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OUTCOMES RESEARCH IN ORTHOPEDICS (O AYENI, SECTION EDITOR)

Towards an understanding of the painful total knee: what is the role of patient biology?

Stephen Preston[1] · **Massimo Petrera**[1] · **Christopher Kim**[1] · **Michael G. Zywiel**[1] · **Rajiv Gandhi**[1,2]

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Abstract Total knee arthroplasty (TKA) remains the treatment of choice for end-stage osteoarthritis of the knee. With an aging population, the demand for TKA continues to increase, placing a significant burden on a health care system that must function with limited resources. Although generally accepted as a successful procedure, 15–30 % of patients report persistent pain following TKA. Classically, pain generators have been divided into intra-articular and extra-articular causes. However, there remains a significant subset of patients for whom pain remains unexplained. Recent studies have questioned the role of biology (inflammation) in the persistence of pain following TKA. This article aims to serve as a review of previously identified causes of knee pain following TKA, as well as to explore the potential role of biology as a predictor of pain following knee replacement surgery.

Keywords Pain · Painful · Knee · Arthroplasty · Inflammation · Biology

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Stephen Preston and Massimo Petrera contributed equally to this work.

✉ Rajiv Gandhi
rajiv.gandhi@uhn.ca

[1] Division of Orthopaedic Surgery, Arthritis Program, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada

[2] Division of Orthopaedic Surgery, Toronto Western Hospital, University of Toronto, 399 Bathurst St, Room 1E439, Toronto, Ontario M5T 2S8, Canada

Introduction

Osteoarthritis (OA) is a progressive musculoskeletal disorder that affects an ever-growing proportion of the North American population. Throughout North America and most industrialized countries, it is estimated that the proportion of senior citizens (age ≥ 65 years) affected by OA will double in the next 30–40 years [1–4]. Currently, over 46 million adults in the USA have been diagnosed with OA, accounting for more than 50 % of the population over 50 years of age. This number is projected to increase to 70 million by 2030 [5]. Similarly, the prevalence of OA in Canada is projected to increase from 17.6 % in 2003 to an estimated 26 % in 2021 [6].

Among major joints affected by OA, the knee remains the most common [7]. As the disease progresses to its end stages, total knee arthroplasty (TKA) remains the treatment of choice for pain relief and functional improvement. With the aging population and the resultant increase in the prevalence of OA, the utilization of TKA is also steadily increasing. In 2008–2009, a total of 47,429 TKAs were performed across Canada. This represents a 10-year increase of 139 %, making TKA the fastest-growing surgical procedure in the country [8] with an annual hospital cost approaching $500 million [9]. Likewise, TKA in the USA saw a 10-year increase of 118 %, with over 675,000 procedures performed at a cost of $10.4 billion in 2008 alone [10]. As surgical techniques and implants continue to improve, the indications for TKA are expanding, and younger patients are undergoing the procedure for end-stage knee OA. This is supported by recent data which suggests that the increase in prevalence of TKA is not fully explained by demographic trends such as population aging and the obesity epidemic [11]. The societal burden imposed by the dramatic increase both the prevalence of knee OA and its surgical treatment is of great concern from both financial and human resource perspectives, particularly in health care

systems that must increasingly operate with limited resources [12–17].

Despite the increasing prevalence of TKA in North America, the efficacy of the procedure is variable. Multiple studies indicate that 15–30 % of patients are dissatisfied with their outcomes at 3 months following TKA for reasons including lack of functional improvement and, more importantly, persistent pain [18, 19]. For these dissatisfied patients, most have no identifiable cause of pain. Furthermore, there is evidence to potentially suggest that some patient-reported pain and physical function scores following TKA are actually getting worse with time, despite perceived advances in surgical technique, implant design and perioperative care/pain control [20•]. This trend is highly concerning for both health care professionals and patients as postoperative unexplained pain has consistently been implicated as one of the leading causes of long-term dissatisfaction following TKA [21, 22].

The burden of the painful TKA notwithstanding, very little has been accomplished in terms developing a solution for this problem. Part of the issue stems from the lack of consensus regarding the definition of a pain: *What is a painful TKA*? Most of the available literature is characterized by marked methodologic heterogeneity, including the use of a variety of patient and physician reported outcome measures. The minimal clinically important difference (MCID) and the patient acceptable symptom state (PASS) have been used more recently to study outcomes following TKA [23]. Calculated for different outcome measures, they represent the magnitude of change associated with patient-perceived important change, and patients' satisfaction or acceptability with an outcome at a point in time following an intervention respectively. Escobar and Riddle found these two measures to be concordant and excellent measures of post-TKA outcome when preoperative scores were taken into account [23]. Unfortunately, these methods have not been applied to the vast majority of outcome studies available in the current literature. Agreement on a time point at which to measure outcomes following surgery is also of critical importance. Consensus on these issues is critical for our ability to study painful TKA, as without it, prevalence estimates, elucidation of the natural history and study of interventions for treatment are impossible.

The second issue with the study of the painful TKA is that the pain experienced by patients following surgery can be multifactorial. Classically, pain following TKA has been divided into intra-articular causes, extra-articular causes (Tables 1 and 2), and the unexplained. While identifiable causes of pain can be treated, those with unexplained pain remain an important group of study. While many studies have evaluated patient level factors associated with these persistent, unexplained pain, the ability of these to explain variations in patient-reported pain and functional outcome scores have been only moderate at best. This strongly indicates a need to identify novel predictors of outcome. We believe based on the published literature, including our own previous work, biology is that needed novel predictor.

Table 1 Intra-articular causes of painful total knee

Intra-articular etiologies
Infection
Instability
Component malposition
Aseptic loosening/osteolysis
Polyethylene wear
Arthrofibrosis
Patellar maltracking
Unresurfaced patella
Overstuffing

Thus, the purpose of the present review was to review the range of potential causes of pain following primary total knee arthroplasty, stratified into (1) intra-articular, (2) extra-articular, and (3) biologic causes.

Intra-articular causes of pain

Infection

Prosthetic joint infection (PJI) is a potentially devastating cause of knee pain that must be ruled out in all situations of painful TKA. The incidence of PJI following TKA in the USA was estimated to be as high as at 2.4 % per year in 2009 [24], yet the diagnosis of this condition remains an inexact science. Parvizi et al. have developed a set of criteria for the diagnosis of PJI according to the Musculoskeletal Infection Society, which remains the best tool for clinicians to diagnose and treat infections following joint replacement [25]. In North America, the gold standard for the treatment of chronic PJI is a two-

Table 2 Extra-articular causes of painful total knee

Extra-articular etiologies
Soft tissue conditions
Pes anserinus bursitis
Patellar tendonitis
Quadriceps tendonitis
IT band tendonitis
Neurologic
Neuroma/injury the infrapatellar branch of saphenous nerve
Radiculopathy
Complex regional pain syndrome
Peripheral neuropathies
Psychological conditions (anxiety, depression, fibromyalgia)
Referred pain (i.e., hip OA)

stage revision arthroplasty with targeted antibiotic therapy. However, successful eradication of infection only occurs in 65–90 % of cases [26, 27], leaving a subset patients who ultimately undergo multiple surgeries in an attempt to eradicate their periprosthetic infection, which in some cases include salvage procedures such as resection arthroplasty or amputation. The importance of proper diagnosis and prompt treatment of PJI cannot be understated.

Instability

Painful knees must also be assessed for potential instability. Patients may complain of the knee feeling unreliable in addition to their discomfort. A thorough physical examination of the knee should include stability testing throughout the range of motion. Acute onset instability can possibly be related to a traumatic event leading to injury of either the collateral ligaments or the posterior cruciate ligament in cruciate retaining TKAs. However, the majority of instability results from a failure of soft tissue balancing at the time of surgery [28]. Instability with varus or valgus stress with the knee in full extension can represent incompetence of one of the collateral ligaments, whereas flexion instability results from improper balancing of flexion and extension gaps. In extreme cases, patients with posterior stabilized TKAs may present with dislocation of the knee whereby the femoral cam is displaced anterior to the tibial post. Revision surgery may be indicated for these patients in order to appropriately re-tension soft tissues or balance the knee in flexion and extension. In many cases, increased constraint may be required.

Aseptic loosening

Polyethylene wear leading to osteolysis and component loosening is another common cause of pain and TKA failure. Improvements in component design, particularly in the locking mechanism of the tibial base plate, have helped to reduce the amount of osteolysis in more recent TKA iterations [29]. More importantly, however, polyethylene sterilization carried out in an oxygen-free environment prevents complications related to oxidative degradation, free radical production, and excessive osteolysis [30]. Despite the fact that the incidence of severe osteolysis has been significantly reduced since the advent of these new technologies, Schrorer et al. reported that 10 % of their TKA revisions were related to issues with polyethylene wear and bone loss, particularly around the tibial baseplate [31]. The diagnosis of polyethylene wear can be often be made on serial radiographs of the knee, and is characterized by loss of polyethylene liner height over time, the accompanying resorption of bone surrounding the implants, and possible associated subsidence of the implant components. In addition, aseptic loosening of the components can be caused by inadequate initial fixation or loss of fixation over time. This is most commonly associated with poor cementing techniques at the time of component implantation [32]. In all of these cases, once infection has been ruled out, pain can be treated with revision TKA.

Anterior knee pain

Anterior knee pain (AKP) is a common problem following TKA, yet it remains poorly understood. The prevalence of AKP has been reported between 0.4 and 49 %, with more recent estimates in the range of 5–10 % [33]. The etiology of AKP appears to be multifactorial. There is an immense body of literature dedicated to the potential association between patellar resurfacing and AKP. Nevertheless, a debate persists as to whether patellar resurfacing is indicated in TKA, with no clear evidence to suggest that AKP can be eliminated by replacing the patellofemoral joint [33, 34]. The design of the femoral and patellar components of TKA has also come into question as a potential contributor to AKP, independent of whether or not the patella is resurfaced. Some authors have suggested that incongruities between the two surfaces that may lead to patellar maltracking or instability are a potential source of pain [33]. However, AKP remains a problem even with more recent TKA designs that have presumably optimized the patellofemoral implant interface. Improper placement of the patellar button in patellofemoral resurfacing has also been linked with patellar maltracking, increased pressure across the patellofemoral joint, issues with patellar height, and anterior pain and stiffness following TKA [33]. This could be an important factor that might explain why secondary patellar resurfacing is not uniformly effective in alleviating AKP following TKA [35, 36].

While the literature has largely focused on the patellofemoral joint when evaluating AKP, soft tissue structures in the anterior aspect of the knee must also be considered when discussing this problem. The retropatellar fat pad, medial and lateral retinacula, and patellar and quadriceps tendons all possess pain receptors that may become activated with altered patellofemoral biomechanics following TKA [33]. Unfortunately, no consensus currently exists regarding the management of any of these problems and the issue of AKP following TKA remains unsolved.

Fracture

Periprosthetic fracture (PPF) following TKA is another albeit relatively rare cause of knee pain. Several patient characteristics have consistently been implicated as risk factors for PPF: age over 70, female gender, high activity level, chronic steroid use, decreased bone mineral density, and rheumatoid arthritis [37]. The majority of fractures occur in the supracondylar area above a well-fixed femoral component, affecting 0.3–2.5 % of TKAs, most resulting from low energy torsional or axial

forces [38]. Biomechanical studies indicate that anterior femoral notching can cause a stress riser that may increase the risk of periprosthetic supracondylar femur fracture [39, 40]. However, notching has not been identified as an independent risk factor for fracture in clinical studies [41, 42]. PPF of the patella occurs in 0.7–1.2 % of TKA, affects resurfaced and unresurfaced patellae, and has been attributed to significant distraction forces across the bone from the extensor mechanism [43–45]. These fractures occur more frequently in men than in women, and it is hypothesized that increased weight and activity levels could be responsible for this trend [43]. In addition, medial parapatellar arthrotomy, patellar eversion, and lateral release have all been show to affect patellar blood supply, possibly contributing to poor bone stock and possibly patellar AVN, which could lead to fracture [46, 47]. PPF of the tibia is by far the least common, affecting less than 0.5 % of TKA [48]. Postoperative fractures are commonly related to osteolysis with subsidence of the tibial component and malalignment of the tibial component, which alters stress on the proximal tibial metaphysis and affects bone integrity. Fractures may also occur intraoperatively with retractor placement, trial reduction, preparation of the tibia for insertion of stemmed components, and removal of components in the revision setting [49]. All of these injuries can easily be identified either at the time of surgery or postoperatively with plain radiographs. Location and displacement of the fracture, stability of the components, and patient factors will ultimately determine treatment.

Extra-articular causes of pain

Several extra-articular factors can also contribute to a painful TKA (Table 2). The most commonly described factors are related to soft tissue inflammation (pes anserinus bursitis, iliotibial band tendonitis, patellar and quadriceps tendonitis), neurologic disorders (spinal stenosis, radiculopathy, neuroma, complex regional pain syndrome), and psychological disorders (fibromyalgia, depression, anxiety).

Soft tissue pain

Soft tissue-related pain can be secondary to overuse or to an aggressive exercise regimen. However, other causes of chronic irritation such as impingement on soft tissue from oversized components should be ruled out. Pain from pes anserinus bursitis is referred over the antero-medial aspect of the proximal tibia and is typically elicited with palpation. Pain from iliotibial band tendonitis is referred over the lateral aspect of the knee and may be secondary to overuse, soft tissue tightness or muscle weakness. Patients with patellar and quadriceps tendonitis present with anterior knee pain. When assessing these patients, it is important to rule out other causes of anterior knee before attributing the source of pain to tendonitis.

Referred sources

Hip osteoarthritis, spine disorders, and peripheral neuropathies should be taken into consideration in the differential diagnosis of a painful TKA. Neuropathic pain affects about 11 % of patients undergoing primary TKA and has its peak incidence between 6 weeks and 3 months postoperatively [50]. Injury to the infrapatellar branch of saphenous nerve has been implicated as a common extra-articular cause of persistent knee pain [51, 52]. Complex regional pain syndrome (CRPS) is a less common cause of painful total knee replacement. Typically, patients with CRPS complain of pain out proportion, unrelated to weight bearing and knee motion, with associated skin hypersensitivity.

Psychosocial factors

Existing studies have suggested demographic/clinical characteristics, such as age, sex, ethnicity, and pain severity may be predictive of a poor response [50, 53, 54, 55•]. Younger age and female gender are factors that seem to be associated with a more intense postoperative pain [50]. Similarly, patients with history of migraine, fibromyalgia, and irritable bowel syndrome might be predisposed to chronic pain after TKR. Several studies have also shown a strong correlation between mental health/psychological factors and persistent pain after TKA [53, 54, 55•]. A recent meta-analysis by Lewis et al. including 32 studies involving almost 30,000 patients showed that poorer mental health status and greater preoperative knee pain are the strongest independent predictors of persistent pain after TKA [55•]. In a prospective study of 104 patients who underwent primary TKA, Hirschmann et al. found that patients with depression, anxiety, and/or psychological distress had poorer clinical outcomes in terms of higher Western Ontario and McMaster Universities' Osteoarthritis Index (WOMAC) and lower Knee Society (KSS) scores [54].

The potential role of biology in the unexplained painful knee

The importance of studying biology in TKR outcomes is supported by the consistent observation that preoperative pain is among the strongest predictors of postoperative pain [56, 57] Inflammation is a key predictor of pain in general and specifically within OA; there are known relationships between knee OA pain severity and local and systemic inflammation. Systemic levels of high sensitivity C-reactive protein (hsCRP), a known marker of inflammation, has been correlated to knee synovial inflammation, knee joint specific pain, and

OA pain levels overall [58, 59]. Locally within the joint, work by one of the senior authors has shown that the SF (synovial fluid) adiponectin/leptin ratio (adipo-cytokines) is associated with knee OA pain prior to TKR [59]. Further, elevated synovial fluid concentrations of interleukin-6 (IL-6) has been correlated with symptoms of pain and stiffness, and disease progression has been largely demonstrated [58, 60–62]. Identification of a characteristic pre- and or post-op inflammatory signature (serum or SF) associated with a lesser pain and functional response to TKR can inform novel therapeutic targets in hopes of improving outcomes. These interventions can be applied pre-, intra-, or postoperatively.

Preoperative biological markers as predictors of post-op pain

A study by Honsawek et al. aimed to investigate the inflammatory process in 49 patients with primary knee osteoarthritis undergoing TKA found that elevated preoperative CRP and IL-6 serum levels were associated with a smaller functional recovery at 12 months and more pain upon discharge [63]. The relationship between CRP and functional outcomes after TKR has also been investigated by Smith et al. [64]. In a prospective study on 31 patients with knee OA undergoing TKR, the authors demonstrated that the group of patients with low CRP serum levels exhibited significant functional improvement (physical component of SF-12) at 6 and 12 months, while the group with high serum CRP level exhibited significant improvement only at 6 months, indicating a better long-term prognosis for patients with lower inflammatory markers. Similarly, high preoperative levels of inflammatory markers in the synovial fluids can predict poorer outcomes after TKA as reported by Gandhi et al. [65•]. The authors studied a cohort of 28 patients undergoing TKA and found that higher preoperative levels of pro-inflammatory cytokines (TNF-A, MMP-13, IL-6) in the synovial fluid were associated with more modest improvement in pain scores at 2-year follow-up. A previous study by Gandhi et al. identified adipokines as a novel biological marker of outcomes following TKR [59]. By studying the synovial fluid samples from 60 patients with severe knee OA undergoing TKA, the authors discovered that the preoperative adiponectin/leptin (A/L) ratio can predict knee pain, with greater A/L ratio associated with less pain [59]. One important limitation of these studies are the small sample sizes, conferring insufficient statistical power to adjust for psychosocial characteristics and other factors known to be associated with outcomes following TKR.

Postoperative biological markers as predictors of post-op pain

Physiologic recovery following TKR has been reported to be affected by patients' postoperative local and systemic inflammatory response, as well as associated metabolic and neuroendocrine changes [66–69]. Consequently, it is reasonable to expect that differences in the postoperative levels of a range of biological markers may help predict outcomes following TKR. There have been few studies investigating postoperative associations between local inflammatory factors and the clinical outcomes of TKR to date. However, one study by Ugras et al. found that higher intra-articular levels of IL-6 at 4 weeks after surgery were associated with a slower recovery in the early postoperative period [69]. Similarly, a strong correlation has been shown between the postoperative systemic inflammatory response and early outcomes after hip arthroplasty surgery. Hall et al. studied this relationship by collecting blood samples for up to 7 days after hip arthroplasty surgery and measuring the concentrations of cortisol, IL-6, and CRP [67]. The authors found that functional recovery (walking distance in hospital) was significantly lower in patients with greater IL-6 and CRP concentrations and that the serum concentration of CRP on postoperative day 2 was a strong predictor of pain on discharge from hospital. The longer-term predictive value of these findings is unclear, however, as no significant correlations were found between the early postoperative concentrations of these inflammatory markers and clinical outcomes at 1 and 6 months [67].

Although it is still unclear if the postoperative inflammatory markers are part of the "biological signature" or a consequence of the intervention, it is reasonable to hypothesize that suppressing the inflammatory response using existing medications (e.g., NSAIDs, corticosteroids, biologics) might improve those patient outcomes. This approach has already been tried with success in other surgical fields, notably in cardiac surgery [70, 71]. The administration of steroids in patients post coronary artery bypass grafting has been associated with improved patient outcomes (significant reduction in postoperative atrial fibrillation) [71]. A randomized clinical trial involving 34 patients undergoing bilateral TKA revealed that the administration of three doses of intravenous hydrocortisone (100 mg per dose) significantly decreased the degree of inflammation as measured by serum IL-6 level at 24 h after surgery compared to the placebo group. Pain scores and presence of fever at 24 h following surgery were also significantly lower in the study group, while range of motion at discharge was significantly greater [72]. Despite the fact that it is currently unknown whether this early clinical benefit translates into longer-term outcomes, this study shows the feasibility of dampening systemic inflammation, with associated early clinical benefit, in patients undergoing knee replacement through steroid administration. Another randomized clinical trial on a larger population (90 patients) reported similar conclusions. The authors showed that the injection of a cocktail of triamcinolone acetonide, bupivacaine, and epinephrine into the peri-articular tissues at the end of unicondylar knee replacement led to a significant reduction in pain at 24 h after surgery

and a better range of motion at 3 months, with no increased risk of complication (infection or tendon rupture) [73]. This study did not include the measurement of any marker of inflammation and certainly the reduction of pain at 24 h after surgery might not be attributable only to the modulation of the inflammatory response.

While current research into potential associations between patient inflammatory profiles and clinical outcomes following joint arthroplasty is limited, the findings to date suggest potential important and modifiable associations between these two domains. As further work in this field continues, a greater understanding of both the pre and postoperative inflammatory profiles in patients undergoing joint arthroplasty might allow clinicians to personalize therapies to maximize patient outcome, and/or potentially identify individuals who are at risk of experiencing limited benefit from TKA. As our understanding of these associations evolves, additional research might also be targeted to the study of genetic factors (proteins associated with inflammation vs. genetic markers that predispose to inflammation) affecting outcomes after TKA.

Conclusions

Osteoarthritis is a progressive musculoskeletal disease whose prevalence is likely to continue to increase as the population ages. Total knee arthroplasty remains the treatment of choice for end-stage OA of the knee when non-operative measures have failed. As the number of patients suffering from OA continues to grow, and as indications for TKA become broader, the financial and societal burden of the procedure will continue to escalate over the coming decades. However, despite the increasing prevalence of TKA, the reported results of the procedure are variable and a significant number of patients report persistent pain following surgery. Numerous theories have been postulated as to the potential cause of persistent pain following TKA, and many etiologies have been identified. Classically, these factors have been separated into intra and extra-articular causes of knee pain. Nevertheless, even with recent advances in implant design, surgical technique and perioperative care, persistent pain following TKA continues to be reported. This would suggest that there are other important and unaddressed factors at play in determining pain after TKA. The biological/inflammatory profile of patients with knee OA is an area that has recently received an increasing amount of attention. Numerous serum and synovial markers have been identified and linked to pain following TKA. Early work in the modulation of these inflammatory markers has also shown some promise in decreasing postoperative discomfort. Further work is needed to identify factors predisposing patients to poor results following TKA in order to develop interventions aimed at improving patient outcomes and reducing the costs associated with the management of painful TKA.

Compliance with ethical standards No ethical review board approval was sought or granted, as this work consists solely of previously published data

Conflict of interest Stephen Preston, Massimo Petrera, Christopher Kim, Michael G. Zywiel, and Rajiv Gandhi declare that they have no conflicts of interest.

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