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Pain in osteoarthritis: Driven by intrinsic rather than extrinsic joint afferents and why this should impact treatment

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ABSTRACT

Pain in osteoarthritis (OA) results from erosion of joint cartilage, resulting in bone contacting bone without an intervening cushion. The periosteum, including its nociceptive innervation, ends at the border of the cartilage. No other innervated tissue is present between the denuded articular bone ends that could serve as a neuronal pathway to carry a bone-on-bone pain signal to the brain. The pain signaling pathway must therefore originate in afferent axons with electrogenic nociceptive sensory endings that reside within the bone itself, specifically in the opposing surfaces of epiphyseal subchondral bone. Selective ablation of this intrinsic nerve pathway, using any of a variety of approaches, is expected to permanently eliminate OA pain.

1. Introduction

Pain associated with pathology in bones and joints is among the top few causes of disability in all of medicine, and has been for decades. Mainly affecting people later in life, it is likely that this scourge will only continue to increase as the population ages. This paper highlights some facts about how the pain system works that account, at least partially, for the current less-than-satisfactory state of management of arthritic pain, particularly in knee and finger joints, and to suggest practical things that might be tried, in the short term, to improve matters.

2. Intrinsic *versus* extrinsic joint afferents

Typically, conclusions about the causes of pain in osteoarthritis (OA) revolve around abnormalities visible in CT and MRI imaging: eroded (hyaline) cartilage and modic changes in bone marrow for example, and reactive changes such as inflammation in synovial soft tissues and periosteum. For lack of better options, however, we have come grudgingly to accept the tenuous correlation between the images and the pain. The degree of pathology only dimly matches the level of pain reported by the patient [1] We are also forced to live with the less-than-optimal pain relief delivered by interventions that focus on cartilage repair or replacement, and by anti-inflammatory drugs. An explanation of this mismatch is straightforward. Simply put, pain felt in bones, like pain felt in all innervated structures, is due to electrical signals that are generated in endings of nociceptive axons that innervate the bone, not by osteocytes or other cell types present in bone. The sensory signal is then transmitted from the sensory endings centrally along peripheral nerves and into the spinal cord in the form of trains of electrical impulses. From there the signal is delivered to a conscious brain.

Pathology seen on imaging shows changes in osseous structures. However, these do not directly reflect the processes responsible for the generation of impulses in nerve endings (electrogenesis) and their propagation along nerve fibers to the central nervous system (CNS). If CT or MRI were able to show the molecules responsible for neuronal hyperexcitability and pain, primarily voltage-gated Na^+ channels [2,3], it would probably be trivial to sort images of joint pathology into cases with and without pain. Today's imaging technologies, unfortunately, are blind to these key pain-signaling molecules. Differences in nociceptive activity among individual patients are invisible. The technology needed to see these things still lies in the future.

There is, however, a proxy available today for "seeing" pain-provoking neural activity: micro-neurographic recording [4,5]. Unfortunately, this accessible technology has not yet gained much traction in orthopedics, or in interventional pain medicine. Even diagnostic nerve blocks are less routine than they ought to be. In practice, pain in OA is simply assumed to be driven by sensitized nociceptors in soft tissues of the joint including synovium and periosteum, and from the grinding of bone-on-bone during weight-bearing and movement, following loss of the normal cartilaginous padding. But there is a problem here. There is no doubt that soft tissues of the joint have nociceptive innervation that can drive pain. Correspondingly, there is no doubt that introducing a local anesthetic into the synovial space will transiently relieve the resulting pain. But cartilage, intact or damaged, is ***not*** itself innervated and the periosteum, which ***is*** innervated, does not extend over the surface of cartilage where its residue in OA might detect forces applied by bone grinding on bone. Nor is periosteum present under the cartilage, i.e. between the cartilage and the underlying subchondral bone, where it might otherwise be exposed in OA and serve as a pain sensor following cartilage erosion (Fig. 1A). Why, then, is bone-on-bone painful at all? What nerve fibers are present at the bone ends that could deliver a bone-on-bone pain signal to the CNS? And why does intra-synovial block

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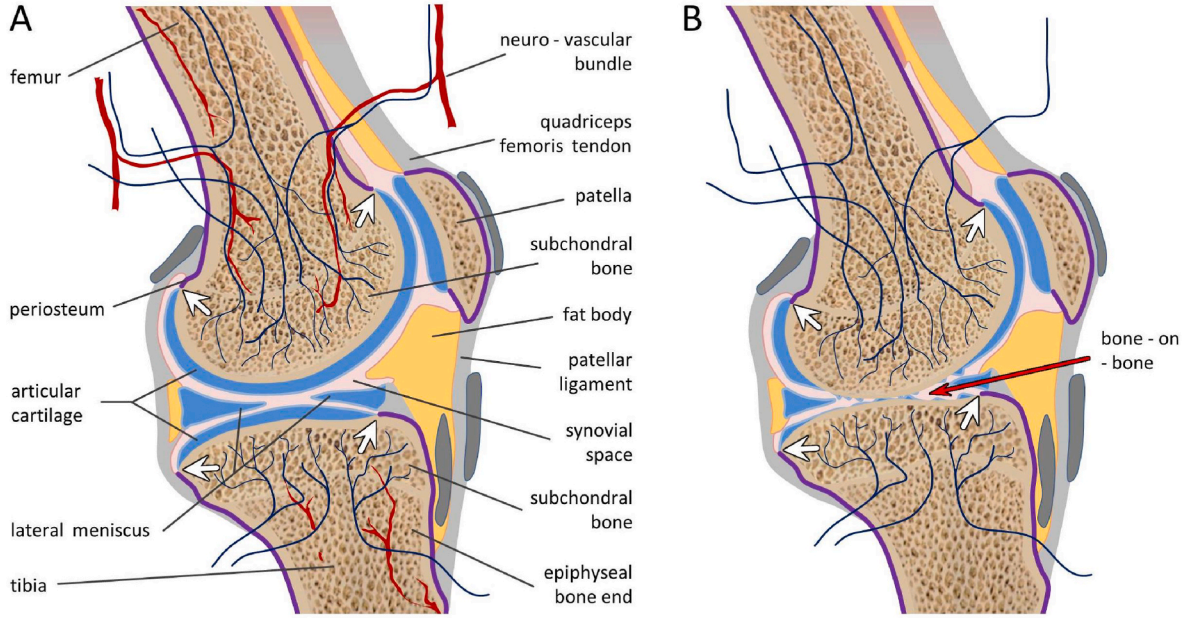

Fig. 1. ***Intrinsic*** innervation of the epiphyseal ends of the femur and tibia at the knee. **A)** Sketch of an intact knee joint illustrating the penetration of neurovascular bundles through foramina in the bone and the termination of afferent nociceptive axons within the marrow chamber, particularly within the subchondral bone. Note that the periosteum (heavy purple line) ends at the lateral edges on the articular cartilage (white arrows). **B)** Identical knee joint, but with erosion of the cartilage of the femoral and the tibial bone ends. The subchondral bone of both femur and tibial are now in direct contact, "bone-on-bone", applying mechanical forces of weight-bearing and movement directly to the nociceptive sensory endings that fill the subchondral bone. The innervation pattern was added to original drawings in the: Atlas of Human Anatomy. Netter Frank H, CIBA-GEIGY Corporation, Ardsley, USA, 1989; Printed in Basil, Switzerland, 1991. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(transiently) relieve OA pain?

The proposed answer to these questions is that subchondral bone is itself innervated. Pain signals are generated by sensory nerve endings ***intrinsic*** to the subchondral bone. The relevant nociceptive nerve fibers enter the bone marrow through penetrating neurovascular foramina, mostly located at the bone end, and terminate within Haversian canals in epiphyseal subchondral bone. These ***intrinsic*** nerve fibers are distinct from the ***extrinsic*** nociceptive nerve fibers that serve soft tissues and periosteum of the joint [6–9] (Fig. 1A). Like virtually all sensory nerve fibers, the cell bodies of these ***intrinsic*** bone nociceptors reside in a para-spinal dorsal root ganglion (DRG). From the DRG intrinsic bone afferents travel in peripheral nerves to their site of termination within the bone. For hard tissues of the spine, they enter dorsal ramus branches which serve both ***extrinsic*** (periosteal) and ***intrinsic*** (basivertebral) nerve fiber elements of the vertebrae, with a similar pattern of innervation serving intervertebral disks. For the limbs, axons of DRG neurons enter the ventral ramus whose main branches to the leg, the sciatic and femoral nerves, carry sensory signals from all innervated hindlimb tissues into the spinal cord and brain. These large nerve trunks progressively split into large collateral branches including the tibial and common peroneal nerves, which in turn split into still smaller nerves, such as the named articular nerves (some alternatively referred to as genicular nerves) that serve the knee. These nerves, in turn, split into still finer nerve fascicles, which in general are not individually named, which finally split into still finer terminal branches that end in sensory transducer terminals in the various component tissues of the knee. These delicate terminal branches provide the innervation of both ***extrinsic*** and ***intrinsic*** targets, extrinsic synovial tissues and periosteum as well as intrinsic structures in the bone marrow, the cortical bone and the subchondral bone itself. The finer the nerve bundle, the more likely its exact path and contents will differ from individual to individual [8,10,11].

The ***intrinsic*** sensory nerve fiber bundles, generally unnamed, enter the bone marrow along neurovascular bundles. These contain sensory afferents, sympathetic "nutritive" efferents and blood vessels. They gain access to the bone interior by passing through numerous small penetrating foramina located along the bone shaft, but mostly near the epiphyseal bone-end [12]. The afferent fibers that enter the marrow chamber along neurovascular bundles are mostly small diameter unmyelinated and lightly myelinated fibers (Aδ and C-fibers) that express peptide markers such as substance P and CGRP suggesting that most, at least, are nociceptors. These are enriched at the epiphyseal bone ends [6–8].

The sensory endings of nociceptive afferent axons are "electrogenic". This means that they are specialized for generating action potentials capable of propagating centrally along the axon, past the DRG and into the CNS. These ***intrinsic*** nociceptive nerve fiber endings are presumed also to mediate pain associated with intrinsic tumors including multiple myeloma, intraosseous inflammation and, together with ***extrinsic*** periosteal fibers, bone fractures. A large fraction of the ***intrinsic*** nociceptive axons innervate the subchondral bone from the inside (Fig. 1a). Their normal role is presumably to detect dangerously strong impacts on the knee joint. This anatomical layout alone should leave little doubt that in the absence of cartilage, bone-on-bone pain during weight bearing and movement will activate ***intrinsic*** nociceptive subchondral nerve endings, causing knee pain. The only other innervated structures in the vicinity are the laterally placed menisci (Fig. 1B) and perhaps surviving fragments of other synovial soft tissues that somehow became caught between the bare bone ends and still contained ***extrinsic*** nociceptive axons. If OA pain were indeed due to such residual tissue scraps rather than to normal ***intrinsic*** nociceptive endings in subchondral bone, the pain could be resolved easily in routine arthroscopy.

Sensory endings ***intrinsic*** to bone ends might be sensitized by the mild inflammation often present in OA, but unlike rheumatoid arthritis and spondyloarthropathies inflammation is probably not essential [1]. The mechanical forces associated with standing and walking in the absence of cartilaginous padding, or of bending finger joints, is enough to activate healthy, non-sensitized nociceptors. The reason that intra-synovial local anesthetic block provides transient pain relief is that the fluids in the synovial space have ready access to subchondral bone nociceptor endings, rendered accessible by fragmentation of the

cartilage (Fig. 1B). Because of this, longer-term pain relief can be achieved in OA by substituting lidocaine for a neurotoxin such as capsaicin which causes axons to dye back from the subchondral bone into the nerve trunk in the marrow chamber. In time, however, such axons regenerate. Regeneration leads to re-innervation of the subchondral bone and return of pain [13,14].

3. Why it matters that OA pain is subserved by *intrinsic* bone afferents

Identification of the nociceptive fiber endings responsible for OA pain as ***intrinsic*** to subchondral bone of the joint may explain the greater clinical success of hip arthroplasty compared to knee arthroplasty. In the hip, both articular surfaces are removed and replaced with metal, plastic, or ceramic; the femoral head by a ball and the ischial acetabulum by a socket. Innervated subchondral bone is distanced from both articular surfaces. In knee arthroplasty, in contrast, the subchondral bone of femur and tibia are trimmed, but not completely removed, and appliances are fastened to the still-innervated subchondral bone using pins and screws. In successful cases mechanical forces generated during weight-bearing and walking are distributed across the bone interface with minimal movement and hence there is only minor activation of residual nociceptive ***intrinsic*** bone afferents. In less successful cases, presumably individuals with softer bone or with an unfortunate distribution of the screws or of intrinsic nerve bundles, forces generated by use of the joint are likely transmitted in greater amount to nerve endings in the subchondral bone, causing persistent pain.

Consider an analogy taken from a distant medical discipline, but a useful avatar of OA in many ways. I refer to the structure and innervation of teeth. Cartilage at the articular surfaces of joints is analogous to the enamel at the occlusive surfaces of teeth; they interface tooth-on-tooth and neither is innervated. Beneath is subchondral bone, analogous to dentine. Both are innervated by thin peptidergic nociceptive afferent axons that end within fine boney canals only tens of microns from the interface with cartilage (bone) and enamel (teeth). Finally, underneath the bone is the bone marrow, filled with blood vessels and ***intrinsic*** nerve fibers some sensory and some sympathetic, analogous to the tooth pulp. External to the boney joint itself is synovial soft tissue and periosteum. This is analogous to gingiva at the base of teeth. Both are served by ***extrinsic*** nociceptive nerve fibers and become sources of pain in (rheumatoid) arthritis and gingivitis, respectively (Fig. 2). Joints, of course, differ from teeth in many ways. But the analogy is helpful, especially as the causes of tooth pain are better understood than those of bone pain, and the treatment of dental pain is more reliable and successful than that of joint pain.

What happens when the overlying non-innervated layer, tooth enamel or articular cartilage, erodes? Dentine exposed when enamel is eroded by wear or dental caries renders teeth exceedingly sensitive to even very weak stimulation. Light touch, air-puff or thermal stimuli evoke intense pain. This is due to nociceptor endings within the dentinal tubules, and perhaps also sensory endings of “algoneurons” that end in the dentine. Algoneurons are non-peptidergic sensory neurons with myelinated axons that respond to weak, non-noxious stimuli (low threshold mechanoreceptor (LTM) endings), but that signal pain to a conscious brain [15,16]. The proposal here is that exposure of nerve fibers in the subchondral bone to biomechanical forces is the primary cause of knee pain in OA. Algoneurons have been identified in teeth, and are likely to be present also in bones and/or joints. But even if not, the mechanical forces present when bone grinds on bone are strong enough to drive normal, healthy nociceptor endings. In teeth, non-inflamed dentine is highly sensitive. Dentists often remove enamel from healthy teeth, for example in the process of anchoring bridgework. The freshly exposed dentine is highly tender. To be sure, when inflammation is present it can augment pain. But as noted, this factor is more important in gingivitis than dental caries (in teeth) and in rheumatoid arthritis than OA (in joints).

Pursuing the tooth-joint analogy, a likely way to obtain better and more prolonged relief from pain in osteoarthritic joints is to do what the dentists do; permanently ablate the ***intrinsic*** innervation of the hard tissue and fill the void with a material like amalgam to prevent reinnervation. This is root canal treatment. A practical approach to doing the same thing in OA was proposed 20 years ago [17]. The idea, which

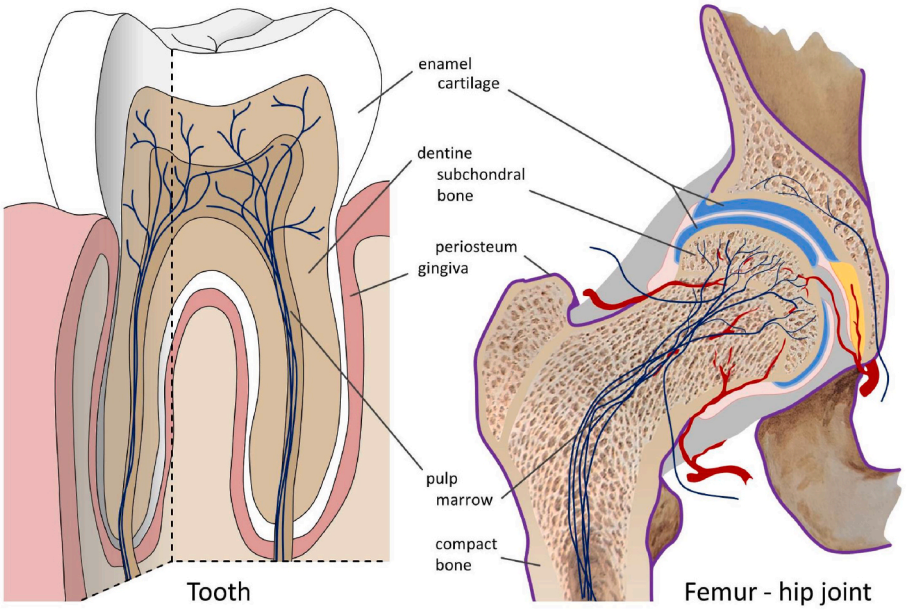

Fig. 2. The structural analogy between teeth and joints provides useful insights into the likely causes of pain in OA and other degenerative bone and joint conditions, and potential therapeutic avenues. As illustrated in this schematic, tooth enamel is analogous to articular cartilage (neither is innervated), dentine is analogous to subchondral bone, the tooth pulp is analogous to bone marrow and the gingiva is analogous to the periosteum and synovial soft tissues of the joint. “Marrow canal treatment” of the joint, the equivalent of dental root canal treatment, ought to provide effective relief from pain of weight-bearing and movement in patients with osteoarthritis. The innervation pattern was added to original drawings in the: Atlas of Human Anatomy. Netter Frank H, CIBA-GEIGY Corporation, Ardsley, USA, 1989; Printed in Basil, Switzerland, 1991.

might be called "marrow canal" treatment, was to denervate the subchondral bone and prevent its reinnervation using a bone cement such as polymethyl methacrylate (PMMA). PMMA would be injected transversely into the epiphyseal bone end(s), or perhaps via the synovial capsule, in liquid form at room temperature. As it sets an exothermic reaction generates sufficient heat (near 95 °C) to cauterize nearby nerve fibers and blood vessels. When it cools a permanent bone-hard barrier is established to prevent subchondral bone reinnervation (Fig. 3D). Prior nerve block or regional anesthesia should permit the procedure itself to be painless. In the presence of osteoporosis, common in OA patients, there should be no need for the specialized introducer needles used for vertebroplasty, or bone marrow aspiration [18]. For OA of the hip, an initial trial targeting the femoral epiphysis might provide sufficient pain relief to obviate the need for surgical hip replacement. If not, the presence of bone cement would not undermine subsequent hip replacement. For OA of the knee or digits both apposed bone ends would presumably need to be treated.

PMMA and related bone cements are biocompatible and cause minimal necrosis of adjacent compact bone. More important still, lesioning ***intrinsic*** bone innervation is very unlikely to induce the formation of painful neuromas that in other locations cause ongoing pain. These things are known, for example, from total hip replacement where insertion of a titanium prosthesis into the femoral bone canal, often anchored by bone cement, has been standard practice for decades. Neither bone necrosis nor spontaneous neuroma pain are common adverse events. Intraosseous neuromas may still be mechanosensitive, but within the bone there should be no transient mechanical events that could evoke a Tinel sign. In dental root-canal treatment as well, painful neuromas are a very rare complication. The reasons for this are uncertain and deserve investigation [3,19].

Extravasation of PMMA out of the epiphyseal bone-end is a significant risk in vertebroplasty and other vertebral augmentation procedures, where it can impact nearby spinal nerves and roots and cause significant neurological damage. Extravasation is unlikely to occur in marrow canal treatment, however, as the surrounding bone is compact, capable of weight-bearing, and not fractured or severely porotic. And if it did occur the only innervation nearby is small fascicles of genicular nerves. Hardened cement caused by local extravasation would be easily removable through a small incision. One potential concern if the procedure failed is the presence of hardened cement in the epiphyseal bone end. This might complicate subsequent execution of routine knee arthroplasty. With this in mind, initial trials might be carried out in

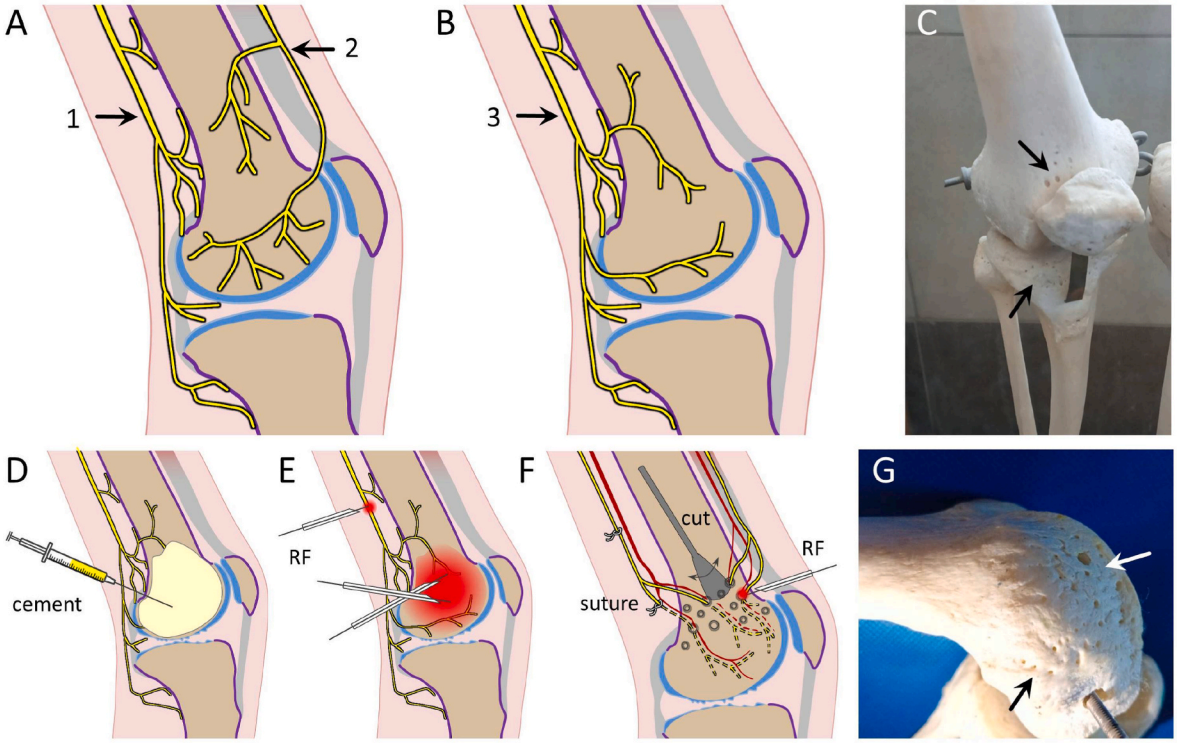

Fig. 3. Alternative patterns of ***intrinsic*** *and* ***extrinsic*** innervation of the epiphyseal ends of the femur at the knee. The same pattern is repeated in the tibia. **A)** Individual collateral branches of larger (named) genicular/articular nerves may carry nociceptive axon branches that exclusively terminate ***extrinsically,*** innervating the periosteum, synovium and other soft external tissues of the knee joint (arrow 1). A second possibility (unlikely) is entry into the bone marrow as part of a neurovascular bundle(s) with exclusive innervation of ***intrinsic*** bone structures, most notably the subchondral bone (arrow 2). **B)** Alternatively, and most likely, individual collateral branches of larger (named) genicular/articular nerves may innervate structures both extrinsic and intrinsic to the knee joint (arrow 3). In each case, yellow lines represent possible branching patterns of articular nerve bundles, or of small near-terminal axon fascicles. Determining the actual pattern of innervation for each named genicular/articular nerve, and the degree of variation present across individuals, will require dedicated anatomical investigation. **C)** Arrows indicate the location of perforating foramina of the femoral (upper) and tibial (lower) bone ends in a human skeletal preparation. **G)** Same, in a second human skeleton. The knee has been flexed to better visualize the numerous penetrating foramina on the femoral bone end. Neurovascular bundles carrying nociceptive afferent nerve fibers pass through these foramina, gaining entry to the bone marrow and innervating subjacent subchondral bone from the inside. **D,E,F)** In principle, it should be possible to selectively ablate the ***intrinsic*** innervation of the subchondral bone of the epiphyseal end of the femur and/or tibia, sparing the ***extrinsic*** innervation that serves soft synovial tissues and the periosteum. Alternative approaches include intra-epiphyseal injection of bone cement **(D)**, cauterization with an RF electrode just external to the neurovascular foramen, or within the epiphysis **(E)**, or ablating neurovascular bundles as they are about to penetrate the bone end by scraping/cutting using a spatula (potentially heated), or by cauterizing penetrators one at a time using an RF electrode. It might even be possible to ligate or otherwise ablate individual axon bundles just proximal to the foramen, sparing the accompanying blood vessel **(F)**. Several additional, non-invasive approaches are noted in the text. RF = radiofrequency ablation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

patients who are not candidates for open knee surgery. Or the problem might be bypassed entirely using one of numerous other possible means of denervating the epiphyseal bone end from within. As noted above, substitution of bone cement with a neurolytic agent is likely to produce transient pain relief because of nerve regeneration. However, one might cauterize using multiple probes with an RF electrode ([20,21]; Fig. 3E). Subchondral bone denervation might even be carried out non-invasively using radiological tomography or focused ultrasound (FUS, [22,23]).

In early clinical trials of marrow canal treatment one might begin with a diagnostic block. Indeed, injection of a local anesthetic into the joint capsule is a common tool for predicting efficacy. However, the usual interpretation of the outcome, and the follow-up procedures of arthroplasty or genicular nerve ablation, do not capitalize on the insight that the effect of intra-synovial block is primarily on the ***intrinsic*** innervation of the subchondral bone, exposed by cartilage erosion. An alternative diagnostic, capable of providing this distinction, is intra-epiphyseal block. Specifically, immediately following local anesthetic injection into the bone end the patient would be encouraged to use the joint in a way that normally evokes his/her typical pain, and as time passes, report on changes as the anesthetic effect fades. Washout of the local anesthetic might be slowed with the addition of adrenalin, and a trial with the same anesthetic delivered systemically would rule out mistaking systemic analgesia for local joint block. Intra-epiphyseal block of this sort is not routine in OA of the knee. However, it is used elsewhere. Quoting an authority in the field, "I can confirm that intraosseous injection of bupivacaine provides at least 2 hours of pain relief when injected in the hip epiphysis" (Prof. Phillippe Hernigou, Hôpital Henri Mondor, Creteil, France, with permission).

The author is not aware of the intervention proposed ever having been tried in OA patients, even in a diagnostic mode as a poof-of-principle. This is despite its having been put forward in a leading pain journal two decades ago [17]. Unfortunately, translation from animals to humans in the pain arena has tended to be iffy across the board with only occasional insights emerging about joint pain. Perhaps this is because the contingencies of weight-bearing in rodents differ so markedly from clinical OA [24,25]. However, beyond the fundamental logic of blocking intrinsic bone innervation (Fig. 1) the promise of long-lasting pain relief in OA might be evaluated on the basis of a related procedure: intraosseous injection of bone cement in the treatment of bone pain caused by malignancies. The primary aims of this procedure are structural, reducing the likelihood of fractures and reducing the volume of the tumor. However, substantial pain relief is frequently reported as a positive side-effect, including pain relief at rest and during movement. This is likely due to incidental cautery of intrinsic bone innervation and not just increased bone stability [26,27].

4. Relation to genicular nerve section in the treatment of OA

A relatively recent randomized controlled trial published by Choi and co-workers reported moderate success in relieving pain in OA by RF cauterization of three named genicular nerves: the superior lateral (SL), the superior medial (SM) and the inferior medial (IM) nerves [28]. This minimally invasive procedure was rapidly adopted in the belief that it is a simple, painless and comparatively successful approach to the relief of OA of the knee. This initial belief has been undermined, to an extent, by technical critiques and additional placebo controlled research [29–33]. Early conclusions may have reflected an undue degree of wishful thinking by patient and physician. Be that as it may, in light of the hypothesis laid out here it is worth considering the mechanism whereby at least partial pain relief is achieved by destroying genicular/articular nerves.

The genicular nerves targeted by Choi et al. undoubtedly provide innervation, including nociceptive innervation, to the soft tissues of the knee, including the periosteum. Partial destruction of this ***extrinsic*** nociceptive innervation is presumed to be the basis for the pain relief reported. However, as noted above, ***intrinsic*** innervation of the bone end is also provided by these same genicular/articular nerves and their fine (unnamed) collateral branches (Fig. 1). Is it lesioning of the ***extrinsic*** or the ***intrinsic*** innervation of the knee that provides the pain relief obtained by RF cauterization of the SL, SM and IM nerves? The answer to this question depends on whether: 1) These three named genicular nerves contain axons that serve ***extrinsic*** tissues exclusively, particularly synovium and periosteum, 2) whether they serve ***intrinsic*** subchondral bone innervation exclusively (*a priori* very unlikely), or 3) whether these nerves mostly serve ***extrinsic*** targets, but that small unnamed fascicles of one or all of them branch off the main nerve trunk and enter the bone marrow along penetrating neurovascular bundles to innervate ***intrinsic*** targets, particularly subchondral bone (Fig. 3 A,B arrows 1,2 and 3 respectively). The answer matters. If Cohen et al.'s [32] suggestion that lesioning SL, SM and IM is not enough, their proposal to ablate additional nerves is indeed likely to yield better pain relief as it will more effectively denervate subchondral bone. However, loss of much of the knee's ***extrinsic*** innervation along with the ***intrinsic*** might risk joint instability, painful genicular/articular nerve-end neuromas, and if too much, perhaps even a Charcot joint.

Information is not available on whether the genicular nerve ablations using Choi et al.'s procedure do in fact carry a substantial number of ***intrinsic*** bone afferent fibers. Indeed, reviews of knee innervation tend not to mention intrinsic bone innervation at all. However, as the lesions are made at some distance from where neurovascular bundles enter the bone marrow (Fig. 3, C,G; [12]), efficacy of the genicular nerve procedure as currently executed is probably due to ablation of those ***intrinsic*** afferent axons that split off of the main genicular nerve distal to the RF lesion site. With ablation of only three genicular nerves, and ones not selected on the basis of their ***extrinsic*** vs. ***intrinsic*** axonal content, subchondral bone denervation would surely be partial at best, with many healthy nerve fibers that do not contribute to the patient's pain being cut unnecessarily. This factor probably also accounts for the variable efficacy across patients. Although the details are apparently not available, there is expected to be a great deal of variability in the specific branching pattern of the fine pre-terminal penetrant fascicles from individual to individual, and in the distribution of these fascicles in relation to the exact site(s) of cartilage erosion.

The anatomical question concerning which of the named genicular/articular nerves preferentially innervate subchondral bone should be straightforward to resolve by careful dissection in the cadaver lab. But as a first step, a strong hint is obtained by simply observing the location of the osseous foramina through which neurovascular bundles penetrate into the femur and tibia on their way to the subchondral bone. As shown in Fig. 3C,G the large bulk of these foramina are located at the epiphyseal bone end, directly adjacent to the target subchondral bone [12]. If these penetrators indeed carry the bulk of ***intrinsic*** nociceptor innervation responsible for OA pain one should aim to ablate them selectively, sparing as much as possible of the knee's ***extrinsic*** innervation. There are several ways of doing this. One approach, discussed above, is to access them from within the epiphyseal bone end (Fig. 3D and E). This spares ***extrinsic*** innervation entirely, but requires accessing the interior of the bone. A second approach is to place RF lesions distally, close to the point of exit of penetrating fascicles from the larger genicular nerve trunks (Fig. 3E). A third potential approach, which would spare ***extrinsic*** innervation entirely, is to access these fascicles at the point where they enter the osseous foramina, just proximal to the articular cartilage. This might be done by scraping with a spatula (presupposing adequate hemostasis), using RF to cauterize each penetrator individually, or a heated spatula capable of cauterizing neurovascular bundles with a sweep. A similar effect might be obtained by "painting" the region with PMMA or a biocompatible epoxy. Finally, in the unlikely event that even fractional loss of blood supply to the epiphysis is problematic, with care it might be possible to ligate, cauterize or otherwise ablate penetrating nerve fascicles in a way that spares accompanying nutritive vessels (Fig. 3F).

5. OA symptoms beyond arthritic pain

Pain relief by root canal treatment solves the dental patient's acute pain problem, but a crown still needs to be fitted to the tooth stump to restore the tooth's masticatory function. The marrow canal treatment proposed here is expected to relieve OA pain, but not the secondary symptoms of joint stiffness, loss of flexibility and limited range of motion, except to the extent that pain contributes to these symptoms. A reasonable concern is that in the absence of pain, increased use of the joint might accelerate degenerative processes. On the other hand, there is also reason to believe that if anything, it is best to encourage physical activity in OA patients [34]. In practice, as OA patients tend to be elderly, marrow canal treatment of hip, knee and/or digital joints might well provide an effective lifelong solution. Accumulating clinical experience will tell the tale. In individuals in whom pain relief did lead to accelerated functional disability, salvage options remain available.

6. Conclusions

In dental practice, pain arising from ***intrinsic*** innervation of the dentine, toothache, is very different from pain arising from ***extrinsic*** innervation of inflamed gingiva. By analogy, pain due to the ***intrinsic*** innervation of subchondral bone needs to be distinguished from pain felt in the external soft tissue of the joint, articular synovium and periosteum. The symptoms due primarily to ***extrinsic*** joint innervation are more typical of trauma and of rheumatoid (inflammatory) arthritis than of OA (degenerative arthritis). More in-depth consideration of the underlying neural substrates of these different painful conditions may point to improved therapeutic options. Dentists are angels of pain relief. The patient who enters a dental clinic with a mind-gouging toothache is almost certain to leave within an hour with the problem solved, the pain gone, forever, with little likelihood of return. OA pain might be treated similarly, and hopefully with equal success, if more thought were given to nerves and the nociceptive innervation of the relevant tissues. This is the proposal on the table [3,17]. For good reasons a mature discipline like orthopedics might not be fully open to new, untested ideas that come from elsewhere, pain science and dentistry in this case, although perhaps this is less so for pain interventionalists. Sometimes, however, cross-fertilization yields tasty new fruit.

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Declaration of competing interest

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References

[1] Dainese P, Wyngaert KV, De Mits S, Wittoek R, Van Ginckel A, Calders P. Association between knee inflammation and knee pain in patients with knee osteoarthritis: a systematic review. Osteoarthritis Cartilage 2022;30(4):516–34.
[2] Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal and pathological pain. Annu Rev Neurosci 2010;33:325–47.
[3] Devor M. Neuropathic pain: pathophysiological response of nerves to injury. Chapter 61. In: McMahon SL, Koltzenburg M, Tracey I, Turk DC, editors. Wall and Melzack's Textbook of Pain. 6 ed. London: Churchill Livingstone; 2013. p. 861–88.
[4] Serra J. Microneurography: towards a biomarker of spontaneous pain. Pain 2012;153(10):1989–90.
[5] Serra J, Collado A, Sola R, Antonelli F, Torres X, Salgueiro M, et al. Hyperexcitable C nociceptors in fibromyalgia. Ann Neurol 2014;75(2):196–208.
[6] Mantyh PW. The neurobiology of skeletal pain. Eur J Neurosci 2014;39(3):508–19.
[7] Steverink JG, Oostinga D, van Tol FR, van Rijen MHP, Mackaaij C, Verlinde-Schellekens S, et al. Sensory innervation of human bone: an immunohistochemical study to further understand bone pain. J Pain 2021;22(11):1385–95.
[8] Brazill JM, Beeve AT, Craft CS, Ivanusic JJ, Scheller EL. Nerves in bone: evolving concepts in pain and anabolism. J Bone Miner Res 2019;34(8):1393–406.
[9] Felson DT. The sources of pain in knee osteoarthritis. Curr Opin Rheumatol 2005;17(5):624–8.
[10] Horner G, Dellon AL. Innervation of the human knee joint and implications for surgery. Clin Orthop Relat Res 1994;(301):221–6.
[11] Tran J, Peng PWH, Gofeld M, Chan V, Agur AMR. Anatomical study of the innervation of posterior knee joint capsule: implication for image-guided intervention. Reg Anesth Pain Med 2019;44(2):234–8.
[12] Yamamoto H, Jones Jr DB, Moran SL, Bishop AT, Shin AY. The arterial anatomy of the medial femoral condyle and its clinical implications. J Hand Surg Eur 2010;35(7):569–74.
[13] Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth 2011;107(4):490–502.
[14] Stevens RM, Ervin J, Nezzer J, Nieves Y, Guedes K, Burges R, et al. Randomized, double-blind, placebo-controlled trial of intraarticular trans-capsaicin for pain associated with osteoarthritis of the knee. Arthritis Rheumatol 2019;71(9):1524–33.
[15] Fried K, Sessle BJ, Devor M. The paradox of pain from tooth pulp: low-threshold "algoneurons"? Pain 2012;152(12):2685–9.
[16] Byers MHMA, Narhi MVO. Dental innervation and its responses to tooth injury. In: Hargreaves KM, Goodis HE, Tay FR, editors. Seltzer and Bender's dental pulp. second ed. Quintessence Books; 2012.
[17] Niv D, Gofeld M, Devor M. Causes of pain in degenerative bone and joint disease: a lesson from vertebroplasty. Pain 2003;105(3):387–92.
[18] Brozovich AA, Incavo SJ, Lambert BS, Sullivan TC, Wininger AE, Clyburn TA, et al. Intraosseous morphine decreases postoperative pain and pain medication use in total knee arthroplasty: a double-blind, randomized controlled trial. J Arthroplasty 2022;37(6S):S139–46.
[19] Tal M, Minert A, Devor M. Resurgent neuropathic discharge: an obstacle to the therapeutic use of neuroma resection? Pain 2023;164(2):349–61.
[20] Mekhail N, Eldabe S, Templeton E, Costandi S, Rosenquist R. Pain management interventions for the treatment of chronic low back pain: a systematic review and meta-analysis. Clin J Pain 2023;39(7):349–64.
[21] Zhao J. Arthroscopic arthroplasty for knee osteoarthritis: denervation of subchondral bone and comprehensive synovectomy. Arthrosc Tech 2021;10(12):e2651–7.
[22] Ozhinsky E, Han M, Bucknor M, Krug R, Rieke V. T2-based temperature monitoring in bone marrow for MR-guided focused ultrasound. J Ther Ultrasound 2016;4:26.
[23] Zhang W, Trivedi H, Adams M, Losey AD, Diederich CJ, Ozhinsky E, et al. Anatomic thermochromic tissue-mimicking phantom of the lumbar spine for preclinical evaluation of MR-guided focused ultrasound (MRgFUS) ablation of the facet joint. Int J Hyperther 2021;38(1):130–5.
[24] 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.
[25] Rice AS, Cimino-Brown D, Eisenach JC, Kontinen VK, Lacroix-Fralish ML, Machin I, et al. Animal models and the prediction of efficacy in clinical trials of analgesic drugs: a critical appraisal and call for uniform reporting standards. Pain 2008;139(2):243–7.
[26] Plancarte R, Guajardo J, Meneses-Garcia A, Hernandez-Porras C, Chejne-Gomez F, Medina-Santillan R, et al. Clinical benefits of femoroplasty: a nonsurgical alternative for the management of femoral metastases. Pain Physician 2014;17(3):227–34.
[27] Dehdashti AR, Martin JB, Jean B, Rufenacht DA. PMMA cementoplasty in symptomatic metastatic lesions of the S1 vertebral body. Cardiovasc Intervent Radiol 2000;23(3):235–7.
[28] Choi WJ, Hwang SJ, Song JG, Leem JG, Kang YU, Park PH, et al. Radiofrequency treatment relieves chronic knee osteoarthritis pain: a double-blind randomized controlled trial. Pain 2011;152(3):481–7.
[29] Iannaccone F, Dixon S, Kaufman A. A review of long-term pain relief after genicular nerve radiofrequency ablation in chronic knee osteoarthritis. Pain Physician 2017;20(3):E437–44.
[30] Abd-Elsayed A, Strand N, Gritsenko K, Martens J, Chakravarthy K, Sayed D, et al. Radiofrequency ablation for the knee joint: a survey by the American Society of Pain and Neuroscience. J Pain Res 2022;15:1247–55.
[31] Malaithong W, Tontisirin N, Seangrung R, Wongsak S, Cohen SP. Bipolar radiofrequency ablation of the superomedial (SM), superolateral (SL) and inferomedial (IM) genicular nerves for chronic osteoarthritis knee pain: a randomized double-blind placebo-controlled trial with 12-month follow-up. Reg Anesth Pain Med 2022;48(4):151–60.
[32] Cohen SP, Mishra P, Wallace M, Sellers A, Veizi E, Hurley RW. Emperor's nakedness exposed: unmasking fairytales for genicular nerve radiofrequency ablation in knee osteoarthritis. Reg Anesth Pain Med 2023;48(5):193–5.

[33] Caragea M, Woodworth T, Curtis T, Blatt M, Cheney C, Brown T, et al. Genicular nerve radiofrequency ablation for the treatment of chronic knee joint pain: a real-world cohort study with evaluation of prognostic factors. Pain Med 2023;24(12):1332–40.
[34] Coaccioli S, Sarzi-Puttini P, Zis P, Rinonapoli G, Varrassi G. Osteoarthritis: new insight on its pathophysiology. J Clin Med 2022;11(20).

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