



## Chronic Postoperative Pain After Joint Replacement

Total joint arthroplasty (TJA) surgery is considered to be an effective intervention to improve function and reduce pain in conditions such as end-stage knee osteoarthritis (OA). In the United States alone, the number of total knee arthroplasty (TKA) procedures has increased from 31.2 per 100,000 person-years in the period 1971–1976 to 220.9 in the period 2005–2008, and from 50.2 in 1969–1972 to 145.5 in 2005–2008 for total hip arthroplasty (THA) procedures [26]. By 2030 the incidence of THA and TKA is predicted to increase by approximately 200% and 700%, respectively [15]. Prosthesis-related outcomes such as radiographic appearance of the prosthesis, implant survival, or surgeon-assessed outcomes are highly successful after TJA, and while most patients experience pain relief after TJA, about 20% of TKA and 10% THA patients develop chronic postoperative pain. Understanding pain is complex, and a single preoperative measure cannot predict chronic postoperative pain. However, several preoperative factors can indicate if a patient is at high risk of developing chronic postoperative pain following TJA. This issue of *Pain: Clinical Updates* is intended

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as a scientific update to review recent evidence on pre-, peri-, and postoperative risk factors for the development of chronic postoperative pain following TJA, focusing on THA and TKA.

### Pain in the Joints

Joint pain is highly individual. Nociceptors have been located in the fat pad, subchondral bone, periosteum, and the

synovium, but not in normal cartilage. This anatomical feature could explain why cartilage features from radiological imaging have not demonstrated robust associations with pain manifestations. In fact, the extent of the bone marrow lesion seems to represent the feature most strongly linked to OA pain intensity [17]. Prolonged inflammation and prolonged excitation of the nociceptors can result in localized sensitization (peripheral sensitization), eventually leading to sensitization of the entire central nervous system (central sensitization), which is further believed to lead to widespread pain hypersensitivity.

### Guidelines

Recently, guidelines on the management of postoperative pain were published by the American Pain Society

The incidence of chronic postoperative pain following total knee and hip arthroplasty is approximately 20% and 10%, respectively. This clinical update highlights the following preoperative factors as being associated with higher chances for developing chronic postoperative pain following total joint replacement:

- High preoperative pain intensity
- High pain sensitization
- High inflammation
- Multiple arthritis-affected joints
- Female gender
- Comorbidities (e.g., diabetes or fibromyalgia)
- Pain catastrophizing

The incidence of increased chronic postoperative pain after revision joint surgery based on the indication of pain is very high, suggesting careful consideration as to which patients should be offered revision surgery as compared to other conservative treatments.

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in collaboration with the American Society of Anesthesiologists, concluding that optimal postoperative pain management should begin in the preoperative period. Further, pain management should be based on an assessment of the patient and development of a plan of care tailored to the individual, including follow-up assessments and adjustments as needed [7]. These recommendations are based on a wide range of surgical procedures, but they highlight the importance of preoperative screening of patients in the effort to modulate acute postoperative pain. Given that acute postoperative pain intensity is known to promote the development of chronic postoperative pain, both preoperative monitoring and adequate postoperative management are important.

### Pre- and Perioperative Indications for Chronic Postoperative Pain

Preoperative pain intensity, pain sensitization, arthritis in multiple joints, comorbidities, pain catastrophizing, genetic factors, inflammation, and previous surgery are factors generally linked with differences in various outcomes after surgery. The following sections review these factors with regard to TJA.

### Pain and Sensitization of the Nervous System

A simple measure of pain intensity is the 10-cm visual analogue scale (VAS), in which 0 cm indicates no pain and 10 cm indicates the worst pain imaginable. High preoperative pain intensities have been associated with the risk of developing chronic postoperative pain [3]. In addition, the risk of chronic postoperative pain is 3–10 times higher if the pain ranges from moderate to intolerable instead of mild in the first postoperative week [28],

and therefore, decreasing preoperative pain intensity before TJA can be hypothesized as advantageous.

More advanced pain measures include quantitative sensory testing (QST), which aims to mechanistically profile patients and, more importantly, identify subgroups of patients. Patients with chronic knee and hip OA pain demonstrate widespread pain hypersensitivity, which can be assessed quantitatively as generally reduced pressure pain thresholds (PPTs) compared with healthy controls. Furthermore, OA patients appear to become increasingly hypersensitive to pressure pain with increasing intensity and duration of clinical pain [3]. Widespread hyperalgesia is believed to be a proxy for central manifestations of pain sensitization. The widespread pain sensitization can be normalized after TJA [3] when patients have no residual pain. Two recent studies have shown an association between preoperative widespread pain and the development of chronic postoperative pain following TKA [20] and THA [29].

Temporal summation of pain (TSP) is assumed to be the human parallel to wind-up assessed from animal dorsal horn neurons. Further, TSP is assumed to reflect the central gain of the spinal processing network. Facilitated TSP has been documented in patients with knee and hip OA compared with healthy age-matched controls [3]. Two recent studies have associated preoperative facilitated TSP with the development of chronic postoperative pain following TKA [19,20], but no studies have been conducted for THA.

Conditioned pain modulation (CPM) is a measure of the net effect of descending pain facilitation and inhibition; it may affect the entire neuroaxis and hence may be responsible for

generating widespread pain hypersensitivity. CPM is impaired in patients with knee and hip OA compared with healthy age-matched controls and is normalized after TJA, and the impairment seems to depend on pain intensity and duration [3]. Preliminary studies indicate that impaired CPM before thoracotomy and abdominal surgery may be predictive for the risk of developing chronic postoperative pain. Recently, preoperative impaired CPM in combination with facilitated TSP was associated with poor pain relief following TKA [20], suggesting that the combination of different pain biomarkers may be the path toward further development of a “predictive pain platform.”

A specific subgroup of patients with OA characterized by high pain, but low radiological severity, seem to be highly pain sensitive [2]. This finding suggests that specific “red flag” criteria should be developed for preoperative screening of patients prior to TJA because these patients would most likely benefit from a tailored preoperative management program.

### Multiple Joints Affected by Arthritis

OA can simultaneously affect multiple joints in the body, and the presence of OA in multiple joints is a strong predictor for the progression of knee OA. Thompson et al. [27] found that patients with knee and hand OA had a diffuse pain pattern compared with patients with only knee OA. Perruccio et al. [18] found that 46% of knee OA patients had four or more symptomatic joints prior to TKA and that these patients had worse fatigue, anxiety, depression, knee function, and knee pain both preoperatively and 12 months after surgery compared with patients with less symptomatic joints. In addition, patients who reported symptomatic ankles, feet, and/or toes had worse

depression and pain scores 12 months after surgery [18].

### Comorbidities

High fibromyalgia scores (using the American College of Rheumatology survey criteria for fibromyalgia) have been associated with high preoperative pain, poor anxiety and depression scores, and increased tendencies toward pain catastrophizing. In addition, compared to OA patients without comorbidities, OA patients with fibromyalgia have higher postoperative opioid consumption, a greater prevalence of postoperative complications, more dissatisfaction with their surgery, and a higher risk of postoperative pain following TJA [5,8].

Patients diagnosed with type II diabetes are more likely to have TJA compared with patients without diabetes [24]; however, no studies have evaluated the outcome after TJA in patients with or without diabetes and with or without painful diabetic neuropathy. Interestingly, a large study investigating more than 1,400 OA patients found no association between obesity and risk of complications after TJA [9].

The postoperative outcomes in patients with rheumatoid arthritis (RA) undergoing TJA have been debated. A recent study comparing OA with RA showed no difference in pain and function 2 years after TKA despite the fact that RA patients had more comorbidities, lower expectations, and higher pain compared with OA patients before surgery [11]. Activities of daily living during the acute postoperative period are more limited in patients with RA compared with OA [25].

### Pain Catastrophizing and Coping Strategies

The pain experience is not limited to purely nociceptive input, but is a

complex sensory experience highly modulated by psychological factors. Pain hypervigilance (assessed by the Pain Catastrophizing Scale) is defined as an automatic prioritization of pain aimed at avoiding physical factors. A recent review concluded that the preoperative presence of catastrophic thinking and poor coping strategies predicted a high level of postoperative pain [4]. Further, the review found no association between preoperative fear of movement and postoperative pain and found conflicting evidence that preoperative depressive symptoms and anxiety would predict postoperative pain after TKA [4]. It is still debated which dimensions of catastrophic thinking can be affected by cognitive therapy (trait versus state).

### Genetic Factors

Factors such as obesity, age, skeletal shape, or bone mass can influence the progression of OA, and it seems evident that females have a higher risk of chronic postoperative pain after TKA.

Less is known about the importance of genetic factors for encoding molecules such as interleukins. The gene coding for catechol-O-methyltransferase (COMT) is associated with hip pain in patients with hip OA, and the gene coding for interleukin-6 (IL-6) has been positively correlated with osteolysis in patients after THA [12]. Other genetic factors that code for genes, such as the single nucleotide polymorphism (SNP) in the SCN9A gene (coding for specific sodium channels), is associated with increased pain levels and different pain thresholds in OA patients [23]. In the future, it may be of equal importance to look for epigenetic changes because animal studies have shown that methylation and acetylation may increase pain sensitization in animals.

## Inflammation

Osteoarthritis is often associated with inflammatory changes in the joint such as synovitis, and inflammation is considered a risk factor for OA progression. It is known that peripheral injury can lead to local inflammation and upregulation of interleukin (IL)-1 $\beta$ , IL-6, IL-8, and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). Peripheral inflammation can lead to increased peripheral pain sensitization, and a recent study showed that increased preoperative levels of TNF- $\alpha$ , matrix metalloproteinase-13 (MMP-13), and IL-6 in synovial fluid were associated with impaired postoperative pain relief [10].

When a nerve is cut, the Schwann cells and other cells in the area of injury release nerve growth factor (NGF). The concept of “nerve sprouting,” which can be promoted by increased NGF release, has been observed in cancer-induced animal bone pain models, which increased the generation of nociceptive

fibers. It is hypothesized that increased NGF release due to surgical trauma could result in nerve sprouting and the formation of microneuromas, which could facilitate pain.

## Previous Surgery and Revision Joint Replacements

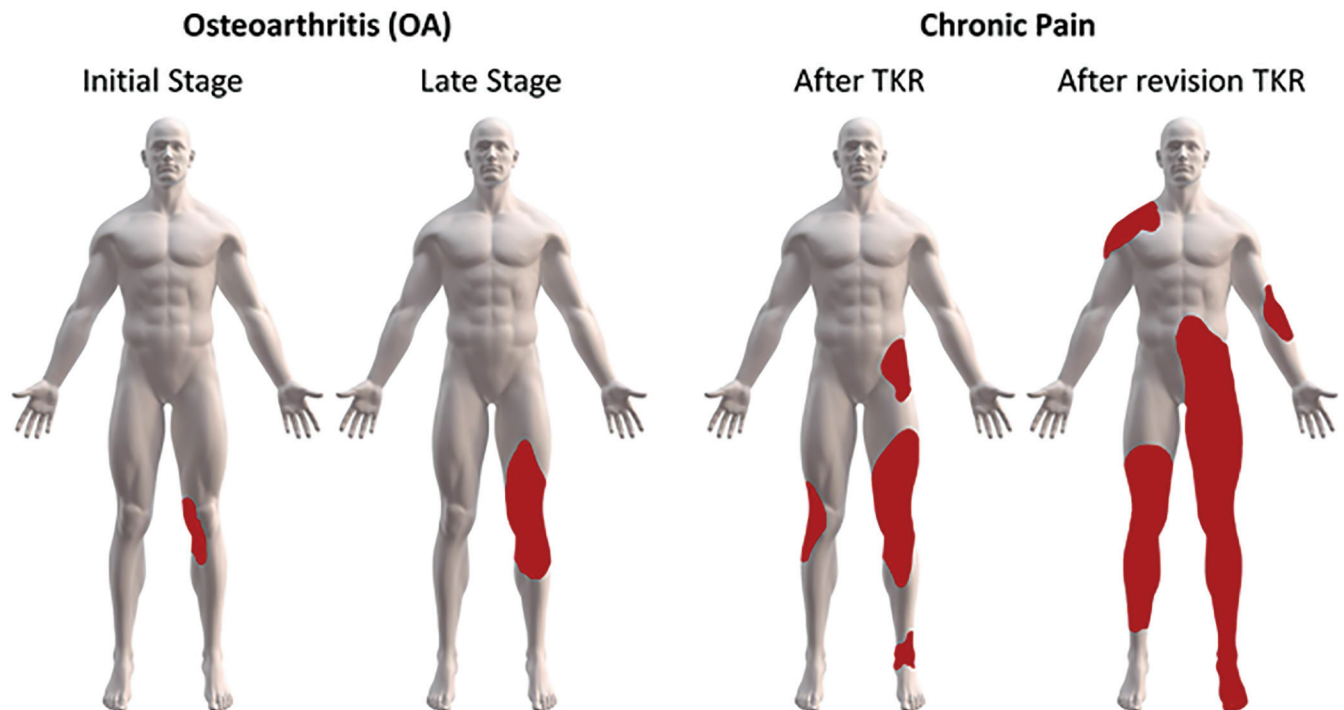
Patients with knee OA are sometimes offered an arthroscopy, but no effects on pain or function have been found as compared with placebo (skin incisions and simulated debridement without the insertion of an arthroscope). In general, previous surgery is a risk factor for postoperative pain, and previous arthroscopy and ligament reconstruction have been linked to earlier onset of TKA, but no studies have investigated the association between previous arthroscopy and chronic pain following TJA.

Revision surgery after TKA is associated with a higher risk of chronic postoperative pain, decreased quality

of life, reduced function, and less satisfaction compared with primary TKA [21]. Furthermore, the sensory profiles of patients with pain after revision TKA seem to worsen [3]. Approximately 50% of OA patients undergoing revision TKA on the basis of the indication of pain will continue to have pain and often more severe pain than they had initially [21] (see Fig. 1).

## Periprosthetic Joint Infections

Periprosthetic joint infections (PJIs) are uncommon (1–2%), but they are associated with severe pain, function deficits, poor quality of life, or death in severe cases. Management of PJI is commonly revision surgery, which is generally associated with a higher risk of chronic postoperative pain, poorer quality of life, and increased pain sensitivity compared with primary surgery and with a further risk of re-infection. A recent meta-analysis concludes that several patient-related factors, such as



**Fig. 1.** A schematic sketch of the pain areas perceived in patients with early- and late-stage knee osteoarthritis. The approximately 20% of patients experiencing continued pain after an otherwise successful total knee arthroplasty (TKA) will have a further enlargement of the pain areas, and approximately 50% of patients undergoing revision TKA because of pain after the primary surgery will experience even more pain, with an even larger pain projection area.



smoking, body mass index (BMI) greater than 30 kg/m<sup>3</sup>, diabetes, depression, and steroid use, are associated with a high risk of PJI [14]. Further, these risk factors should be identified and modulated prior to surgery to reduce the incidence of PJI, thereby reducing chronic postoperative pain.

## Treatment for Predictors

Several pre- and perioperative factors have been identified as predictors of chronic postoperative pain, but limited evidence for treatments is available. This section will cover treatment paradigms such as fast-track surgery and preoperative medical treatments to minimize the risk of chronic postoperative pain after TJA.

### Fast-track Surgery

Fast-track surgery programs based on the principle of multimodal rehabilitation aim to reduce perioperative morbidity, optimize physiological anesthesiological procedures and pain management, and allow for aggressive early mobilization. Applying the fast-track surgery programs for THA and TKA has reduced the length of hospital stay from 4–12 days to 1–3 days. Bilateral TKAs have similar results at 3 months and 2 years compared with unilateral TKAs using fast-track settings.[22] Recent reviews conclude that future research should focus not only on reducing the length of stay, but also on lowering the inflammatory response and reducing acute postoperative pain intensity, and should include indications of high-risk patients for complications to optimize fast-track surgery programs and avoid complications.

### Medical Treatments

Gabapentinoids (pregabalin and gabapentin) are believed to be antihyperalgesic, but preoperative administration

of these drugs before TJA has shown conflicting results. Lunn et al. [16] could detect no effect of preoperative administration of gabapentin on acute postoperative pain after TKA, whereas Buvanendran et al. [6] reported reduced neurogenic postoperative pain 3 months after TKA after preoperative administration of pregabalin. These findings need to be reproduced in large randomized, controlled trials.

A recent study showed that cyclooxygenase-2 inhibitors reduced pain intensity and improved function in patients with knee OA, and as a novel aspect the study showed that these effects were partly mediated by drug interactions with central sensitization mechanisms [1].

Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is approved for depressive disorders, generalized anxiety disorders, diabetic peripheral neuropathy, fibromyalgia, and musculoskeletal pain, but a recent randomized control trial showed that administration on the day of surgery and 14 days following TKA had no effect on pain compared with placebo [30]. A recent review highlights that antidepressant treatment is not for acute analgesic effects, but requires long-term treatment to relieve neuropathic pain [13], which could explain the lack of results from the recent trial [30].

Preoperative pronociceptive profiles have been associated with chronic postoperative pain following TKA [19,20] and THA [29], for which reason it is hypothesized that preoperative improvement of sensory profile could lower the risk of chronic postoperative pain following TJA; however, no studies support this hypothesis.

## Recommendations

This issue of *Pain: Clinical Updates* has focused on pre-, peri-, and acute postoperative factors associated with chronic postoperative pain following TJA. It seems evident that high preoperative pain intensity, high pre- and perioperative inflammation levels, high catastrophizing, and preoperatively elevated pain sensitization are all associated with a higher chance of developing chronic postoperative pain and should be targets for further investigation in an attempt to minimize the burden of postoperative chronic pain after joint replacement. Other factors such as comorbidities, genetic factors, and multiple arthritic affected joints are all possible contributors to enhanced likelihood of developing chronic pain after joint replacement.

Evidence suggests that previous arthroscopy may promote processes important for the development of the risk of requiring TKA, but no studies have investigated whether it could influence postoperative outcome. Finally, the role of targeted pre-, peri-, and acute postoperative pain management should be investigated in large randomized studies. Recent developments in mechanism-based pain profiling of joint pain patients should be further explored to identify specific subgroups of patients who may be most at risk of developing postoperative pain.

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