6) and there were no popeye deformities.

In the chronic group the average pre-operative DASH score was 37.2 (range 29.2 to 55, $P$ = 0.859) and at follow-up there was a significant improvement to 11.2 (range 0 to 35, $P$ = 0.679) with a score change of 26 (range 20 to 29.2, $P$ = 0.001). In the acute group the average pre-operative DASH score was 35.9 (range 30 to 45.8, $P$ = 0.859) and the post-operative score was 7.3 (range 2.5 to 10.83, $P$ = 0.679) showing a significant decrease of 28.6 (range 25.4 to 38.3, $P$ = 0.001) points. We found no statistical significant difference between the two groups with the DASH score ($P$ = 0.679).

In the chronic group the pre-operative Mayo performance was 57.5 (range 45 to 70, $P$ = 1.0) and at follow-up the average score significantly increased ($P$ = 0.001) to 86 (range 85 to 100, $P$ = 0.859). In the acute group the pre-operative Mayo performance score was poor in most the patients (mean score 57, range 50 to 65, $P$ = 1.0), and there was a significant improvement ($P$ = 0.001) to excellent or good in all the patients following surgery (mean score 91, range 85 to 100, $P$ = 0.859). Statistical analysis showed no significant difference between the chronic and acute group in assessment with the Mayo performance score ($P$ = 0.859).

## DISCUSSION

LHBT tenodesis is possible more than 3 mo after rupture, and outcomes were similar to that after acute tenodesis.

**Table 5 Physical exam of the shoulder: Pre- and post-operative strength in the chronic group**

| Patient | Strength | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-op | | | Post-op | | | Contralateral | | |
| | AB | ER | IR | AB | ER | IR | AB | ER | IR |
| 1 | 4/5 | 4/5 | 3/5 | 4/5 | 4/5 | 4/5 | 5/5 | 5/5 | 5/5 |
| 2 | 2/5 | 3/5 | 3/5 | 2/5 | 3/5 | 3/5 | 3/5 | 5/5 | 5/5 |
| 3 | 4/5 | 5/5 | 4/5 | 4/5 | 5/5 | 5/5 | 4/5 | 5/5 | 5/5 |
| 4 | 4/5 | 4/5 | 3/5 | 4/5 | 4/5 | 4/5 | 5/5 | 5/5 | 5/5 |
| 5 | 3/5 | 4/5 | 3/5 | 3/5 | 4/5 | 4/5 | 5/5 | 5/5 | 5/5 |
| 6 | 5/5 | 5/5 | 3/5 | 5/5 | 4/5 | 4/5 | 5/5 | 5/5 | 5/5 |
| 7 | 5/5 | 5/5 | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| 8 | 5/5 | 5/5 | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| 9 | 4/5 | 4/5 | 4/5 | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| 10 | 5/5 | 5/5 | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| 11 | 4/5 | 4/5 | 3/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 | 4/5 |

AB: Abduction; ER: External rotation at 0 degree of arm abduction; IR: Internal rotation at 0 degree of arm abduction.

**Table 6 Physical exam of the shoulder: Pre- and post-operative strength in the acute group**

| Patient | Strength | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-op | | | Post-op | | | Contralateral | | |
| | AB | ER | IR | AB | ER | IR | AB | ER | IR |
| 1 | 4/5 | 4/5 | 3/5 | 4/5 | 4/5 | 4/5 | 5/5 | 5/5 | 5/5 |
| 2 | 4/5 | 4/5 | 4/5 | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| 3 | 4/5 | 4/5 | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| 4 | 5/5 | 5/5 | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |
| 5 | 4/5 | 5/5 | 4/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 | 5/5 |

AB: Abduction; ER: External rotation at 0 degree of arm abduction; IR: Internal rotation at 0 degree of arm abduction.

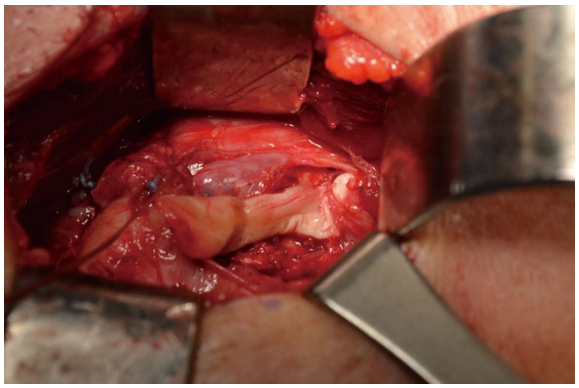

**Figure 2 Intraoperative image of the biceps tenodesis: Suprapectoralis tenodesis at the bottom of bicipital groove using 7 mm × 23 mm bioabsorbable interference screw (Milagro, DePuy Mitek, MA, United States).**

In the chronic group, we found a 90% excellent to good clinical outcomes and a 20% rate of popeye deformity. Only 1 of the 2 patients with popeye deformity reported a poor outcome. This is comparable to results reported prior following acute LHBT tenodesis[14]. Mariani *et al*[10] reported a mild to moderate biceps deformity in 37% of patients and a complete recovery of daily activities in 89% of patients. De Carli *et al*[18] reported excellent to good clinical outcome in 94.2% of patients. Checchia *et al*[19] reported a 93.4% rate of satisfactory results. Hsu *et al*[20] reported a 25% incidence of recurrent rupture; Boileau *et al*[7] reported a 3% incidence of recurrent rupture, 9% incidence of muscular cramping, and 30% rate of pain at the bicipital groove. Koh *et al*[21] reported 83.7% of excellent to good clinical outcomes, 4.6% incidence of cramping pain, and a 9.3% rate of recurrent rupture. Lastly, in a systematic review Slenker *et al*[22] found excellent to good clinical outcomes in 74% of patients, an 8% incidence of recurrent rupture, and a 24% rate of bicipital pain.

While chronic rupture of the LHBT is usually asymptomatic, successful biceps tenodesis is important for some active patients who suffer with long-term cramping, pain and weakness. It also is helpful in the treatment of patients with persistent symptoms who first seek treatment more than 3 mo after LHBT rupture and in others in whom the diagnosis was missed. It also eases the difficulty surgeons have in making the decision for surgery within 3 mo as contrary to the beliefs of most surgeons, if symptoms persist in the long-term, biceps tenodesis can still be successful. Lastly, when tenolysis of the LHBT results in pain and biceps spasm that persist for more than 3 mo, LHBT tenodesis is still possible.

Many proximal biceps tenodesis techniques, both arthroscopic[13,23-26] and open[12,27-29] have been described. We used interference screw fixation as prior biomechanical study had found it to have cyclic displacement and load at failure that are better than other fixation techniques immediately after surgery[28]. No infection, stiffness or other complications were found consistent with prior studies that found low incidence

of complications after open LHBT tenodesis, specifically a 0.28% incidence of infection and a 0.28% incidence of neuropathies[30]. After more than 3 mo from LHBT rupture, an arthroscopic tenodesis is not currently suitable for two reasons. First, the LHBT is usually retracted to the pectoralis tendon or distal to it. Second, the LHBT is sometimes short, warranting tenodesis more distal than usual.

There are few reports of tenodesis of chronic LHB ruptures. Tucker[31] described their technique of chronic LHBT tenodesis in three patients but no results were reported. Ng and Funk[14] reported their patient's subjective self-assessments of strength and pain and improvements of 74% and 79% respectively but only 3 of 11 patients had a normal cosmetic appearance. We achieved a normal cosmetic appearance in many more of our patients, 80% in all. This may have been partly from our retrieval of the LHBT with a separate 4 cm incision at the superior aspect of the "popeye" muscle when it could not be found with a deltopectoral incision, partly from our tensioning of the biceps tenodesis at 60° of elbow flexion and partly from our being able to reliably tenodesis the LHBT with an interference screw. Different from prior studies, we also performed objective scores and our improvements in these scores surpassed those prior demonstrated to be clinically relevant[32,33].

Our study has several limitations. More patients with chronic rupture were included in the study because the senior author was known in his community that he was willing to operate on them. Still, the number of patients is small and while an interference screw could reliably be used for the tenodesis, surgeons should counsel patients and be prepared for other techniques in accordance with prior study[14] despite the surgical improvements we report. In addition, associated morbidities could have influenced the outcome scores however the Popeye deformity was restored in 80%. While there were no statistical differences between the outcome scores after chronic and acute tenodesis, there were 2 recurrent ruptures in the chronic group and none in the acute group. A post hoc power analysis revealed that over a thousand of patients would be required to detect a statistical difference ($\alpha$ = 0.05, $\beta$ = 0.8) between outcome scores between the two groups.

## COMMENTS

### Background

The long head of the biceps tendon (LHBT) is a flexor of the elbow and a supinator of the forearm. Rupture of the LHBT is common, and is generally treated non-operatively. However disabilities could persist after LHBT rupture such as muscle pain, biceps spasm, strength loss and popeye deformity.

### Research frontiers

Tenodesis more than 3 mo after LHBT rupture has been thought to be complicated by scarring and retraction of the biceps tendon that precludes success. So, most surgeons do not offer surgery for individuals more than 3 mo after rupture.

### Innovations and breakthroughs

Contrary to what many surgeons think, tenodesis with an interference screw more than 3 mo after LHBT rupture is possible and this confirmed the authors' hypothesis. Outcome is similar to that after tenodesis within 3 mo of rupture but there were 2 recurrent ruptures in those treated more than 3 mo after rupture. Those results are comparable to acute LHBT tenodesis recently performed by other authors (De Carli *et al*, 2012; Koh *et al*, 2010; Gumina *et al*, 2011; Ng and Funk, 2012).

### Applications

Tenodesis after LHBT rupture should be considered for patients with persistent complaints of pain, weakness and biceps muscle spasm and should not be limited to those within 3 mo of rupture. It also is helpful in the treatment of patients with persistent symptoms who first seek treatment more than 3 mo after LHBT rupture and in others in whom the diagnosis was missed. It also eases the difficulty surgeons have in making the decision for surgery within 3 mo as contrary to the beliefs of most surgeons, if symptoms persist in the long-term, biceps tenodesis can still be successful.

### Terminology

Bicep tenodesis: This procedure involves the reattachment of the LHBT to the humeral bone. A guide wire and reamer is used to make a bone tunnel in the humerus; Interference screw: The fixation of the LHBT into the humeral bone tunnel is performed using a resorbable threated screw; Muscular spasm: Is a sudden involuntary contraction of a muscle, or a group of muscles, accompanied by pain, but is usually harmless and ceases after few minutes.

### Peer-review

The authors investigated the outcomes of tenodesis of the long head of the biceps tendon more than 3 mo after rupture compared with those performed within 3 mo, and found that the outcomes are similar after 3 mo rupture to those within 3 mo rupture.

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ORIGINAL ARTICLE

Retrospective Study

# Knee awareness and functionality after simultaneous bilateral *vs* unilateral total knee arthroplasty

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Author contributions: Latifi R performed the initial drafting of manuscript; Latifi R and Thomsen MG collected the data; Latifi R, Thomsen MG, Kallemose T, Husted H and Troelsen A performed the data analysis, interpretation, the revision and final approval of manuscript; Thomsen MG, Husted H and Troelsen A designed the study.

Institutional review board statement: According to the national laws, questionnaire surveys and retrospective studies are exempt from obtaining approval from the National Research Ethics Committee (equivalent to IRB) (see Committee Acts at http://www.dnvk.dk/).

Informed consent statement: According to the national laws, it is not required to obtain informed written consent prior to conducting questionnaire surveys. Subjects were sufficiently anonymized and cannot be identified. Data were handled according to the acts of the Danish National Data Protection Agency. The Danish National Data Protection Agency approved this study (AHH-2014-010).

Conflict-of-interest statement: There are no conflicts of interest related to the present study.

Data sharing statement: The technical appendix, statistical code, and dataset associated with the present study are available from the corresponding author at roshan_latifi@yahoo.com. The data used in this study were sufficiently anonymized, and the Danish National Data Protection Agency approved this study (AHH-2014-010).

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## Abstract

**AIM:** To investigate knee awareness and functional outcomes in patients treated with simultaneous bilateral *vs* unilateral total knee arthroplasty (TKA).

**METHODS:** Through a database search, we identified 210 patients who had undergone unilateral TKA (UTKA) and 65 patients who had undergone simultaneous bilateral TKA (SBTKA) at our institution between 2010 and 2012. All TKAs were cemented and cruciate retaining. The mean follow-up period was 3.2 (2 to 4) years. All the patients had symptomatic and debilitating unilateral or bilateral osteoarthritis for which all conservative and non-surgical treatments were failed, thus preoperatively the patients had poor functionality. All patients were asked to complete Forgotten Joint Score (FJS) and Oxford Knee Score (OKS) questionnaires. The patients were matched according to age, gender, year of surgery, Kellgren-Lawrence score and pre- and

postoperative overall knee alignment. The FJS and OKS questionnaire results of the two groups were then compared.

**RESULTS:** A mixed-effects model was used to analyze differences between SBTKA and UTKA. OKS: The mean difference in the OKS between the patients who had undergone SBTKA and those who had undergone UTKA was 1.5, which was not statistically significant (CI = -0.9:4.0, *P*-value = 0.228). The mean OKS of the SBTKA patients was 37.6 (SD = 9.0), and the mean OKS of the UTKA patients was 36.1 (SD = 9.9). FJS: The mean difference in the FJS between the patients who had undergone SBTKA and those who had undergone UTKA was 2.3, which was not statistically significant (CI = -6.2:10.8, *P*-value = 0.593). The mean FJS of the SBTKA patients was 59.9 (SD = 27.5), and the mean FJS of the UTKA patients was 57.5 (SD = 28.8).

**CONCLUSION:** SBTKA and UTKA patients exhibited similar joint functionality and knee awareness. Our results support the use of SBTKA in selected patients suffering from clinically symptomatic bilateral osteoarthritis.

**Key words:** Unilateral total knee arthroplasty; Knee awareness; Patient-reported outcomes; Simultaneous bilateral total knee arthroplasty; Forgotten Joint Score

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**Core tip:** We investigated the functional outcomes and knee awareness of patients who had undergone simultaneous bilateral compared with those who had undergone unilateral total knee arthroplasty (TKA). To accomplish this, we used the well-known Oxford Knee Score and the recently introduced Forgotten Joint Score (FJS). The FJS is based on a novel concept, or a patient's ability to forget about an artificial joint as a result of successful treatment; this result is considered as the ultimate goal of joint replacement surgery. No differences in final outcomes were observed between the groups. Therefore, individuals for whom bilateral TKA is indicated should be offered this option.

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## INTRODUCTION

The number of patients undergoing simultaneous bilateral total knee arthroplasty (SBTKA) has steadily increased. Currently, approximately 6% of all total knee arthroplasties (TKAs) performed in the United States are simultaneous bilateral procedures[1].

The potential benefits of SBTKA compared with staged procedures include a decreased length of hospitalization, decreased time under anesthesia, decreased rehabilitation time, and decreased cost to the healthcare system[2-5]. The disadvantages of SBTKA include an increased need for blood transfusions and increased physiological stress induced by simultaneous surgery[1,6-9]. Although these benefits and disadvantages are accepted in the medical community, it remains a matter of debate whether functional outcomes, pain relief and patient satisfaction are equivalent between bilateral and staged procedures.

The need to rehabilitate two knees after SBTKA could be hypothesized to result in inferior functional outcomes for each knee compared with those achieved following rehabilitation of a single knee, as in unilateral TKA (UTKA)[10]. Furthermore, the increased length of time required to perform SBTKA compared with UTKA could result in inferior technical performance toward the end of the procedure. This decreased performance could possibly be reflected in functional outcomes and knee awareness[11]. Hence, functional outcomes and knee awareness following SBTKA could be inferior following UTKA according to the two aforementioned hypotheses. If functional outcomes and knee awareness are indeed inferior after SBTKA relative to UTKA, then the indications for performing SBTKA will be limited, and reconsideration of current SBTKA treatment strategies will be warranted.

The purpose of this study was to compare knee awareness and functional outcomes between patients who had undergone SBTKA and those who had undergone primary UTKA.

## MATERIALS AND METHODS

This study was performed in accordance with the Declaration of Helsinki of the World Medical Association.

In the current retrospective, matched, case-control cohort study, we identified 69 patients who had undergone SBTKA with insertion of prostheses with the same TKA design in both knees at our institution between January 2010 and December 2012. During that period, the same TKA design was used in 240 UTKA procedures. Selected patients had symptomatic and debilitating unilateral or bilateral osteoarthritis for which conservative and non-surgical treatments were failed. Hence, preoperatively all the patients had poor functional performance. These UTKA patients were enrolled in the study as controls. The large size of the UTKA group ensured that as many patients as possible could be matched. Patients who had undergone knee surgery before primary TKA or who had undergone revision surgery with replacement of the prosthetic components after primary TKA were excluded. All TKA procedures had been performed using a medial para-patellar approach and were cemented and cruciate retaining (AGC, Biomet, Warsaw, Indiana). Additionally, all procedures included patellar resurfacing. The AGC prosthesis is a widely used TKA system that demonstrated good clinical results and longevity in earlier

studies[12-14]. All patients had undergone surgery in a fast-track setting and had followed the same standardized postoperative rehabilitation program[15]. Patients had been selected for SBTKA if they had bilateral disabling osteoarthritis and no cardiopulmonary comorbidity (ASA 1 to 2).

Gender, age at the time of surgery and year of surgery were documented for all patients. Preoperative radiographs were available for all knees and were analyzed for the degree of osteoarthritis using the Kellgren-Lawrence (KL) grading scale[16,17]. Pre- and postoperative anteroposterior knee anatomical alignment was measured using short-film radiographs according to the method described by Petersen *et al*[18]. The same observer performed all radiographic assessments.

SBTKA patients and UTKA controls were invited to participate in this study in January 2014. Each patient received Forgotten Joint Score (FJS) and Oxford Knee Score (OKS) questionnaires. The patients in the UTKA group received one set of questionnaires, whereas those in the SBTKA group received two sets of questionnaires, with one clearly marked for each knee. The questionnaire responses left 65 SBTKA and 210 UTKA patients eligible for matching and further analysis.

Each knee in the SBTKA group was matched 1:1 to the knees in the UTKA group regarding gender, age at the time of surgery, year of surgery, KL grade and pre- and postoperative anatomical knee alignment (Table 1). This resulted in a study cohort of 94 knees in 47 patients in the SBTKA group and 94 knees in 94 patients in the UTKA group. The FJS and OKS were then calculated and compared between the matched groups. The follow-up period in this study was 2 to 4 years (mean 3.2 years). A flow chart describing the study's participants can be found in Figure 1.

For all participants, the OKS was calculated. The range of the OKS is 0 to 48, with 48 being the best possible score[19].

The FJS[20] is based on a 12-item questionnaire that evaluates a patient's ability to forget about his or her artificial joint in everyday life (awareness of the knee). The range for the FJS is 0 to 100, with 100 being the best possible score; the properties of the FJS questionnaire have been reported in earlier studies[20-22].

The data used in the current study were sufficiently anonymized, and The Danish National Data Protection Agency approved the project (AHH-2014-010).

### Statistical analysis

The statistical methods used in this study were reviewed by Thomas Kallemose, a biomedical statistician from Clinical Research Center, Copenhagen University Hospital Hvidovre, Kettegaard Alle 30, DK-2650 Hvidovre, Copenhagen, Denmark.

Matching was performed for all patients who completed both the FJS and the OKS questionnaires. The matching was prioritized by operation year, gender, KL score, age at the time of surgery, postoperative anatomical knee alignment and preoperative anatomical knee alignment. The year of surgery was most highly prioritized because of the small amount of overlap between the UTKA and the SBTKA patients. Pooled squared differences corresponding to age at the time of surgery, postoperative anatomical knee alignment and preoperative anatomical knee alignment were used to determine the best matching; 100000 permutations were used, and the best was selected based on the smallest pooled squared difference.

Sample size estimation was based on the ability to detect an inter-group difference (power 90%, *P*-level 0.05, SD: 10) of 5 points or more (considered to be clinically relevant) in the OKS. This resulted in a need for 85 cases per group.

A mixed-effects model was used to assess the differences between UTKA and SBTKA patients in terms of both the FJS and the OKS. The score difference between the UTKA and the SBTKA patients within each matched knee pair was used as an outcome in the model. Because of the assumed within-patient variance in the SBTKA group, a random effect corresponding to the SBTKA patients' scores was added. Because of the matching, no other factors were added to the model. A *P*-value less than 0.05 was considered statistically significant. All matching and analyses were performed using R 3.02 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### OKS

The mean difference in the OKS between the SBTKA and the UTKA groups was 1.5, which was not statistically significant (CI = -0.9:4.0, *P*-value = 0.228). The mean OKS was 37.6 (SD = 9.0) in the SBTKA group, and it was 36.1 (SD = 9.9) in the UTKA group (Table 2).

### FJS

The mean difference in the FJS between the SBTKA and the UTKA groups was 2.3, which was not statistically significant (CI = -6.2:10.8, *P*-value = 0.593). The mean FJS was 59.9 (SD = 27.5) in the SBTKA group, and it was 57.5 (SD = 28.8) in the UTKA group (Table 2).

## DISCUSSION

Whether the advantages of SBTKA outweigh its potential disadvantages has been a topic of much debate. Numerous studies have investigated the risk of perioperative complications after SBTKA[1,4-9,23-29] and the cost-effectiveness of the procedure[2,30-33] in comparison with UTKA. However, the majority of these studies have not focused on long-term functional outcomes or knee awareness. In the current study, we investigated functional outcomes and knee awareness during daily-living activities using patient-reported outcome measures following SBTKA and UTKA.

**Table 1 Post-matching distribution of demographic parameters**

| | | Bilateral | Unilateral |
|---|---|---|---|
| Gender, No. of knees (%) | Male | 34 (36%) | 34 (36%) |
| | Female | 60 (64%) | 60 (64%) |
| Age at operation, mean (SD) range | | 66 yr (8.2) | 65 yr (7.4) |
| | | 45, 81 | 46, 80 |
| Osteoarthritis grade, No. of knees (%) | KL 1 + 2 | 27 (29%) | 27 (29%) |
| | KL 3 + 4 | 67 (71%) | 67 (71%) |
| Alignment, mean (SD) range | Preoperative | 1.2 (5.3) | 1.3 (5.9) |
| | | -16.3, 16.2[1] | -12.1, 21.8[1] |
| | Postoperative | 5.2 (3.0) | 4.9 (3.4) |
| | | -1.1, 12.8[1] | -11.2, 12.8[1] |
| Operation year, No. of knees (%) | 2010 | 24 (26%) | 24 (26%) |
| | 2011 | 62 (66%) | 62 (66%) |
| | 2012 | 8 (9%) | 8 (9%) |

[1]Varus (-), Valgus (+). KL: Kellgren-Lawrence.

We hypothesized that the longer duration required to perform SBTKA could lead to inferior technical performance when operating on the second knee and that difficulties during postoperative rehabilitation of two knees after SBTKA could result in an overall inferior functional outcome and higher knee awareness compared with those for UTKA. We found that the SBTKA group did not significantly differ from the UTKA group with respect to functional outcomes or knee awareness at 2 to 4 years post-surgery. This result is consistent with the findings from a previous study[34], in which 150 consecutive, but selected, SBTKA cases were compared with 271 UTKA cases in a standardized fast-track setting between 2003 and 2009. Husted *et al*[34] demonstrated that the outcome at three months and two years was similar or better in the SBTKA group with regard to satisfaction, the range of motion, pain, the use of a walking aid and the ability to work and perform activities of daily living. However, this previous study did not use a validated PROM, such as those used in the present study.

In a retrospective review of 697 TKAs in 511 consecutive patients (SBTKA: 186, UTKA: 325) with bilateral knee arthritis and a follow-up period of 2 to 8 years, using the Knee Society Score and its subscales as endpoints, Bagsby and Pierson[35] demonstrated a statistically significant better postoperative functional outcome, including an increased total range of motion ($P$ = 0.001), improved flexion ($P$ = 0.003), and an increased function score ($P$ < 0.001) associated with SBTKA. They presumed that this finding was related to the absence of contralateral arthritis, which would produce pain and restrict rehabilitation. This contradicts our hypothesis that simultaneous surgeries on two knees would make rehabilitation more difficult and potentially result in an inferior outcome compared with that associated with UTKA. However, their findings are ultimately consistent with our conclusions regarding the performance of SBTKA.

**Table 2 Results for the Oxford Knee Score and Forgotten Joint Score**

| | | SBTKA | UTKA |
|---|---|---|---|
| PROM outcomes, mean (SD) range | OKS | 37.6 (9.0) | 36.1 (9.9) |
| | | 10, 48 | 9, 48 |
| | FJS | 59.9 (27.5) | 57.5 (28.8) |
| | | 0, 100 | 0, 100 |

FJS: Forgotten Joint Score; OKS: Oxford Knee Score; SBTKA: Simultaneous bilateral TKA; UTKA: Unilateral TKA; TKA: Total knee arthroplasty; PROM: Patient-reported outcome measure.

In a study by Zeni and Snyder-Mackler[36], 15 subjects who had undergone SBTKA were observed prospectively for a period of 2 years. Subjects in this group were matched with subjects who had undergone UTKA by age, sex and BMI, providing equal samples of 15 subjects in each group. These 2 groups were then compared with a group of 21 orthopedically healthy subjects, which served as the control group. Pre- and post-operative self-reported functional measures and objective clinical tests were then applied to the groups. At 2 years, the long-term outcomes of the bilateral group were similar to those of the matched sample of patients who had undergone UTKA and to those of the control subjects. These findings are again in accordance with the findings of the current study, which unanimously support the practice of SBTKA according to the long-term outcomes.

Seo *et al*[11] reviewed SBTKA outcomes in 420 patients at 1 year post-surgery. Similar to what was hypothesized in the current study, they hypothesized that the postoperative results produced by SBTKA would vary as a result of disparate surgical scenarios between knees. In support of their hypothesis, they found that the second TKA had a greater incidence of outliers in limb coronal alignment (16.2% *vs* 9.0%, $P$ = 0.003), more blood loss (735 mL *vs* 656 mL, $P$ < 0.001) and a slightly longer operation time (61 min *vs* 58 min, $P$ < 0.001) compared with the first TKA. This supports our hypothesis that lengthier surgeries could lead to inferior technical performance near the end of a procedure, possibly resulting in inferior functional outcomes and higher knee awareness of the knee operated on last. However, at the 1-year follow-up, neither knee showed a difference in its range of motion after surgery ($P$ = 1.000). The postoperative flexion angle improved equally, to 129° and 127°. Moreover, no significant differences in the postoperative Knee Society Function Score or the total Western Ontario and McMaster Universities Arthritis Index scores were observed between the sides ($P$ = 0.316 and 1.000, respectively).

However, a significant difference in the postoperative Knee Society Knee Score was observed ($P$ < 0.001). Concerns that SBTKA produces inferior functional outcomes in one or both knees thus appear to be unwarranted.

A review of previous SBTKA studies concluded that there are no sound counterarguments against

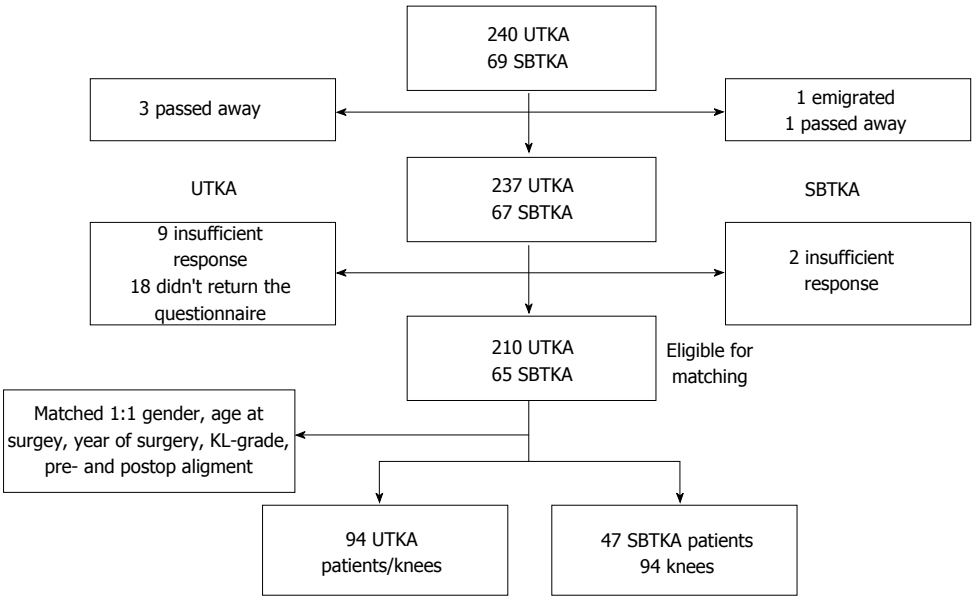


**Figure 1 Flowchart describing the patients who were invited to participate in the study and those included in the analysis.** UTKA: Unilateral TKA; SBTKA: Simultaneous bilateral TKA; TKA: Total knee arthroplasty; KL: Kellgren-Lawrence.

the orthopedic advantages of SBTKA[8]. Any remaining debate centers on medical and anesthetic contraindications. Age and preoperative comorbidities play important roles in postoperative morbidity and mortality. In addition, 81% of the participants in the Consensus Conference on Bilateral Total Knee Arthroplasty Group[37] agreed that SBTKA is associated with an increased risk of perioperative adverse events when performed on unselected patients. The consensus group also agreed that physicians and hospitals should consider using more restrictive patient selection criteria and should exclude those with a modified cardiac risk index greater than 3 to mitigate the potentially increased risk of adverse events. Furthermore, the entire group agreed that when there is a conflict between orthopedic need and medical adequacy with regard to SBTKA, the medical concern for a patient's safety should prevail over the orthopedic need. Hence, only patients with no evidence of cardiopulmonary disease, ASA scores of 1 or 2 and bilateral disabling osteoarthritis are considered as acceptable candidates for SBTKA at our institution. In the current study, because cardiopulmonary disease tends to increase with age, we found that patients in the SBTKA group were younger before matching was performed. It can be argued that younger patients might experience fewer degenerative changes in the knees. To account for this, we matched the SBTKA and UTKA groups in terms of gender, age at the time of surgery, year of surgery, KL grade and pre- and postoperative anatomical knee alignment to minimize potential bias.

The FJS has recently been introduced and validated as a post-surgical assessment tool for total joint replacement[20]. The FJS specifically evaluates a patient's level of awareness of their artificial joint in 12 scenarios commonly encountered in daily life. Joint awareness includes strong sensations, such as pain, and the ability to perform activities of daily living, as well as more subtle feelings, such as mild stiffness, subjective dysfunction and any other discomfort that a patient might encounter. The forgotten joint concept, which is based on the level of knee awareness, is a more discerning assessment method that has shown better discriminatory power and less of a ceiling effect than traditional questionnaires measuring pain or function do. These features are especially appealing for more active patients with good to excellent outcomes after TKA. The FJS also allows detection of potential subtle differences between patients and between follow-up time points[20,21].

The current study has certain limitations. We matched patients according to the abovementioned parameters, whereas other factors (*e.g.*, BMI, social status, psychological profile, preoperative duration and pain intensity, comorbidities and ASA score) that may potentially affect functional outcomes and knee awareness, were not accounted for in this study. However we have chosen parameters, which have a high influence on functional outcomes and involved in this study. The primary strength of the present study is the matching of patients between the study groups in terms of gender, age at the time of surgery, KL grade and pre- and postoperative knee alignment. Because of this matching procedure, we believe that our study groups are comparable, counteracting the study's limitations.

SBTKA and UTKA patients exhibit similar knee function and knee awareness. Our results support the use of SBTKA in selected patients without cardiopulmonary comorbidity who suffer from clinically symptomatic bilateral osteoarthritis.

## COMMENTS

### *Background*

The potential benefits of simultaneous bilateral total knee arthroplasty (TKA)

include a decreased overall length of hospitalization, shorter overall anesthesia time and decreased cost to both the patient and the institution. Although many prior studies examining differences between unilateral and bilateral TKA have focused on short-term postoperative outcomes, costs, and complications, few have assessed differences in long-term results and functional outcomes.

### Research frontiers

To the authors' knowledge, this is the first review to analyze patient-reported outcomes (PROs) after simultaneous bilateral TKA using the newly introduced Forgotten Joint Score (FJS). The FJS was validated in Danish in a parallel study at the authors' institution and was used to compare PROs between simultaneous bilateral TKA patients and unilateral TKA patients.

### Innovations and breakthroughs

Several reports have shown the potential effects of knee alignment on PRO measures after TKA. Therefore, the authors measured osteoarthritis severity and pre- and post-operative overall knee alignment based on the radiographs of 340 patients. Moreover, the authors used the forgotten joint concept, which is a more discerning assessment method that has shown better discriminatory power and less of a ceiling effect than traditional questionnaires measuring pain or function do. These features are especially appealing for more active patients with good to excellent outcomes after TKA. The authors obtained perfect matching regarding age, gender, year of surgery, Kellgren-Lawrence score and pre- and post-operative overall knee alignment, which allowed comparison of parameters of interest without confounding by other elements. Concurrently with the FJS, the authors also used the well-known Oxford Knee Score (OKS) to investigate patient functionality after joint replacement.

### Applications

The results support the use of simultaneous bilateral TKA in selected patients without cardiopulmonary comorbidity who suffer from clinically symptomatic bilateral osteoarthritis.

### Peer-review

This is an interesting retrospective study. The patients were evaluated using subjective scores (FJS and OKS Questionnaires) and therefore the results are "more reliable".

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