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Osteoporosis Theory of Non-Contact Anterior Cruciate Ligament Injury and Delayed Onset Muscle Pain

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Abstract

Osteoporosis is a condition with a mostly unidentified pathomechanism that is frequently referred to be a "silent thief" because it typically only manifests when fractures happen. This suggests that pathological harm takes place before pain is felt. Therefore, in a quad-phasic non-contact injury pathway, aging may eventually lead to the metabolic imbalance of primary osteoporosis. It is also emphasized that delayed onset muscle pain, non-contact anterior cruciate injury, and osteoporosis may all have the same initiating proprioceptive non-contact *Piezo2* channelopathy at different sites, but with different environmental risk factors and a different genetic predisposition, leading to different longitudinal outcomes.

Keywords: Osteoporosis • Delayed onset muscle soreness • Non-contact injury • *Piezo2* ion channel • Channelopathy • Quad-phasic non-contact injury

Introduction

Osteoporosis is a condition characterized by fragility brought on by the systemic microdegeneration of bone structure. It is frequently referred to as a "silent thief" because it typically only manifests itself when a fracture occurs. The symptoms of Delayed Onset Muscle Soreness (DOMS), which also include muscle stiffness, loss of force-generating ability, decreased joint range of motion, and diminished proprioceptive function, are listed below. Approximately 3/4 of all Anterior Cruciate Ligament (ACL) injuries are Non-Contact (NC) Anterior Cruciate Ligament (NC-ACL) injuries, which happen when the ligament fibers are strained or partially torn. The full pathomechanism for any of the aforementioned illnesses is unknown. In all three cases, the pathological damage is suspected earlier than the onset of pain, suggesting varying lengths of quiet pathological periods previous to the onset of pain [1]. This study's goal is to adapt the quad-phasic non-contact injury mode to osteoporosis, where the fundamental microdamage may be the same proprioceptive terminal *Piezo2* channelopathy as in other NC injuries like DOMS or NC-ACL. In order to better understand and improve the management of osteoporosis and find even more specialized therapeutic interventions, this manuscript also aims to facilitate an interdisciplinary approach between physiology, pathology, neuroscience, endocrinology, rheumatology, orthopedics, and immunology [2].

Injury Phases

Primary non-contact injury phase: According to the acute compression axonopathy explanation of DOMS, it is a dichotomous muscular NC injury in which the Type 1a proprioceptive terminal of the Muscle Spindle (MS) experiences major micro damage.

The Cox2-PGE2 and Cox2-bradykinin Nerve Growth Factor (NGF) pathways cause the neuromodulator muscle and nearby tissue cells to undergo hyper-excitation in response to unusual or vigorous eccentric contractions. However, a cognitively-demand-induced Acute Stress Response (ASR) could become active as a driver if the performance of muscle cells is not maintained properly. However, during an ASR, the Type 1a proprioceptive sensory nerves' terminal arbors in MS could sustain a mechano-energetic micro-injury. In a dose-limiting, threshold-driven manner, the superposition of compression forces resulting from eccentric contractions may be relevant in this microdamage. Chemotherapy may have taught us that there are distinct somatosensory terminal impairment mechanisms that can develop both acutely and chronically without leading to conventional Wallerian degeneration. A silent and temporary channelopathy of the *Piezo2* ion channels is also suggested as the essential entryway to pathology [3]. It is interesting to observe that these *Piezo2* ion channel micro injuries may not cause any pain when the succeeding lengthening contractions stop abruptly soon after the channelopathy begins. In terms of the neuromodulation and hyperexcitation of the proprioceptive system, not to mention their related signaling pathways, it is significant to remember that bones and muscles form a continuum. Additionally, the suggested ASR is osteocalcin-induced and bone-derived. Another recent idea for NC-ACL injury contends that similar to DOMS, the main injury is a silent proprioceptive terminal lesion in the medial proximal tibia's periosteum. The spine also had primary afferent mechano-sensitive encapsulated endings [4]. ACL injury could only result from secondary, more severe tissue damage brought on by a proprioceptive deficit. It is notable that this new theory, which focuses on the pre-ovulatory transient luteinizing hormone-derived NGF-Tropomyosin Receptor Kinase A (TrkA) signaling pathway, may also explain the important sex variations in NC-ACL epidemiology as neurons. This signaling axis might make the sensory terminals even more susceptible to micro-injury under an ASR by facilitating unpleasant hyperexcitation. Additionally, although *Piezo2* ion channels are primarily seen on proprioceptive and tactile fibers, a sizeable fraction of A mechano-nociceptors in bone tissue also express these channels. Accordingly, current animal studies demonstrate that bone afferent sensory neurons with a high affinity for NGF are those that express *Piezo2* and TrkA together. Additionally, *Piezo2* plays a function in painful mechanical stimulation of bone afferent neurons as well as NGF-induced bone afferent sensitization to mechanical stimulation, supporting the idea that *Piezo2* is a key factor in both diseases [5].

The non-autonomous morphologic repair of micro-fractured bones or remodeling depends on the proprioceptive signaling of MSs and Golgi Tendon Organs (GTOs). Additionally, it has been proposed that the static phase firing encoding of the stretch reflex is impaired by the primary transient proprioceptive terminal *Piezo2* micro injury concurrent with microfractures and that this impairment could be corrected by the dynamic encoding of MSs and GTOs. Consequently, it is believed that proprioceptive sensory neurons play a role in both remodeling and the direction of development and regeneration.

Secondary injury phase: Due to reduced proprioception, the secondary phase of NC traumas results in harsher tissue damage in a subluxated position. During this stage, the temporal summation of pain is provided by the contribution of the C sensory fiber. If we take into account the theory that the cessation of lengthening contractions and the lack of harsher secondary tissue damage or compression fractures after the transient primary injury keep these micro-injuries and concomitant micro-cracks pain-free, the parallel that vertebral compression fractures, NC-ACL injury, DOMS, and osteoporosis may pertain to the same primary proprioceptive micro-injury in a dichotomous NC injury.

Notably, it is hypothesized that even in the absence of the secondary injury phase, the repetitive recurrence of the primary micro damage could start the tertiary injury phase. A later stage, when pain perception enters the clinical picture, is required for C-fiber involvement with severe tissue damage in the form of fractures, which is the equivalent of the secondary injury phase [6].

Tertiary injury phase: Additionally, the tertiary stage of the initial primary *Piezo2* channelopathy is suggested by the novel DOMS and NC-ACL hypotheses. It is referred to as the Repeated Bout Effect (RBE) in the case of DOMS and as osteoarthritis in the case of NC-ACL. Interestingly, NC-ACL injuries result in early aging of the knee joint, with OA developing in 4/5 of instances. Recent OA research discoveries on osteoporosis in particular are fascinating. Similar to osteoporosis, Acid-Sensing Ion Channel 3 (ASIC3) is critical for secondary hyperalgesia of joint inflammation in OA rats, but not for original hyperalgesia. In line with this, the development of secondary hyperalgesia and the degeneration process of OA are mostly dependent on the gradual elevation of ASIC3 channels found in Dorsal Root Ganglion (DRG) primary afferent neurons of knee joints. According to the present authors' hypothesis, the tertiary injury phase is analogous to repetitive or chronic *Piezo2* micro damage because it causes overexpression of ASIC3. NGF, osteoclast hyperactivity, and the production of inflammatory mediators all contribute to the activation and overexpression of ASIC3 and transient receptor potential cation channel subfamily V member 1 (TRPV1). This lowers extracellular pH [7]. As a result, Lin et al. showed in mice that ASIC3 also participates in mechano-transduction in proprioceptors, in addition to *Piezo2* , which is the main player in this process. In fact, in this diseased context, proprioceptive ASIC3 DRG neurons continued to exhibit acid-induced inward currents that were similar to ASIC. Furthermore, if N-methyl-D-aspartate receptors are activated and memory pathways are opened as a result of initial *Piezo2* microdamage, including immunological memory on the spinal dorsal horn, ASIC3 channels may also play a long-term role in memory formation. As a result of the *Piezo2* micro injury-derived "leakiness," it is proposed that these persistent ASIC-like currents are also induced in osteoporosis and sustained by the subthreshold-imbalanced Piezo Ca^{2+} currents [8]. In a chronically overloaded environment, the micro-injured *Piezo2* channels in the periosteum, or spine, may help to gradually upregulate ASIC3 channels in the DRG. The elevation of *Piezo1* in the afflicted neuromodulator tissues, such as the chondrocytes in a feed-forward process, may also be a result of this *Piezo2* microdamage in the periphery of OA. *Piezo1* channels are noteworthy for their ability to sense shear stress, which suggests that this signaling may also be necessary for remodeling. *Piezo1* channels also assist in sensing cell alignment. The paradox continuum of initially pain-free dry eye disease into neuropathic corneal pain suggests that *Piezo1* micro injury could develop into *Piezo2* micro injury gradually in osteoporosis. In addition, the "leakiness" to subthreshold-imbalanced Piezo Ca^{2+} currents due to these *Piezo* micro injuries could explain the "calcium stealing" from bones for years before pain develops due to fractures. This tertiary phase degenerative process is expensive in terms of neuro-energetics because it utilizes an increasing number of synaptic connections and secondary compensatory microcircuits in the Central Nervous System (CNS). As a result, it promotes increased neuroinflammation in the CNS as well as the upregulation of cytokines and inflammatory mediators on the periphery, not to mention that bone sensory innervation grows with aging. This third NC injury phase in osteoporosis consequently results in the progressive activation of NMDA receptors, activation of microglia, overexpression of ASIC3 and TRPV1 ion channels on nociceptive sensory neurons, and an increase in $TrkA^{+}$ nerve fibers. The potentiation of NMDA receptor activity, the activation of microglia and astrocytes, and the production of peptides like substance P are additional central sensitization pathways. Changes in GABA vesicular transport, GABA re-uptake, the changing of intracellular chloride concentration, and the modification of GABA receptor composition could also disrupt longitudinal synaptic Gamma-Aminobutyric Acid (GABA)-mediated inhibition (both at the pre-and post-synaptic level). Older women who have fractures from osteoporosis had much decreased GABA levels. All of these micro fractures and associated *Piezo* channelopathies, however, could go unnoticed in the absence of additional, more severe tissue damage, compression fractures, or C-fiber temporal summation [9].

Quadric injury phase: The quadric phase of the primary proprioceptive *Piezo2* micro-injury, the aging process, also known as inflammageing, could further exacerbate the tertiary degeneration process both in the CNS and on the periphery. Additionally, the aging-augmented processes could result in suppressed sensory signaling, such as the NGF-TrkA axis and osteocalcin, paving. The spinal proprioceptive system's micro trauma is persistent. In addition to the imbalance of osteoblastic and osteoclastic activity, *piezo2* and the aging process together could hasten the imbalance of the aforementioned alignment process and result in osteoporotic fractures. It is crucial to note that proprioceptive sensory function gradually declines with age [10].

Conclusion

In conclusion, the current authors propose that aging could eventually lead to the metabolic imbalance of primary osteoporosis in a quad-phasic non-contact injury pathway, but chronic overloading of the previously micro-injured *Piezo2* of the spinal proprioceptor terminals could lead to re-injury and earlier aging in a dose-limiting and threshold-driven way. It is also emphasized that different regions may have the same beginning proprioceptive *Piezo2* micro-injury, but varied environmental risk factors and genetic predispositions may result in different longitudinal outcomes for DOMS, NC-ACL injury, OA, and osteoporosis. Improved knowledge of the pathomechanism of osteoporosis could be achieved by adopting an interdisciplinary and neurological perspective, which could lead to more accurate therapeutic management in the future.

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