AAAPT Diagnostic Criteria for Acute Knee Arthroplasty Pain

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Abstract

Objective. The relationship between preexisting osteoarthritic pain and subsequent post-total knee arthroplasty (TKA) pain is not well defined. This knowledge gap makes diagnosis of post-TKA pain and development of management plans difficult and may impair future investigations on personalized care. Therefore, a set of diagnostic criteria for identification of acute post-TKA pain would inform standardized management and facilitate future research. **Methods.** The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTION) public-private partnership with the US Food and Drug Administration (FDA), the American Pain Society (APS), and the American Academy of Pain Medicine (AAPM) formed the ACTION-APS-AAPM Pain Taxonomy (AAAPT) initiative to address this goal. A multidisciplinary work group of pain experts was invited to conceive diagnostic criteria and dimensions of acute post-TKA pain. **Results.** The working group used contemporary literature combined with expert opinion to generate a five-dimensional taxonomical structure based upon the AAAPT framework (i.e., core diagnostic criteria, common features, modulating factors, impact/functional consequences, and putative mechanisms) that characterizes acute post-TKA pain. **Conclusions.** The diagnostic criteria created are proposed to define the nature of acute pain observed in patients following TKA.

Key Words: Acute pain; taxonomy; ACTION; AAAPT; knee arthroplasty

Introduction

Total knee arthroplasty (TKA) is one of the most commonly performed surgical procedures, with more than 750,000 arthroplasties performed in the United States in 2017 [1]. Acute pain post-TKA is often severe [2], can delay early rehabilitation [3], interferes with functional

ability [4], causes deterioration of health status [5], and places a burden on health care resources [6].

Despite its prominent impact on all stakeholders in the perioperative process, a definition of acute post-TKA pain is lacking. For example, the chronologic demarcations between preexisting osteoarthritic knee pain, acute

post-TKA pain, and commonly occurring chronic post-TKA pain are not clear. Similarly, the localization, characteristics, frequency, severity, and natural course of this pain are described using heterogeneous criteria with widespread variability and translational capability, thus obscuring expectations among the stakeholders. Furthermore, a lack of clarity regarding the somatic and neuropathic components of this pain may interfere with efforts to screen and quantify this pain, as well as evaluate its functional impact. This ambiguity extends further to include predictors, mechanisms, and modulators of this pain. Therefore, a consensually agreed definition of acute post-TKA pain may serve to facilitate accurate diagnosis, aid clinical management, and define relevant research.

The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the US Food and Drug Administration (FDA), the American Pain Society (APS), and the American Academy of Pain Medicine (AAPM) has combined efforts to develop an evidence-based acute pain classification system. The resultant Pain Taxonomy (AAAPT) provides an evidence-based, multidimensional classification of the acute pain experience. The taxonomic framework classifies acute pain conditions based on the recommendations of the multidimensional chronic pain taxonomy (ACTTION-APS, AAPT) according to five dimensions, including 1) core diagnostic criteria, 2) common features, 3) putative mechanisms, 4) modulating factors, and 5) impact and functional consequences [7]. Despite intrinsic differences between surgical procedures and other initiating events precipitating acute pain, this taxonomic framework is thought to be broadly generalizable to all acute pain conditions, including TKA.

In this special article, the working group on acute pain examines the post-TKA acute pain experience, aiming to translate the aforementioned taxonomic classification system and its five dimensions [7].

Methods

We assembled an eight-member interdisciplinary work group of pain scientists and clinicians possessing expertise in diagnosing and managing pain following arthroplasty (FWA, IG, RBF, PT, HKP, NG, MS, and CJLM). This group convened during the AAAPT meeting in November 2017 in Washington, DC. The meeting was preceded by three webinars where the goal of developing acute pain diagnostic criteria and the process, an evidence-based multidimensional approach analogous to what has been developed and used to classify chronic pain [8,9], were described. During and after the meeting, the group shared relevant literature focusing on the definitions, epidemiology, and risk factors for acute pain post-TKA. Work on describing the taxonomic classification system and the five dimensions of post-TKA acute

pain was assigned to members of the group with corresponding expertise. Members worked closely and communicated on a regular and as-needed basis to prepare a preliminary draft.

From a methodological perspective, the group agreed that the literature informing our work on the classification and dimensions was too diverse to be retrieved in a single systematic review and would not align with the goals or precedent of previously reported AAPT and AAAPT characterizations. Consequently, we decided not to conduct a systematic review. Instead, we requested that each of the experts conduct their own literature review using definitions relevant to acute post-TKA pain, and focusing on the key terms inherent to their assigned sections. The literature provided by the AAAPT steering committee was also reviewed by the group to guide their contributions.

Subsequently, the individual members' contributions were collated into a preliminary draft by two of the authors (FWA and CJLM), who ensured that the draft complied with the structure and terminology suggested by the AAAPT steering committee. This draft was then shared among the group members for input and suggestions. The feedback received over several rounds allowed further refinement of the proposed classification system and consensus over the details of the five dimensions. The final manuscript reflects the consensus of all group members.

Results

Dimension 1. Core Diagnostic Criteria for Acute Pain After TKA

The AAAPT criteria for acute pain after TKA are presented in [Table 1](#). The medical history must include TKA within the past 30 days, as indicated by one of the following ICD10 codes: Z96.651, Z96.652, Z96.653, Z96.65, or Z96.659. All variants of surgical procedures should be considered, including unicompartmental vs tricompartmental, unilateral vs bilateral, and primary vs revision TKA. These criteria excluded the knee mega-prostheses in the setting of surgical oncology. The pain may be spontaneous or provoked (by function or palpation), or both. Five diagnostic subtypes of pain are proposed based on anatomical sources of pain: 1) incisional pain, 2) muscle and joint capsule pain, 3) bone pain, 4) ischemic pain, and 5) neuropathic pain. More than one of these subtypes may be present in a patient. The primary differential diagnosis involves distinguishing post-TKA pain from other post-TKA sensory changes, including paresthesias, dysesthesias, and functional limitations.

Dimension 2: Common Features of Acute Post-TKA Pain

Acute post-TKA pain refers to those features of pain resulting from the surgery itself, which is considered to

Table 1. Core Diagnostic Criteria

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<ol style="list-style-type: none"> Recent history of TKA. Pain reported at or around the surgical site(s). Must report at least one of the following: <ol style="list-style-type: none"> Spontaneous pain. Pain during external stimulation of the surgical site, such as with palpation of the incision or changing the dressing. Pain during movement or function of the affected knee(s). There is no other diagnosis that better explains the reported symptoms. 	
Subtypes of post-TKA acute pain:	
<ol style="list-style-type: none"> Incisional Pain. Spontaneous pain that is localized to the surgical incision site, or pain that is provoked by stimulation of the incision during palpation or other external stimulation or with movement of the knee. Muscle Pain. Pain that is localized to the muscles surrounding the surgical site. Muscle pain can be spontaneous or provoked by movement or function that activates the muscles around the surgical site. Bone Pain. Pain that is localized to the bony areas affected by the surgical procedure. Bone pain can be spontaneous or provoked by movement or function of the affected knee(s). Ischemic Pain: Atypical rare throbbing quality, poorly localized excruciating pain that is not relieved with typical analgesics or nerve blockade. Neuropathic Pain: Pain caused by damage to nerves that is described with qualities consistent with neuropathic features (e.g., burning, shooting, tingling/prickling). Neuropathic pain can be assessed using validated questionnaires (e.g., the Pain DETECT [10], the McGill Pain Questionnaire, version 2 [11]). 	

TKA = total knee arthroplasty.

be distinguishable from knee pain related to preceding pathology such as osteoarthritis (OA) or infection. The common features of acute pain following TKA are summarized in Table 2.

Pain in TKA patients is generally characterized as somatic pain with occasional neuropathic components [12]. Patients may differentiate somatic pain stemming from the anterior skin incision from that of the femoral and tibial osteotomies given the differing qualitative and mechanistic profiles of bone pain [13]. In our experience, given the co-innervation of the anterior cutaneous structures with the periosteum of the tibia and femur, patients seldom report isolated discomfort resulting from the skin incision itself, as this nociceptive source is generally overshadowed by the significant pain resulting from the femoral and tibial osteotomies. Although patients who have peripheral nerve block may note intraoperative tourniquet pain [14], and tourniquet use may be associated with increased postoperative pain [15–17], postoperative ischemic pain is rare and should raise concern for compartment syndrome and/or vascular injury [18]. Although a relative compartment syndrome is feasible from tight dressings, it is less common in straightforward primary TKA.

Our understanding of the locations of acute post-TKA pain is partially the result of a variety of peripheral nerve

block strategies employed over the past few decades [19]. Pain following TKA is not localized to the incision, but is predominantly in the anterior knee, a finding supported by anatomical studies of femoral nerve branch innervation to the surgical site, and the effects to blockade of said nerves [20]. Isolated blockade of relevant branches of the femoral nerve may uncover predominant posterior knee pain transmitted through branches of the sciatic, and variably obturator, nerves if these remain unblocked [20–22]. Posterior knee pain is postulated to occur not from violation of the posterior knee capsule, but instead from referred intra-articular pain via involvement of sciatic and, variably, obturator nerves [22]. Pain in the lateral aspect of the knee is uncommon following TKA, such that the lateral femoral cutaneous nerve is usually not targeted in contemporary regional anesthetic practices. However, a recent meta-analysis of regional anesthesia for TKA pointed toward a potential contribution of the lateral femoral cutaneous nerve to postoperative pain, postulated to arise due to tourniquet pain and/or “tissue manipulation” [19]. Complaints of isolated medial knee pain are relatively rare following TKA. In the presence of intraoperative thigh tourniquet use, our experience suggests that complaints about proximal, peri-tourniquet site pain after surgery remain relatively minimal compared with surgical site pain itself. Although not well characterized in the literature, we have also observed that the location of predominant pain may fluctuate over time. These spatiotemporal changes in pain could be due to different rates of wound healing, descending modulation, and/or pharmacokinetic heterogeneity of nerve block and systemic analgesics, among other postulates in need of further investigation.

The temporal trajectory of early acute post-TKA pain is complex and largely dependent upon a mixture of patient, surgical, and anesthetic factors [23]. There exists a paucity of reports on the “natural history” of untreated post-TKA pain in the era of modern TKA techniques, such that the temporal trajectory of post-TKA pain is inevitably tied to consideration of analgesic modalities and their pharmacokinetic profiles [24]. Although nociceptive loading begins with skin incision, patients receiving spinal anesthesia may report zero pain in the first hours in the recovery room due to lingering effects from the intrathecal local anesthetics. Conversely, patients receiving general anesthetics may report discomfort early in their recovery following emergence from general anesthesia. Depending upon the type and quality of regional anesthetic techniques and multimodal adjuncts used, patients undergoing general anesthesia may have received intraoperative titration of opioids and other systemic analgesics, and so may have a smoother analgesic transition when compared with patients receiving spinal anesthesia, who may report a relatively sudden onset of acute pain in areas not covered by regional anesthetics as the intrathecal block recedes.

Table 2. Summary of additional dimensions of acute pain following TKA

Dimension 2: Common features

Presentation

- Combines somatic and neuropathic characteristics
- Localized to the anteromedial and posterior knee

Course

- Onset depends on type and quality of intraoperative anesthesia; can be sudden if systemic analgesics or nerve blocks are not administered
- Increases as surgical nerve blocks wear off
- Movement exacerbates pain and interferes with rehabilitation
- Decreases gradually between days 1 and 3
- Posterior pain self-attenuates before anteromedial pain, usually within 24 h
- Decreased mobility because of pain results in stiffness and immobility

Dimension 3: Modulating factors

Comorbidities

- Osteoarthritic preoperative pain associated with worse acute pain
- Hypertension may moderate pain sensitivity

Demographic

- Age negatively correlates with acute pain

Affective

- Depression, anxiety, and psychosocial distress seem to worsen acute pain

Behavioral

- Pain catastrophizing associated with worse acute pain

Dimension 4: Impact/functional consequences

Pain

- Substantial improvement compared with presurgery

Function

- Improved functional status, but long-term increase in physical activity can sometimes be modest

Dissatisfaction

- Reported in patients characterized by young age, residual chronic pain, depression, anxiety, and fibromyalgia

Quality of life

- Improved but not on par with general population

Sleep

- Returns to normal within 1 year

Dimension 5: Putative mechanisms

Peripheral sensitization

- Injury triggers cellular immune response, recruiting circulatory neutrophils and monocytes and activating resident $\gamma\delta$ T cells and Langerhans cells

- Damage to fibroblasts, keratinocytes, synovial cells, and osteoclasts increases inflammatory mediators

- Inflammatory response mediators potentiate acute pain response

Central sensitization

- Excitatory neurotransmitters in the spinal cord dorsal horn

TKA = total knee arthroplasty.

The heterogeneity of the temporal trajectory of post-TKA pain in the early hours following postanesthesia care unit discharge may also be complicated by preoperative and intraoperative analgesic decisions. Patients receiving single-injection nerve blocks may report increases in pain in the six to 24 hours following block placement as the block resolves [25]. Although perineural catheter techniques can extend the duration of analgesia, our

experience suggests that the use of a high-dose bolus technique followed by a lower-dose infusion may still yield a considerable escalation in pain intensity in a time frame similar to that of the single-injection approach.

Between postoperative days 1 and 3, patients generally reported a reduction in pain intensity [26,27]. It is in this time frame that femoral nerve blockade can often be discontinued without resulting in a considerable step-up in pain intensity, with the administration of supplemental multimodal analgesia. Anteromedial and posterior pain may fluctuate over the course of recovery, and intensity may vary from patient to patient. But regardless of analgesic strategies, our experience suggests that posterior knee pain seems to resolve before anterior knee pain, generally between postoperative days 1 and 2. To this point, while evidence points toward analgesic benefits from sciatic nerve blockade within 24 hours of surgery, available data have not yet shown benefit beyond 24 hours, suggesting a differential pain trajectory between anterior and posterior knee pain within the first few days following surgery [28].

Pain remains a principal limitation to postoperative physical therapy and recovery [3]. A critical aspect of pain following TKA is the distinction between pain at rest and pain evoked by movement [29]. This distinction is important because movement-evoked pain is more intense than pain at rest, analgesic treatments may have a differential effect on rest vs movement pain; finally, movement-evoked pain likely has a more substantial negative impact on postoperative functional recovery [30]. Although pain-induced inhibition of movement is a common conundrum across a variety of surgical insults, it is especially problematic given that inadequate rehabilitation after surgery may contribute to stiffness in the replaced knee [31,32]. The pain resulting from post-TKA stiffness can feed forward to additional immobility and progressive stiffness that require additional anesthetics to surgically manipulate the joint in order to restore mobility [33].

Acute post-TKA pain is commonly assessed in the clinical setting using visual or numerical pain intensity ratings [34]. Although simple and easily implementable, such tools unfortunately only offer information on pain intensity, represent snapshots of the pain state at the particular time of assessment, and provide little to no information on other domains of consideration [35]. These snapshots are largely dependent on the time/frequency of assessment and do not always reflect overall pain level. In research settings, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [36], Quality of Recovery (QoR) [37], and explicit physical performance measures such as the Timed Up and Go and the six-minute walk test [38] offer a more comprehensive assessment of the impact of pain on functional recovery, although such tools increase patient burden and require additional time for accurate implementation.

Dimension 3: Modulating Factors of Acute Post-TKA Pain

Acute pain-modulating factors include comorbid medical conditions, as well as sociodemographic, biological, behavioral, affective, and other clinical conditions [7]. The modulating features of acute pain following TKA are summarized in Table 2. Likely the most prevalent comorbid medical condition in patients undergoing TKA is OA—a common (age- and sex-standardized incidence estimated as 240 per 100,000 person-years for knee OA) inflammatory, degenerative, and, painful condition affecting cartilage, synovial tissue, and bone in often more than one joint, which is often more prevalent in older patients and those with obesity [39]. Chronic preoperative pain due to OA, both at the surgical site and often at other affected joints remote to the surgical site, is likely one of the most important modulating factors affecting the acute pain experience after arthroplasty. Pain is one of the most common indications for arthroplasty with the intended outcome of the surgery to reduce or eliminate chronic pain in the operated joint. Thus, before surgery, patients are likely to be receiving a wide variety of pain management interventions including nonpharmacological therapies and pharmacological therapies including acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids [40]. Preoperative opioids in particular may be problematic given reports of increasing opioid prescribing to treat OA pain [41] and some evidence suggesting increased pain and other suboptimal postoperative outcomes in opioid-treated patients undergoing arthroplasty [42–44]. Of great relevance to acute pain after arthroplasty is the repeated observation that the severity of chronic preoperative pain is associated with the severity of acute pain after TKA [45–47]. Several explanations for this association have been postulated in addition to other biopsychosocial modulating factors affecting the pain experience and/or pain reporting [47].

Other clinical conditions associated with OA and therefore with patients undergoing TKA include hypertension and other cardiovascular diseases, back and neck disorders, and obesity [48–51]. Other than the association between these conditions and a higher prevalence of preoperative chronic pain, it is unclear specifically how these other coexisting conditions may affect the acute pain experience. As TKA is generally performed in older patients, it is important to note that several studies report a negative correlation between age and acute postoperative pain, with older patients being less likely to report more severe pain [46,47]. The observation that hypertension is a common comorbid condition in patients undergoing arthroplasty is perplexing given previous observations of an inverse relationship between blood pressure and pain sensitivity (i.e., baseline blood pressure may moderate pain sensitivity) [52,53]. However, recent observations using data from the Tromso cohort study suggest that cardiovascular regulation, as evaluated by heart rate

variability and baroreflex sensitivity in the setting of an experimental cold pressor test, is impaired in individuals with chronic pain [54]. Although these observations are important to the cardiovascular health of patients with OA and coexisting hypertension, their relevance to the modulation of acute pain after TKA is unclear.

Depression, anxiety, and other features of psychological distress have been repeatedly associated with a higher risk of more severe acute postsurgical pain in general [47], and this has specifically been demonstrated in patients undergoing arthroplasty [45,46,55]. These observations have led to the hypothesis that treatment with antidepressants might reduce acute postoperative pain, and research in this area is gaining interest [56,57]. Also, the acknowledged association between psychological distress and more frequent and severe postsurgical pain has provided the rationale for ongoing clinical evaluations of the efficacy of mindfulness training before surgery [58].

Another psychological construct relevant to the postoperative pain experience is catastrophizing, which is defined as “an exaggerated negative ‘mental set’ brought to bear during actual or anticipated pain experience” and characterized by rumination, pain magnification, helplessness, and exaggeration of the threat value or seriousness of the pain sensations [59]. Specific to patients undergoing arthroplasty, catastrophizing has been reported to be associated with higher postoperative acute pain intensity on the day of surgery, trends toward higher opioid consumption on postoperative days 2 and 3, and longer length of hospital stay [41]. As catastrophizing has been associated with increased pain responses, recent efforts have focused on pain-modulating interventions to use with “catastrophizers.” In particular, Lunn et al. conducted a placebo-controlled trial of the antidepressant escitalopram in high-pain catastrophizing patients undergoing TKA [56]. Although escitalopram vs placebo differences for the primary outcome of movement-related pain 24 hours after surgery were not significantly different, pain at rest and with movement on postoperative days 2–6 was significantly lower in the escitalopram-treated group of catastrophizing patients [56].

Other modulating factors of acute TKA pain include pain modulatory balance, which can be quantified using quantitative sensory testing measures of conditioned pain modulation and temporal summation of pain [7]. Relevant to these factors, Izumi et al. conducted a detailed quantitative sensory testing study of arthroplasty patients and reported that temporal summation (i.e., increasing pain intensity in response to repeated phasic cuff algometer stimulation) was associated with higher postoperative pain at six weeks, but no such association was observed with measures of conditioned pain modulation [60]. Unfortunately, no significant correlations were observed between the study measure of temporal summation and any modifiable clinical factors [60].

Dimension 4: Impact and Functional Consequences of Pain After TKA

In 2003, the National Institutes of Health published a consensus statement [61] supporting the success of TKA based on decades of data. An interesting conclusion in this statement was that “there appears to be rapid and substantial improvement in the patient’s pain, functional status, and overall health-related quality of life in about 90% of patients; about 85% of patients are satisfied with the results of surgery.” This summarizes the current state of TKA quite well; however, there remains a subset of patients who do not realize the predicted or expected pain relief after surgery. Moreover, despite substantial improvements in pain, function, and quality of life, long-term increases in physical activity are quite modest [62]. The impact and functional consequences of acute pain following TKA are summarized in Table 2.

There has been a dramatic increase in the utilization of TKA in the last three decades [63], with a 161.5% increase in volume between 1991 and 2010 in Medicare recipients alone. In 2008, 615,050 total knee replacement procedures were performed in the United States, an increase of 134% from 1999 [64]. During this time, the population grew by 11%, people classified as obese by 23%, and people aged 45–60 by 29%. Expanded indication for knee replacement was one suggestion to explain this disproportionate growth in procedures being done annually [64]. The increased volumes of this procedure, as well as the expanding indications, raise concerns for a higher rate or higher burden of patients who have persistent pain and dissatisfaction after TKA.

One single-center series reported that 14.8% of patients were dissatisfied after TKA unrelated to time from surgery, and preoperative disease severity was the best predictor of satisfaction [65]. An independent single-center series [66] reported dissatisfaction rates as high as 18.8% more than two years after surgery in patients who had less severe knee arthritis. Interestingly, they reported higher incidences of conditions such as depression, anxiety, and fibromyalgia in this group. A separate report from this group revealed that early dissatisfaction correlated with mid- to late-term dissatisfaction [67]. This issue seems magnified in younger patients, where one-third of patients aged 19–60 who underwent TKA reported residual symptoms including pain. When judging a satisfactory outcome at one year after TKA, there is discordance between surgeons and patients, with surgeons determining success more frequently than patients (94.5% vs 90.3%) [68]. Regarding patient expectations after TKA, as many as 30% of patients report persistent pain or that TKA failed to meet their expectations [69,70]. There is no comparable information from large patient groups or population-based databases, as patient-reported outcomes and satisfaction scores are not currently captured on these scales. From a litigation standpoint, a review of malpractice cases related to TKA over three decades in New York

State revealed that chronic pain or dissatisfaction after TKA was the most common reason for litigation [71].

The significance and impact of dissatisfaction and persistent pain after TKA are difficult to quantify due to the multifactorial nature of pain, disability, and the overall patient experience. Additionally, disability and quality of life are often impaired before surgery and could be unrelated to the knee disease itself. A large sample of Danish patients was evaluated for 12 years before and 12 years after TKA and compared with a matched reference population [72]. Patients who underwent TKA had higher overall health care costs, higher medication costs, and higher outpatient and home care costs compared with the reference group. Patients who underwent TKA had less employment income but higher disability pension and sick pay than the reference group. Interestingly, these differences existed before surgery and persisted for the 24 years of evaluation. Considering the preoperative and persistent postoperative status, any cost to society or the health care system attributable to persistent pain would be hard to differentiate.

When looking at health-related quality of life (HRQoL) as related to TKA, there are similar findings [73]. There were significant improvement in HRQoL after surgery, but this was slower than other parameters and did not return to the level of the general population. Again, the specific impact of persistent pain on this measure has not been distinctly reported.

From a socioeconomic perspective, there seems to be a higher probability of persistent pain and disability after TKA, with lower socioeconomic status [74]. Additionally, any disparity between patients of African descent and Caucasian patients on pain and disability is more marked with higher levels of poverty. In fact, in segments of little poverty, there were no significant discrepancies indicating the major impact of economic status on outcomes [75].

It appears that patients return to baseline sleeping patterns within one year after TKA [76]. Compared with the general population, however, it appears that patients have impaired sleep before and after TKA [73]. The specific impact of persistent pain on sleep is unclear. There has been a large body of literature correlating preoperative depression and other psychological factors with poorer outcomes and persistent pain after TKA [77–81]. There have, however, been no reports of the impact of persistent pain after TKA on psychological health and psychosocial outcomes.

If we assume that opioid use is a surrogate for persistent pain after surgery, then the significance of this as it relates to likelihood of future surgery is concerning. More than one-third (39.1%) of predominantly male patients in the Veterans Affairs (VA) system were categorized as long-term opioid users after TKA, and this group had a significantly higher revision rate within one year of TKA as compared with the nonopioid group [82].

Similar findings were also reported in a non-VA system [83] and underscore the impact of persistent pain after TKA, whether related to or unrelated to surgery.

Dimension 5: Putative Mechanisms of Acute Post-TKA Pain

Despite our best efforts, acute pain relief will remain sub-optimal for some patients, with those patients experiencing severe postoperative pain most likely to develop chronic postsurgical pain [84]. Only by better understanding the cellular and molecular underpinnings of the acute pain response can this be addressed. The primary type of pain responsible for the acute response to TKA is due to the wound incision, along with damage to the muscle and bone [85]. Incisional pain is an acute response that results from inflammatory, ischemic, and nociceptive mechanisms, whereas damage to the muscle and bone potentiate the inflammatory response. These result in peripheral, and to a lesser extent central, sensitization [86]. Identifying and understanding the molecular and cellular mechanisms mediating these effects are critical to the development of new therapeutics for the control of acute post-TKA pain. The putative mechanisms of acute pain following TKA pain are summarized in Table 2.

Peripheral sensitization resulting from trauma following TKA results in the interaction of inflammatory mediators with sensory neurons [87], and therefore pain. Inflammatory mediators secreted by activated immune cells include growth factors, cytokines/chemokines, proteases, purines, amines, and lipids, among others [88]. These mediators can act either directly on sensory fibers innervating the site of injury via their cognate receptors, or indirectly by sensitizing the cell or potentiating the inflammatory response. Recent single-cell sensory neuron analyses have found that different neuronal subsets express a variety of immune receptors, including receptor tyrosine kinases and G-protein coupled receptors [89,90]. Activation of these receptors via their ligands often leads to activation of downstream signals that result in peripheral sensitization. Ligand-gated ion channels can also be activated immune cells, which are known to secrete factors such as acetylcholine and serotonin [91,92]. Fortunately, the immune system has built-in controls that help to resolve this inflammatory response, allowing for tissue homeostasis to occur in most cases. However, the mechanisms controlling the transition from acute to chronic pain remain largely unknown [93–95]. This failure to control the progression of pain outcomes may be due to an ineffective resolution of the inflammatory response, genetic variables affecting subpopulations of patients, treatments used, or a combination of these and various unknown factors. Interestingly, the interaction between the nervous and immune systems can be bidirectional [96]. It is now appreciated that sensory neurons will secrete neuropeptides, inflammatory cytokines, and lipids, which in turn help modulate immune

cell activity and function [97]. This complex interplay between the nervous and immune systems may play an important role in the pathogenesis of acute post-TKA pain, as well as regulation of the inflammatory response at the site of injury.

As with most injuries, there is an early and well-orchestrated cellular immune response including the recruitment and activation of myeloid and lymphoid cells from the circulation and tissue-resident cells [98–100]. The cellular component of the inflammatory response includes, for the large part, the recruitment of circulatory neutrophils and monocytes in the acute phase, followed by T cells at chronic phases of the inflammatory response, to the site of injury. Tissue-resident immune cells such as $\gamma\delta$ T cells and Langerhans cells may also contribute to this response [101–104]; they are often the first inflammatory cells to be activated at the site of injury and help spur the recruitment/activation of circulatory cells to the site of damage. These tissue-resident cells also secrete a variety of mediators that act on sensory neurons, potentiating the pain response.

Which cell subset(s) are critical for the pain response in acute post-TKA pain remain unknown, though this may be inferred from animal studies of postincisional pain. Inflammatory pain is most commonly studied in the laboratory setting using the intraplantar injection of complete Freund's adjuvant (CFA) and plantar incision. Here, a subset of myeloid cells (e.g., monocytes/macrophages or dendritic cells but *not* neutrophils) have been recently identified as critical players in acute mechanical hypersensitivity [105]. Some groups have suggested that neutrophils also help to mediate pain outcomes [106,107], while others still point to an antinociceptive role for these cells through their release of opioids in the affected dorsal root ganglia [108,109]. Interestingly, a recent study using a transgenic mouse model lacking tissue-resident mast cells suggests that these cells do not contribute to acute inflammatory pain [110]; mast cells have, however, been found in relatively high abundance in the osteoarthritic synovium and may associate with structural damage [111]. The role of other tissue-resident cells remains largely unknown but could provide further insight into the pathogenesis of acute post-TKA pain. T and B cells likely do not contribute to acute post-TKA pain, as they are often the last cells to infiltrate the wound site (often once pain has subsided) [110].

Recent evidence has shown that fibroblasts, keratinocytes, synovial cells, osteoclasts, and other cells likely damaged following TKA can also contribute to this response through the secretion of inflammatory mediators. The contribution of these resident nonimmune cells to the acute pain response post-TKA, however, also remains largely unknown. Animal studies have begun to uncover some very important functions for these cells in mediating the pain response. For instance, Bautista and colleagues have found keratinocytes and other epithelial cells to produce inflammatory mediators including

Thymic Stromal Lymphopoietin (TSLP), which activates channels and receptors on sensory neurons [112]. A recent study of post-TKA patients with pain found that fibroblasts within the scar promote inflammation and pain, likely via the secretion of the chemotactic cytokine CCL2 [113]. Although these findings were for chronic post-TKA pain, acute activation of fibroblasts also likely contributes to the pain response. Indeed, various inflammatory mediators are upregulated in the synovial fluid, infrapatellar fat pad, and synovial membrane after TKA [112,114]. Furthermore, examination of subchondral bone from TKA patients revealed the presence of pronociceptive mediators including cytokines, growth factors, and neuropeptides [115]. Whether these factors were secreted by osteoclasts, endothelial cells, or white blood cells remains unclear; osteoclasts and endothelial cells are known to secrete such factors [116–119].

Apart from the site of incisional damage, changes in the spinal cord may also contribute to acute post-TKA pain outcomes via central sensitization, a critical component to the development and maintenance of chronic pain [120,121]. These effects are likely not as critical as those caused by direct nociceptor activation by inflammatory mediators or peripheral sensitization. Here, peripheral inputs after injury often drive spinal expression of excitatory neurotransmitters, including glutamate and substance P, in the spinal cord by spinal neurons that in turn reduce the effectiveness of inhibitory neurotransmitters. Glial cells, in particular microglia and astrocytes, are also capable of secreting pro-inflammatory mediators (e.g., cytokines, growth factors, etc.) that in turn increase excitatory processes and decrease inhibitory ones in the dorsal horn of the spinal cord [122,123]. Taken together, the processes occurring both peripherally at the site of injury and centrally in the spinal cord dorsal horn contribute to the increased pain responses observed after TKA. A better understanding of the specific cellular and molecular mechanisms underlying these effects will provide the best opportunity to target and effectively treat acute post-TKA pain.

Discussion

As TKA has become a popular surgical intervention, care providers looking after TKA patients may find acute post-TKA pain an ever-challenging diagnosis. The reason is that this pain may represent a transitional phase between preexisting OA pain and persistent post-TKA pain. To inform stakeholders and guide clinical management, we summarize our current state of knowledge regarding this pain. Acute post-TKA pain can be defined as pain precipitated by TKA at or around the knee. It can be spontaneous or elicited by movement or other stimuli. Based on the source tissue of this pain, patients can usually differentiate between incisional, muscular, or bone pain resulting from tibial and femur osteotomies. Pain

localization is predominantly anterior, with occasional posterior knee pain. The posterior component of knee pain generally self-attenuates between 24 and 48 hours, whereas the anterior component diminishes significantly between 48 and 72 hours.

Within the first 24 hours, acute post-TKA pain is quite heterogeneous; it varies based on anesthetic and analgesic strategies used. Based on the duration of spinal anesthetic used, pain usually has an abrupt onset after spinal anesthesia wears off, but the onset may be slower and progressive when general anesthesia combined with systemic opioids is used. Supplemental nerve blocks can place acute post-TKA pain between these two extremes, depending on the type and duration of these blocks. The duration of pain relief provided by nerve blocks usually depends on the modality used (single-injection vs continuous), and exacerbation of pain can occur as the surgical block wears off.

From a functional stance, TKA generally results in improved functional status. In contrast, poorly managed acute post-TKA pain can interfere with physiotherapy and rehabilitation, and ineffective physiotherapy is associated with stiffness and reduced range of motion. Hence assessment of acute pain post-TKA should not be limited to severity, but should also incorporate measurements of the impact on function. The vast majority of patients report satisfaction with outcomes after surgery, but satisfaction may be reduced with younger age and when depression, anxiety, fibromyalgia, chronic opioid use, and persistent postsurgical pain exist. These risk factors are also associated with postsurgical deterioration in quality of life, disability, opioid dependence, and greater burden to health care resources.

Several factors have been identified as determinants of the severity of acute post-TKA pain. Osteoarthritic chronic joint pain is not only an indication for TKA, but it is also one of the main modulating factors of acute post-TKA pain. The severity of preexisting chronic pain often correlates with the severity of acute post-TKA pain. Similarly, anxiety, depression, distress, and pain catastrophizing have been identified as predictors of the severity of acute post-TKA pain. In contrast, older age is negatively correlated with this severity. Nonetheless, studies examining these predictors have occasionally yielded conflicting results, indicating the need for further research in this area.

From a neuro-immune perspective, the surgical incision, along with the damage to the muscle and bone, result in peripheral and central sensitization. Inflammatory mediators have been implicated in peripheral sensitization, and in cases where this inflammatory response fails to resolve because of genetic factors or otherwise, acute post-TKA pain may develop into chronic pain (beyond 30 days post-TKA). Cellular components of the inflammatory response are also a part of the acute post-TKA pain response, but their role remains largely unknown. Finally,

concomitant central sensitization contributes to both acute and persistent post-TKA pain, but the underlying mechanisms continue to be poorly understood.

We identified several gaps in the TKA literature, particularly surrounding the risk factors and the transition from acute and chronic post-TKA pain. The neuro-immune mechanisms underlying acute post-TKA pain are also characterized by important knowledge gaps that need to be resolved by future research. We acknowledge these gaps as limitations in generating this taxonomy and our attempt to provide a framework for acute post-TKA pain. We hope that our efforts will help improve the understanding of this pain, guide clinical management, and facilitate future research.

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