



Review Article

Knee Joint Neural Sources and Pathways and Their Osteoarthritis Pathogenic Linkages and Pain Control Implications

Ray Marks^{1*}

¹Department of Research, Osteoarthritis Research Center, Box 5B, Thornhill, ONT L3T 5H3, Canada

*Correspondence author: Ray Marks, OARC Clinical Research and Education Director, Ontario L3T 5H3, Canada;

Email: Dr.RayMarks@osteoarthritisresearchcenter.com; rm226@columbia.edu

Citation: Marks R. Knee Joint Neural Sources and Pathways and Their Osteoarthritis Pathogenic Linkages and Pain Control Implications. J Ortho Sci Res. 2024;5(2):1-11.

<https://doi.org/10.46889/JOSR.2024.5205>

Received Date: 24-06-2024

Accepted Date: 15-07-2024

Published Date: 22-07-2024



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CCBY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract

Background: Knee joint osteoarthritis, a widespread disabling disease with no known cause continues to produce considerable bouts of intractable pain and disability as a result of multiple disease associated health problems despite years of research.

Aim: This paper examines if there is sufficient reason to believe one or more neural based abnormalities in the knee neural network may be involved or implicated in inducing and perpetuating at least some forms of knee joint osteoarthritis, but is often unrecognized and thus untreated or ignored.

Methods: Peer reviewed data retrieved from several sources were examined to highlight and discuss the structural and functional nature of the knee joint nerves and their ramifications in various knee joint tissues, the spinal cord and central nervous system and motor control pathways. **Results:** Knee joint nerve pathways that are damaged or functioning abnormally can affect normal joint biomechanics, plus joint stability and thereby can influence the onset or perpetuation of knee joint pathology and exaggerated activation of pain fibers and cognitions.

Conclusion: To improve the effectiveness of strategies designed to avert knee joint osteoarthritis pain and disability, attention to its possible ongoing neuropathology as well as possible declines in joint protective, perceptual and stability mechanisms in older vulnerable adults are indicated.

Keywords: Cartilage Degeneration; Neural Pathways; Knee Joint; Osteoarthritis; Pain

Introduction

Osteoarthritis, a widespread oftentimes progressive albeit non-fatal disabling joint disease affecting many older as well as younger adults commonly produces high levels of intractable pain, stiffness and movement dysfunction, especially at the knee joint that normally affords mobility as well as stability adaptively and functionally [1,2]. A debilitating disease now acknowledged to not only involve the progressive destruction of the cartilage tissues lining the joint, but also its surrounding and intrinsic tissues, including the synovial membrane lining the joint capsule, the muscles and nerves surrounding the joint, the joint ligaments, tendons, menisci and bone as well as the joint capsule, ligament, bone, menisci and muscle sensory endings its complexity highlights why any simplistic universal solution is unlikely to reverse the overall disease process readily and completely [3]. Indeed, the treatment of osteoarthritis remains highly challenging and commonly induces limited functional results even if joint surgery or injections are forthcoming and despite many decades of endeavor. However, some degree of disease mitigation is highly desirable because if unaddressed, related disease problems of joint mal-alignment, instability, alterations in joint sensitivity and responsiveness of muscles, plus joint inflammation and increasing nociceptively induced cartilage chondrocyte apoptosis may prevail or ensue and prove highly disabling and hard to reverse as time progresses [4,5].

Unfortunately, despite a host of pharmacologic strategies developed to allay the disease, most fail to not only impact the disease process and extent to any permanent degree. Moreover, they may not take into account the presence of possible muscle pathology, reflex muscle inhibition, nerve damage and discordant sensory and motor inputs to and from the spinal cord and

central nervous system that may all hasten the magnitude and extent of the disease and degree of disability even if advanced invasive approaches are employed. In fact, no mention is made of one or more potentially impactful nerve-based associations as either risk or important knee osteoarthritis targets for intervention even when etiological and therapeutic approaches have undergone comprehensive investigations [3,6].

Data do imply however that efforts to override pain may do more harm than good, as may some forms of medication. Moreover, pain fibers in the target joint may remain hyper-excitabile in response to both noxious as well as non-noxious stimuli even after joint replacement or reconstructive surgery if one or more knee joint nerves are injured or lacerated.

It is possible however, that concerted efforts to more clearly examine and uncover or clarify the key sources of knee joint osteoarthritis pain, especially those of neural origin as these pertain to the individual case, followed by carefully construed clinically oriented intervention selection that can both reduce and prevent excess pain and joint damage, rather than placing reliance on generic recommendations alone. Moreover, due considerations for remedial applications that are not invasive and possibly injurious to the nervous pathways of the knee may prove of substantive value in multiple respects, including a lowering of social and economic costs, plus lower levels of undue suffering and dysfunction. For example, the application of isometric exercises, electro acupuncture, electrotherapy devices that can enhance neuromodulation, as well as joint mobilization techniques applied individually or collectively, may be beneficial, especially if enacted over a lengthy time period [5,7].

By contrast, any persistent impairment of any component of the nervous pathways supplying the diseased knee joint, plus the strong likelihood of age associated nervous system alterations, including direct damage to the sensory receptors embedded in the joint tissues of the knee, along with various neuropathies [8] or other neural conditions [9] is likely to influence the pain experience and nature thereof, as well as limb position sensitivity and acuity, tissue healing potential, the generation of well-balanced coordinated movement patterns and timely and effective responsiveness to perturbations [10]. At the same time, the emergence of pain and its persistence along with mechanical loading excesses or lack thereof often induces a state of generalized pain sensitization plus multiple physical and mental health challenges, but this is often not well detailed or discussed in the related knee osteoarthritis research [11]. These pain sources may also emerge in the presence of various degrees of knee muscle atrophy and weakness, ligamentous degeneration and laxity, bone microfractures, vascular derangements and poor muscle endurance, essential for adequate joint protection [9,12,13]. Moreover, if untreated or unidentified, there may be a further breakdown in the protective role of the intricate neural network at the knee joint that significantly impacts functional performance in some way. In addition, even if treated the influence of the treatment may depend on how carefully the joint is used, especially after selective and invasive nerve cutting or blocking strategies via anesthetic injections [14,15]. While yielding some degree of short-term pain relief, this latter mode of intervention may yet expose the joint to more damage and joint destruction. plus abnormal joint biomechanics and their oftentimes dire and painful consequences [9,16].

To examine if current evidence points to one or more neural disturbances as possible contributing factors to the dysfunction that emerges in cases with knee osteoarthritis, this narrative report which builds on others, attempts to reexamine if there is an important association between the knee joint neural circuitry and exposure to trauma, inflammation, or abnormal sensorimotor manifestations and osteoarthritis associated pain [9], as well as patient centered 'demands' for rapid pain relief.

This information was sought in the belief that if more care is directed toward conceptualizing the causes of knee joint pathology and selecting the best possible methods of intervention for ameliorating the knee osteoarthritis symptoms based on this analysis it is possible that popular approaches such as infiltration of the knee nerves by various anesthetic agents or surgically destroying the nerves may be less widely used and with fewer negative repercussions.

Specific Aim

The specific review aim was to examine and provide accurate information concerning what we currently know about the anatomy and function of the nerves and nerve branches that supply the knee joint and their central connections and to thereby provide a basis for evaluating whether more attention to the contribution of the nerve supply of the knee joint should be placed on its role in provoking osteoarthritis pain, as well as possible joint destruction.

Hypotheses

It was hypothesized that existing evidence would point to the knee joint sensory-motor pathways as clearly important probable determinants of knee joint health and stability.

Conversely, where nerve damage or dysfunction of the knee sensory-motor systems exists and is not identified or is treated by invasive attempts to alter or block knee nerve transmission processes artificially, more knee pain and joint damage can possibly be anticipated.

To this end, this paper is a narrative one divided into three major components, including the implications of this information for research and practice. It houses full length peer reviewed articles extracted largely from PubMed, PubMed Central and Google Scholar published between January 1, 1945-June 20, 2024 using the key words: innervation of the knee joint, mechanoreceptors, muscle spindles, osteoarthritis. The focus was placed on articles depicting the neuronal pathways underpinning motor control and pain sites located in the periphery rather than any psychosocial factors as applied to osteoarthritis. The discussion centers on how this information might be employed to foster conservative forms of joint protection and intervention, rather than surgical and invasive approaches for ameliorating knee osteoarthritis pain. Studied since the 1940s show there are currently 1086 knee joint articles inclusive of an innervation theme listed on PubMed in this respect as of June 2024, but as on the other websites reviewed not all are clinical studies and only a few have focused specifically on human osteoarthritis, or can be deemed robust reports without flaws. No uniform theme or trend can be discerned among the available data however, even when key words are carefully entered. Any systematic analysis or analytic examination was clearly limited and thus was not contemplated or conducted. In addition, although a considerable body of current data discuss invasive methods of treating knee osteoarthritis pain, such as radio frequency ablation, these were not studied here, as they may be costly and fail to yet protect the joint structurally. See references 17-21 for further reading.

Major Findings

The knee joint, vital for human functioning and comprising a total of three key thigh and leg bones plus the patella or knee cap is normally protected by cartilage tissue at its ends, plus a surrounding joint capsule, multiple ligaments and tendons and muscles, all of which house an extensive array of sensory and motor nerve branches and endings that convey mechanical and chemical messages to and from the central nervous system. In cases where the joint is injured and degenerative joint changes are evident, the nerves supplying the diseased knee joint may react by conveying pain messages rather than only protective messages to and from the damaged joint tissues to the central nervous system with adverse results [24-27].

This scenario is likely to be quite common and may have a negative impact in turn on upright mobility, knee range of motion, sensibility and stability. Additionally, knee muscle reflexes that underpin joint mobility and joint protection under normal circumstances as well as autonomic nervous system functions may become impaired as may the functional properties of muscle afferents [28-30].

Indeed, since multiple nerves serve or are embedded in all joint tissues involved in knee function and help to regulate the knee blood supply needed to maintain joint homeostasis and sustain tissue health [20] it appears safe to predict that any form of nerve damage that is excessive or prolonged can be expected to severely compromise knee function over time, regardless of whether this is due to intrinsic or cognitive factors [31]. In the case of knee osteoarthritis where multiple biomechanical forces may prove injurious to joint and nerve tissues, a cycle of dysfunction may well arise that is potentially additive, or cumulative if its mediating sources remain unrecognized and untreated or prevented. Miyakawa, et al., suggest that neuropathic pain often reported in knee osteoarthritis may reflect the fact that it appears the substantia gelatinosa in the spinal cord dorsal horn receives primary afferent inputs in this respect and can hence be considered a source of neuropathic pain [32]. This possible situation and others may explain the nature of some non-uniform osteoarthritis pain phenotypes that were observed by Neelapala, et al., including indistinct pain [27]. Indeed, even if not well established, the sensory nerves and their knee joint branches that act to normally protect the knee joint may be inextricably linked to knee osteoarthritis dysfunction because these nerves supply most of the stabilizing structures found deranged or destroyed or impaired in knee osteoarthritis as time unfolds, such as the joint capsule and ligaments as well as afferent and efferent corticospinal pathways [33,34].

Pain, a predominant feature of knee osteoarthritis commonly elicited by the mechanical or chemical irritation of joint pain receptors that are conveyed by pain nerves to the cerebral cortex may induce a state of excessive pain sensitization, along with the perpetual release of pain modulators such as nerve growth factor that underpin joint inflammation [33-38]. It is also observed that efforts to rest the joint may have a pain provoking effect rather than an arresting effect [21,35,39-42]. Alternately, exposure to persistent inflammation and excess joint stresses that heightens pain transmission may induce a state of joint nerve tissue sprouting or increases in the innervation density of the synovium as well as abnormal sensitization of the subchondral bone channel regions and menisci that can exacerbate pain and joint derangement [43,44].

Recent studies show pain is also not solely a subjective experience, but one that occurs in tandem with a cascade of noxious proteinase-activated receptors and ion channel ligands and other molecules involved in transmitting pain and tissue destructive products [19,38]. Moreover, over time, instead of providing optimal loading responses to various tensile, compressive and shear deformities placed on knee joint tissues, the resultant neural alterations induced by the disease as well as age may fail to stimulate appropriate stress adaptations and the capacity of the knee tissues to withstand stress and avert pain [45]. In the case of a specific impact of joint inflammation on muscle spindle function, further pain may ensue due to a possible deficit in overall motor control including muscle contractile amplitudes and velocity, timing and force production and that can all arguably induce injurious biomechanical imbalances, cartilage mechanical and morphological disruptions and further pain [19,21,28,45].

Additional emergent observations show nerves subjected to persistent insults undergo a remarkable form of reorganization in terms of subsuming an altered morphology, plus evidence of an increase in nerve fiber density and sprouting into poorly innervated joint sites that magnifies pain. Other data reveal there may also be inappropriate remodeling of sensory and sympathetic nerve fibers that can be accompanied by increases in toxic tissue destroying molecules and enzymes that induce skeletal as well as nonskeletal pain and the experiences of intractable movement- as well as rest pain [46]. The entry of sensory and sympathetic nerves into the normally aneural articular cartilage plus inflammation and a host of possible neuroimmune reactions has also been discussed quite recently [47] as has the adverse impact of joint immobilization [48].

Studies by Martin, et al., examining the molecular records that emerge on abnormal activation of pain transmission markers in the dorsal root ganglia and spinal cord during development of osteoarthritis show these nerve bodies to be responsible for the manifestation of neuropathic pain, a very painful form of joint pathology [39]. Morgan, et al., further note artemin/GFR α 3 signaling has an additional role to play in the pathogenesis of osteoarthritis pain [49]. Miyakawa, et al., note that persistent nerve compression in rats with root constriction can induce a state of mechanical hypersensitivity, hyperalgesia and thermal hyperalgesia [32]. At the opposite extreme, immobilization- often recommended in various forms for people with knee osteoarthritis- can elicit motor neuronal degeneration and possible demyelination of some knee muscle axons in its own right and should be avoided [48].

Unsurprisingly, Dye, et al., note that the entire degree to which the richly innervated knee and its intraarticular components are maintained optimally at a high structural and functional level is probably crucial in all likelihood for fostering optimal tissue homeostasis and integrity [24]. In contrast, serious ramifications are predicted in the presence of any deficit or derangement in this regard such as reflex muscle inhibition common in knee osteoarthritis and that may reflect a gamma loop or spindle system disturbance, as well as persistent nerve entrapment or stretching, focal swelling, changes in nerve signaling, denervation edema and muscle fat infiltration [16,28,50-52]. Recent data further show associated inflammatory signs and changes in muscle gene and protein expression may contribute substantively to osteoarthritis knee pain, if the mechanisms of joint protection fail or are exceeded by joint overuse or abuse [3,53,54].

In particular, even if unproven, it appears both noninvasive and invasive interventionists must clearly guard against their client's tendency to provoke unwanted pain mediators and adverse nerve based cross talk responses [55]. This is owing to some evidence that progressive increases in pain due to joint tissue destruction and inflammation, subchondral joint nerve activation processes, plus the development of neuropathic joint features and/or central sensitization could lead to a predisposition to further or new joint trauma and rapid and severely accelerated joint derangement and with this persistent synovitis, chronic inflammation, pain sensitization and pain catastrophizing and a higher than desirable degree of obesity, even if surgery is forthcoming [6,56-60].

In sum, the importance of acknowledging the complexity and functional relevance of the periarticular nerve supply to the knee and its potential role in osteoarthritis as put forth in 1999 by Salo appears to have considerable merit as far as understanding its pathogenesis and underlying molecular pathways and sources of therapeutic promise [13]. Indeed, over time, mapping, histological, biochemical and neuro-physiological studies of the extensive network of the knee sensory nerves and their influence on sensation and movement have shown these are important regulators of motor control albeit with differing distributions and modes of gene expression [61].

Additional Observations

Categorized into four distinct morphological and functional sensory receptor endings termed mechanoreceptors including pain sensitive nerve endings, the knee joint nerve endings designated as types I-IV are sensitive to chemical, mechanical and thermal stimuli [62-64]. Located to varying degrees and in multiple sites within the knee anterior and posterior cruciate ligaments, the knee medial and lateral collateral ligaments, menisci and the patellar and popliteal tendons these receptors are very vulnerable to abnormal or injurious osteoarthritis derived stimuli [22,27,60]. Alone, their excessive damage or dysfunction or exposure to inflammation can hence be shown to have the potential to mediate problems of functional instability, muscle inhibitory responses, pain and multiple functional and structural gene expression changes that in turn can exacerbate inflammation and reduce joint protection [10,22] while hastening cartilage damage rather than cartilage maintenance [64-68]. Tamaj, et al., discuss the fact that the transient receptor potential channel known as ankyrin 1 - which is involved in the regulation of vascular function and is located on sensory neuron membranes and nerves is also apparently involved in mediating knee osteoarthritis pain and disease severity [37,66].

Thus, the knee neural networks and their differing anatomical and functional attributes as well as their potential towards a failure to function optimally may not only prove less than protective, but may raise the risk of an injury that could further compromise joint stability, joint coordination functions and reflexive modulation and precise co variation among the different knee muscle extensors during locomotion [64,68]. Since a majority of these knee sensory afferents that extend from the knee joint receptor network are indeed unmyelinated and respond to strong mechanical stimulation or noxious forced movement, even under conditions of nerve blocks, a majority of these fibers can yet be expected to relay noxious stimuli to the central nervous system that in time may override any invasive form of intervention designed to ablate or impact nerve conduction at the knee if damaged or destroyed [69,70].

Wotjys, et al., for example identified that substance-P containing nerve fibers associated with pain production in the retinaculum, fat pad, periosteum and subchondral plate of patellae that could all be affected by osteoarthritis, thus protection of these tissues is vital at all times. In addition, owing to their widespread and possibly non uniform distribution, denervation procedures at the knee may yet fail to reduce pain or permanent results especially if these procedures damage the joint capsule and its sensory innervation and thereby the ability to withstand or respond to strong force, repeated forces, or deep pressure [71-74]. As in the case of sports injuries that involve the knee, macro or micro loading or usage derived injuries and others can persist and if so, can result in further in damage to the joint receptors and their protective mechanisms, while fostering persistently abnormal internal joint stresses and strains [64].

Salamanna, et al., found that the posterior cruciate ligaments of people with knee osteoarthritis did appear to be associated with impaired joint sensory nerve firing accuracy, possibly due to associated structural alterations within the ligament and/or surrounding tissues, especially in the case of severe knee osteoarthritis [68]. This negative proprioceptive outcome was largely attributed to a failure of the damaged joint receptors to mediate effective joint protection strategies, an idea supported by Chen, et al., where the knee osteoarthritis subjects' functional scores varied relative to numbers of prevailing mechanoreceptors observed in the diseased posterior cruciate ligament of the knees that were examined [75].

Elfvin, et al., further emphasizes the importance of acknowledging and addressing the role of knee joint nerves and their ramifications as a potent source of destructive pain mediators as well as central nervous system adaptations that may well contribute to osteoarthritis disability as well as progressive joint damage at the knee and at other joints [76]. In particular, even if temporarily effective, injection or surgical approaches that fail to avert further injury to the joint in the absence or decrease of pain and do not account for central features of pain and pain sensitization manifestations may fail even if directed accurately

towards selected nerve branches or diseased tissue components [77,78]. Moreover, a specific failure to consider the nature of the surrounding muscle tendon complexes in the face of chronic pain and osteoarthritis inflammation and muscle pathology and their contributions to the maintenance and perpetuation of biomechanical imbalances alone may also be expected to exacerbate cartilage damage even in the face of the most up to date invasive knee joint treatments in the hands of highly skilled practitioners [64,79]. Additionally, the sole use of isolated injections to counter long standing knee pain may not prove sufficient if multiple joint nerves are compromised and remain unaffected [80].

Indeed, hyperalgesia as well as any prevailing unaccounted for joint mechanoreceptor abnormalities, such as declining sensory receptor numbers or transmission ability and sensibility, pain stimulation in the joint can predictably foster a state of abnormal neuromuscular junction remodeling and atrophy in the quadriceps and other lower leg muscles [81]. As well, abnormal capsular and ligament stretches, possible muscle spasm due to inflammatory disease impacts and abnormal bone vascular pressure increases may excite one or more joint and bone pain receptors persistently, cumulatively and irrevocably even if joint damage is not extensive [60].

Discussion

In an effort to better understand why knee joint osteoarthritis is increasing rapidly in aging persons, as well as why many treatments fail to alleviate its painful progression, it was felt that efforts to reexamine the neural implications of the network surrounding the knee joint in the context of osteoarthritis would prove insightful. A prevalent disease affecting the knees and other joints of older adults, the present approach was also taken given that many in multiple countries have limited advanced resources or practitioners to advance highly technical intervention approaches. In addition, this undertaking strove to advance our understanding of the complex nature of knee osteoarthritis and treatment challenges.

Although the value of this line of inquiry has been put forth for some time, it has not truly advanced, despite some insightful standalone reports in the last few decades and our review approach clearly revealed this idea that linkages exist between knee joint nerves and osteoarthritis pathology has much merit but is not yet pursued to any meaningful degree, or in well detailed or tested clinically oriented studies. This is despite some emergent data that supports a possible causative or reactionary link between the knee joint and/or its neural network and the ability to resist impact in the face of excessive joint reactive forces [82, 84, 85]. The bulk of the informative data that does exist is also somewhat problematic because it stems predominantly from those examining animal models of osteoarthritis or basic anatomical and physiological responses to artificial patterns of stimulation in cat, rat, mouse and rabbit knee joints that may not reflect the human condition or the clinical syndrome of knee osteoarthritis at all accurately.

The possibility of an impairment in some component of the knee joint sensory and/or proprioceptive pathways and a subsequent irritation in and around the knee joint tissues in response to secondary joint changes is also rarely examined in conjunction with joint biochemical, biomechanical and neuromotor measures that may help pinpoint distinct postural changes in the lower leg during standing and walking that are likely to contribute to reflex or centrally induced muscle efferent alterations and joint derangement, repeated bouts of extensive joint injury, unrelenting pain, inflammation and functional deficits [17,64].

As a result, no singular theory or distinctive pathogenic pathway of knee joint destruction has been put forth even though many older adults experience pain that is unrelieved by standard approaches and points to a neural array of possible dysfunction. Most current recommendations tend to overlook the key importance of examining and possibly uncovering the many possible neural sources of osteoarthritis pain, wherein some forms of targeted intervention may prove beneficial in attenuating or mitigating the severity of the condition as time elapses. By contrast, a failure to target one or more suboptimal or deficient neural influences may fail to prevent sensory nerve density increases as observed in painful knee osteoarthritis models [18].

In addition, preventing excess joint loading and pressures, while avoiding complete rest appears imperative in this regard because all the knee joint tissues house pain mediators and transmitters as well as mechanoreceptors that could induce pain and with this abnormal proprioception and possible subnormal cortical responses, as well as postural control deficits [38,83]. To this end, a comprehensive biomechanical assessment followed by carefully tailored and titrated intervention approaches that do no harm are indicated. In particular, because mechanical stimuli are essential for the growth and maintenance of cartilage and

aberrant mechanical loading can lead to cartilage damage, it appears that careful mechanical manipulation of the cell micro-environment through careful movements, muscle strengthening and joint protection strategies along with sensory stimulation approaches such as TENS may arguably help to foster a state of tissue reconstitution, while reducing excess cartilage matrix damage and intractable pain.

In the interim, while this report is not a definitive one and may have assumed preclinical data are generalizable and have some bearing on enhancing our understanding of knee afferent and efferent mediators in human osteoarthritis, no compelling alternate hypotheses of note has been forthcoming for some time. However, when there is some degree of osteoarthritis there is likely to be some measurable neural associations and correspondingly as these worsen, more joint destruction appears probable.

This idea is thus important to elaborate on in the future in our view, given that many cases of knee osteoarthritis are deemed to have no underlying cause and age cannot explain why one joint only may be affected and most older adults will not have knee osteoarthritis. However, it is possible, some cases may stem from lesions at the lumbar sacral spinal level and their altered afferent and efferent nerve messages to and from the knee, others from secondary derangement of nerves embedded in tissues surrounding the osteoarthritic joint, including the joint and muscle nerves. As well, peripheral as well as central nerve pathway alterations may foster increased pain sensitivity and damage vulnerability if unrecognized.

In addition to trauma, diseases that impact nerves adversely, such as diabetes, as well as injuries to joint tissues that damage joint receptors, age associated declines in joint receptor and muscle spindle function may all undermine the complex mechanoreceptor functions that protect the knee joint from impact and may prove responsible for inducing osteoarthritis joint damage or its perpetuation and possible increase in the density of knee sensory nerves that transmit pain.

At present, since the level of suffering worldwide as a result of knee osteoarthritis is increasing markedly, while health resources are not uniformly available to all and cannot be safely used by all older adults and the costs of the disease to both the individual and society is enormous [3], it would seem especially valuable to pursue the idea as to whether neural dysfunction is an osteoarthritic mediator to some degree [19] and if so, if exercise or other non-toxic carefully conceived and practiced interventions are implemented will alleviate osteoarthritis disability to an acceptable degree.

This may have a profound influence on the ability to prevent as well as mitigate some degree of osteoarthritis joint damage and suffering and is thus strongly advocated.

Conclusion

From the above arguments and mindful of the many gaps in this realm of inquiry we conclude:

- The nervous supply of the tissues in the knee joint and surrounding muscles and tendon and their less-than-optimal interactions may have a bearing on the expression and perpetuation of chronic osteoarthritis
- If unaddressed, even laudable anticipated molecular based knee osteoarthritis interventions are likely to fail.
- As well, denervation strategies and others that may relieve pain, may yet foster a state of increasing susceptibility to joint destruction and a chronic opioid addiction if efforts are not made to protect the joint from excess loading subsequent to an improved post intervention ability to function
- To be effective, osteoarthritis preventive and intervention strategies must account for the unique or collective influence of the disease on the neural pathways affecting knee joint function and structure
- At the very least, regardless of the disease state, it appears every effort should be made to avert excessive joint loading and to promote favorable joint sensibility functions, while directing interventions such as laser therapy in a targeted carefully construed manner
- At the same time, the knee sensory-motor factors that appear to sub-serve movement and joint sense, plus overall motor control and their protective and pathological potential should be studied intently
- Since many older people with painful disabling knee osteoarthritis may be driven to become chronic opioid users with dire consequences, the ability to help them engage without undue distress in meaningful social actions and functional activities promises to alleviate the immense costs of failing to do this

Conflict of Interests

Author has no conflict of interest to disclose.

Funding Sources

No funding was obtained for this study.

References

1. Yuan Y, Shen W, Han Q, Liang D, Chen L, Yin Q, et al. Clinical observation of pulsed radiofrequency in treatment of knee osteoarthritis. *Int J Clin Exp Med*. 2016;9(10):20050-5.
2. Lee SH, Choi HH, Kwak SG, Chang MC. Effectiveness of radiofrequency ablation of the genicular nerves of the knee for the management of intractable pain from knee osteoarthritis. *Pain Physician*. 2024;27(4):E419-29.
3. Pradelli L, Sinigaglia T, Migliore A, Checchia GA, Franceschi F, Frediani B, et al. Non-surgical treatment of knee osteoarthritis: multidisciplinary Italian consensus on best practice. *Ther Clin Risk Manag*. 2021;17:507-30.
4. Grässel S. The role of peripheral nerve fibers and their neurotransmitters in cartilage and bone physiology and pathophysiology. *Arthritis Research Therapy*. 2014;16:1-3.
5. He J, Zuo J, Fan X, Li Z. Electro-acupuncture modulated miR-214 expression to prevent chondrocyte apoptosis and reduce pain by targeting BAX and TRPV4 in osteoarthritis rats. *Braz J Med Biol Res*. 2024;57:e13238.
6. Driban JB, Harkey MS, Barbe MF, Ward RJ, MacKay JW, Davis JE, et al. Risk factors and the natural history of accelerated knee osteoarthritis: a narrative review. *BMC Musculoskelet Disord*. 2020;21(1):332.
7. Courtney CA, Steffen AD, Fernández-de-Las-Peñas C, Kim J, Chmell SJ. Joint mobilization enhances mechanisms of conditioned pain modulation in individuals with osteoarthritis of the knee. *J Orthop Sports Phys Ther*. 2016;46(3):168-76.
8. Damarey B, Demondion X, Wavreille G, Pansini V, Balbi V, Cotten A. Imaging of the nerves of the knee region. *Eur J Radiol*. 2013;82(1):27-37.
9. Zhang L, Liu G, Han B, Wang Z, Yan Y, Ma J, et al. Knee joint biomechanics in physiological conditions and how pathologies can affect it: a systematic review. *Appl Bionics Biomech*. 2020;2020:7451683.
10. Çabuk H, Kuşku Çabuk F. Mechanoreceptors of the ligaments and tendons around the knee. *Clin Anat*. 2016;29(6):789-95.
11. Adatia A, Rainsford KD, Kean WF. Osteoarthritis of the knee and hip. Part I: aetiology and pathogenesis as a basis for pharmacotherapy. *J Pharm Pharmacol*. 2012;64(5):617-25.
12. Roberts SL, Stout A, Dreyfuss P. Review of knee joint innervation: implications for diagnostic blocks and radiofrequency ablation. *Pain Med*. 2020;21(5):922-38.
13. Salo P. The role of joint innervation in the pathogenesis of arthritis. *Can J Surg*. 1999;42(2):91-100.
14. Burckett-St Laurant D, Peng P, Girón Arango L, Niazi AU, Chan VW. The nerves of the adductor canal and the innervation of the knee: an anatomic study. *Reg Anesth Pain Med*. 2016;41(3):321-7.
15. Kwon SS, Chazen JL, Kishore S, Habibi BA, Chi M, Rand E, et al. Investigation of genicular neurotomy of the knee: MRI characterization of anatomy and implications for intervention. *Clin Imaging*. 2020;59(1):78-83.
16. Esrafilian A, Stenroth L, Mononen ME, Tanska P, Avela J, Korhonen RK. EMG-assisted muscle force driven finite element model of the knee joint with fibril-reinforced poroelastic cartilages and menisci. *Sci Rep*. 2020;10(1):3026.
17. Slosberg M. Effects of altered afferent articular input on sensation, proprioception, muscle tone and sympathetic reflex responses. *J Manipulative Physiol Ther*. 1988;11(5):400-8.
18. Lee W, Georgas E, Komatsu DE, Qin YX. Daily low-intensity pulsed ultrasound stimulation mitigates joint degradation and pain in a post-traumatic osteoarthritis rat model. *J Orthop Translat*. 2023;44:9-18.
19. McDougall JJ. Arthritis and pain. Neurogenic origin of joint pain. *Arthritis Res Ther*. 2006;8(6):220.
20. McDougall JJ. Osteoarthritis is a neurological disease-an hypothesis. *Osteoarthritis and Cartilage Open*. 2019;1(1-2):100005.
21. Abd-Elsayed A, Henjum LJ, Shiferaw BT, Yassa PE, Fiala KJ. Infrapatellar branch of the saphenous nerve: therapeutic approaches to chronic knee pain. *Curr Pain Headache Rep*. 2024;28(4):279-94.
22. Saito T. Neurogenic inflammation in osteoarthritis of the knee. *Modern rheumatology*. 2003;13(4):301-4.
23. Belluzzi E, Stocco E, Pozzuoli A, Granzotto M, Porzionato A, Vettor R, et al. Contribution of infrapatellar fat pad and synovial membrane to knee osteoarthritis pain. *BioMed Res Int*. 2019;2019(1):6390182.
24. Dye SF, Vaupel GL, Dye CC. Conscious neurosensory mapping of the internal structures of the human knee without

- intraarticular anesthesia. *Am J Sports Med.* 1998;26(6):773-7.
25. Tran J, Peng PWH, Chan VWS, Agur AMR. Overview of innervation of knee joint. *Phys Med Rehabil Clin N Am.* 2021;32(4):767-78.
 26. Supper P, Radtke C, Hirtler L. Anatomical variation of infrapatellar innervation determines clinical risk of infrapatellar neuropathy. *Pain Physician.* 2024;27(2):E293-304.
 27. Yan J, Sasaki W, Hitomi J. Anatomical study of the lateral collateral ligament and its circumference structures in the human knee joint. *Surg Radiol Anat.* 2010;32(2):99-106.
 28. Dimitriou M. Human muscle spindles are wired to function as controllable signal-processing devices. *Elife.* 2022;11:e78091.
 29. Sohn R, Assar T, Kaufhold I, Brenneis M, Braun S, Junker M, et al. Osteoarthritis patients exhibit an autonomic dysfunction with indirect sympathetic dominance. *J Transl Med.* 2024;22(1):467.
 30. Wu Q, Henry JL. Functional changes in muscle afferent neurones in an osteoarthritis model: implications for impaired proprioceptive performance. *PLoS One.* 2012;7(5):e36854.
 31. O'Neill TW, Felson DT. Mechanisms of Osteoarthritis (OA) pain. *Current osteoporosis reports.* 2018;16:611-6.
 32. Miyakawa T, Terashima Y, Takebayashi T, Tanimoto K, Iwase T, Ogon I, et al. Transient receptor potential ankyrin 1 in spinal cord dorsal horn is involved in neuropathic pain in nerve root constriction rats. *Mol Pain.* 2014;10:58.
 33. Neelapala YVR, Neogi T, Kumar D, Jarraya M, Macedo L, Kobsar D, et al. Exploring different models of pain phenotypes and their association with pain worsening in people with early knee osteoarthritis: the MOST cohort study. *Osteoarthritis Cartilage.* 2024;32(2):210-9.
 34. Fonkoué L, Behets C, Kouassi JK, Coyette M, Detrembleur C, Thienpont E, et al. Distribution of sensory nerves supplying the knee joint capsule and implications for genicular blockade and radiofrequency ablation: an anatomical study. *Surg Radiol Anat.* 2019;41(12):1461-71.
 35. Zhang L, Li M, Li X, Liao T, Ma Z, Zhang L, et al. Characteristics of sensory innervation in synovium of rats within different knee osteoarthritis models and the correlation between synovial fibrosis and hyperalgesia. *J Adv Res.* 2021;35:141-51.
 36. Onodera T, Iwasaki K, Matsuoka M, Morioka Y, Matsubara S, Kondo E, et al. The alterations in nerve growth factor concentration in plasma and synovial fluid before and after total knee arthroplasty. *Sci Rep.* 2024;14(1):8943.
 37. Martins GC, Camanho G, Rodrigues MI. Immunohistochemical analysis of the neural structures of the posterior cruciate ligament in osteoarthritis patients submitted to total knee arthroplasty: an analysis of thirty-four cases. *Clinics (Sao Paulo).* 2015;70(2):81-6.
 38. Altaie A, Campbell TM, Owston H, Jones E, Doyle R, Feibel RJ, et al. Soluble low affinity nerve growth factor receptor (sLNGFR) may regulate pain in knee osteoarthritis. *Clin Exp Rheumatol.* 2024;42(3):713-7.
 39. Martin Gil C, Raoof R, Versteeg S, Willemen HLDM, Lafeber FPJG, Mastbergen SC, et al. Myostatin and CXCL11 promote nervous tissue macrophages to maintain osteoarthritis pain. *Brain Behav Immun.* 2024;116:203215.
 40. Liu Z, Li M, Zhang L, Shi X, Liao T, Jie L, et al. NGF Signaling exacerbates KOA peripheral hyperalgesia via the increased TRPV1-labeled synovial sensory innervation in KOA rats. *Pain Res Manag.* 2024;2024:1552594.
 41. Gan D, Jin X, Wang X, Tao C, Yan Q, Jia Q, et al. Pathological progress and remission strategies of osteoarthritic lesions caused by long-term joint immobilization. *Arthritis Res Ther.* 2023;25(1):237.
 42. Salo PT, Theriault E. Number, distribution and neuropeptide content of rat knee joint afferents. *J Anat.* 1997;190(4):515-22.
 43. Obeidat AM, Miller RE, Miller RJ, Malfait AM. The nociceptive innervation of the normal and osteoarthritic mouse knee. *Osteoarthritis Cartilage.* 2019;27(11):1669-79.
 44. Hoshino T, Tsuji K, Onuma H, Udo M, Ueki H, Akiyama M, et al. Persistent synovial inflammation plays important roles in persistent pain development in the rat knee before cartilage degradation reaches the subchondral bone. *BMC Musculoskelet Disord.* 2018;19(1):291.
 45. Logerstedt DS, Ebert JR, MacLeod TD, Heiderscheid BC, Gabbett TJ, Eckenrode BJ. Effects of and response to mechanical loading on the knee. *Sports Med.* 2022;52(2):201-35.
 46. Jimenez-Andrade JM, Mantyh PW. Sensory and sympathetic nerve fibers undergo sprouting and neuroma formation in the painful arthritic joint of geriatric mice. *Arthritis Res Ther.* 2012;14(3):R101.
 47. Suri S, Gill SE, Massena de Camin S, Wilson D, McWilliams DF, Walsh DA. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Ann Rheum Dis.* 2007;66:1423-8.
 48. He X, Dishman V. Spinal motor neuronal degeneration after knee joint immobilization in the guinea pig. *J Manipulative Physiol Ther.* 2010;33(5):328-37.

49. Morgan M, Nazemian V, Ooi LS, Burger S, Thai J, Ivanusic J. Artemin sensitizes nociceptors that innervate the osteoarthritic joint to produce pain. *Osteoarthritis Cartilage*. 2023;31(10):1342-52.
50. Konishi Y, Yoshii R, Ingersoll CD. Gamma loop dysfunction as a possible neurophysiological mechanism of arthrogenic muscle inhibition: a narrative review of the literature. *J Sport Rehabil*. 2022;31(6):736-41.
51. Saeed Alshahrani M, Reddy RS, Asiri F, Tedla JS, Alshahrani A, Kandakurti PK, et al. Correlation and comparison of quadriceps endurance and knee joint position sense in individuals with and without unilateral knee osteoarthritis. *BMC Musculoskelet Disord*. 2022;23(1):444.
52. Pelletier JP, Paiement P, Dorais M, Raynauld JP, Martel-Pelletier J. Risk factors for the long-term incidence and progression of knee osteoarthritis in older adults: role of nonsurgical injury. *Ther Adv Chronic Dis*. 2023;14:20406223231169715.
53. Cunha JE, Barbosa GM, Castro PATS, Luiz BLF, Silva ACA, Russo TL, et al. Knee osteoarthritis induces atrophy and neuromuscular junction remodeling in the quadriceps and tibialis anterior muscles of rats. *Sci Rep*. 2019;9(1):6366.
54. Hodgkinson T, Kelly DC, Curtin CM, O'Brien FJ. Mechanosignalling in cartilage: an emerging target for the treatment of osteoarthritis. *Nat Rev Rheumatol*. 2022;18(2):67-84.
55. Diracoglu D, Vural M, Baskent A, Dikici F, Aksoy C. The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis. *J Back Musculoskelet Rehabil*. 2009;22(1):1-9.
56. Morgan M, Thai J, Nazemian V, Song R, Ivanusic JJ. Changes to the activity and sensitivity of nerves innervating subchondral bone contribute to pain in late-stage osteoarthritis. *Pain*. 2022;163(2):390-402.
57. Malek N, Mlost J, Kostrzewa M, Rajca J, Starowicz K. Description of novel molecular factors in lumbar drgs and spinal cord factors underlying development of neuropathic pain component in the animal model of osteoarthritis. *Mol Neurobiol*. 2024;61(3):1580-92.
58. Huang D, Liu YQ, Liang LS, Lin XW, Song T, Zhuang ZG, et al. The diagnosis and therapy of degenerative knee joint disease: expert consensus from the Chinese Pain Medicine Panel. *Pain Res Manag*. 2018;2018:2010129.
59. Kurien T, Kerslake RW, Graven-Nielsen T, Arendt-Nielsen L, Auer DP, Edwards K, et al. Chronic postoperative pain after total knee arthroplasty: The potential contributions of synovitis, pain sensitization and pain catastrophizing-An explorative study. *Eur J Pain*. 2022;26(9):1979-89.
60. Shumnalieva R, Kotov G, Ermencheva P, Monov S. Pathogenic mechanisms and therapeutic approaches in obesity-related knee osteoarthritis. *Biomedicines*. 2023;12(1):9.
61. Han YH, Li B, Wen Y. Distribution, quantity and gene expression of mechanoreceptors in ligaments and tendons of knee joint in rabbits. *J Mol Histol*. 2020;51(3):233-40.
62. Vasconcelos DP, Jabangwe C, Lamghari M, Alves CJ. The neuroimmune interplay in joint pain: the role of macrophages. *Front Immunol*. 2022;13:812962.
63. Banios K, Raoulis V, Fyllos A, Chytas D, Mitrousias V, Zibis A. Anterior and posterior cruciate ligaments mechanoreceptors: a review of basic science. *Diagnostics (Basel)*. 2022;12(2):331.
64. Alessandro C, Prashara A, Tentler DP, Tresch MC. Inhibition of knee joint sensory afferents alters covariation across strides between quadriceps muscles during locomotion. *J Appl Physiol*. 2023;134(4):957-68.
65. Segarra-Queralt M, Crump K, Pascuet-Fontanet A, Gantenbein B, Noailly J. The interplay between biochemical mediators and mechanotransduction in chondrocytes: unravelling the differential responses in primary knee osteoarthritis. *Phys Life Rev*. 2024;48:205-21.
66. Tamai H, Yamanaka M, Taniguchi W, Nishio N, Fukui D, Nakatsuka T. Transient receptor potential ankyrin 1 in the knee is involved in osteoarthritis pain. *Biochem Biophys Rep*. 2023;34:101470.
67. Ariel de Lima D, Helito CP, Lacerda de Lima L, Dias Leite JA, Costa Cavalcante ML. Study of the nerve endings and mechanoreceptors of the anterolateral ligament of the knee. *Arthroscopy*. 2019;35(10):2918-27.
68. Salamanna F, Caravelli S, Marchese L, Carniato M, Vocale E, Gardini G, et al. Proprioception and mechanoreceptors in osteoarthritis: a systematic literature review. *J Clin Med*. 2023;12(20):6623.
69. Langford LA, Schmidt RF. Afferent and efferent axons in the medial and posterior articular nerves of the cat. *Anat Rec*. 1983;206:71-8.
70. Schaible HG, Schmidt RF, Willis WD: Responses of spinal cord neurones to stimulation of articular afferent fibres in the cat. *J Physiol*. 1986;373:575-93.
71. Wojtys EM, Beaman DN, Glover RA, Janda D. Innervation of the human knee joint by substance-P fibers. *Arthroscopy*. 1990;6(4):254-63.

72. Freeman MAR, Wyke B: The innervation of the knee joint. An anatomical and histological study in the cat. *J Anat.* 1967;101:505-32.
73. Wei JY, Simon J, Randie M, Burgess PR. Ascending spinal axons that signal the position of the hindlimbs under static conditions: location and receptor input. *Exp Brain Res.* 1984;54:7-22.
74. Rachmaran JE, Wyke B. Articular reflexes at the knee joint: an electromyographic study. *Am J Physiol.* 1972;223:1276-80.
75. Chen J, Chen S. Relationship between mechanoreceptors in the posterior cruciate ligament and patient age or osteoarthritis severity. *Orthop J Sports Med.* 2023;11(6):23259671231168894.
76. Elfvin LG, Holmberg K, Johansson J, Aldskogius H. The innervation of the synovium of the knee joint in the guinea pig: an immunohistochemical and ultrastructural study. *Anat Embryol (Berl).* 1998;197(4):293-303.
77. Zhao J, Wang Z, Xue H, Yang Z. Clinical efficacy of repeated intra-articular pulsed radiofrequency for the treatment of knee joint pain and its effects on inflammatory cytokines in synovial fluid of patients. *Exp Ther Med.* 2021;22(4):1073.
78. McCormick ZL, Reddy R, Korn M, Dayanim D, Syed RH, Bhavne M, et al. A prospective randomized trial of prognostic genicular nerve blocks to determine the predictive value for the outcome of cooled radiofrequency ablation for chronic knee pain due to osteoarthritis. *Pain Med.* 2018;19(8):1628-38.
79. LongFei X, Yan G, XiLin C, TingYao H, WenTing Z, WeiWei M, et al. Application of acupotomy in a knee osteoarthritis model in rabbit. *J Vis Exp.* 2023;(200).
80. Burckett-St Laurant D, Peng P, Girón Arango L, Niazi AU, Chan VW, et al. The nerves of the adductor canal and the innervation of the knee: an anatomic study. *Reg Anesth Pain Med.* 2016;41(3):321-7.
81. Ishihara S, Obeidat AM, Wokosin DL, Ren D, Miller RJ, Malfait AM. The role of intra-articular neuronal CCR2 receptors in knee joint pain associated with experimental osteoarthritis in mice. *Arthritis Res Ther.* 2021;23(1):103.
82. O'Connor BL, Brandt KD. Neurogenic factors in the etiopathogenesis of osteoarthritis. *Rheum Dis Clin North Am.* 1993;19(3):581-605.
83. Henry M, Baudry S. Age-related changes in leg proprioception: implications for postural control. *J Neurophysiol.* 2019;122(2):525-38.
84. Johansson H, Sjölander P, Sojka P. Receptors in the knee joint ligaments and their role in the biomechanics of the joint. *Crit Rev Biomed Eng.* 1991;18(5):341-68.
85. Mayer WP, Murray AJ, Brenner-Morton S, Jessell TM, Tourtellotte WG, Akay T. Role of muscle spindle feedback in regulating muscle activity strength during walking at different speed in mice. *J Neurophysiol.* 2018;120(5):2484-97.

Journal of Orthopaedic Science and Research



Publish your work in this journal

Journal of Orthopaedic Science and Research is an international, peer-reviewed, open access journal publishing original research, reports, editorials, reviews and commentaries. All aspects of orthopaedic health maintenance, preventative measures and disease treatment interventions are addressed within the journal. Orthopaedicians and other researchers are invited to submit their work in the journal. The manuscript submission system is online and journal follows a fair peer-review practices.

Submit your manuscript here: <https://athnaeumpub.com/submit-manuscript/>