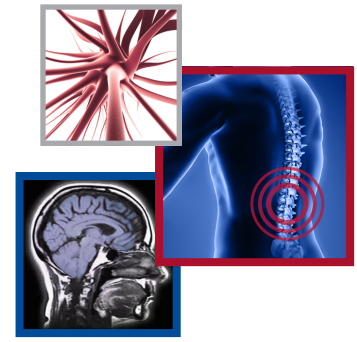
SPECIAL REPORT

Pain Management

Vitamin D status and pain sensitization in knee osteoarthritis: a critical review of the literature



Toni L Glover[1,2], Ann L Horgas[1], Roger B Fillingim[2,3] & Burel R Goodin*[,4]

Practice points

- Osteoarthritis (OA) is the most common of the arthritic conditions, with the knee being the most commonly affected joint.
- Knee OA is often accompanied by significant experiences of pain; however, the severity of pain often varies widely between individuals.
- Radiographic measures of disease severity have been relatively poor predictors of knee OA pain and disability, suggesting that other factors contribute to clinical symptoms in this condition.
- Sensitization of the peripheral and central pathways that process nociceptive information (i.e., pain sensitization) is becoming increasingly recognized as an important contributor to knee OA clinical symptoms.
- Low vitamin D levels are associated with the presence of pain sensitization as well as the severity of knee OA clinical symptoms, particularly pain and disability.
- African–Americans appear to be at risk for poorer knee OA clinical outcomes in comparison to non-Hispanic whites. This may be partly related to lower levels of vitamin D and greater pain sensitization often found in African–Americans.
- Clinical trials addressing whether vitamin D supplementation improves knee OA clinical outcomes have produced mixed findings, with some evidence suggesting that supplementation improves pain severity and other evidence suggesting it does not.
- Future clinical trials on vitamin D supplementation must enroll adequate numbers of racially diverse participants to fully characterize the impact of improved vitamin D status on pain sensitization and knee OA clinical symptoms.

Diagnostic imaging of disease severity has been found thus far to be a relatively modest predictor of knee osteoarthritis (OA) pain and disability, suggesting that other factors likely contribute to clinical symptoms in this condition. Recent evidence suggests that sensitization of the peripheral and central pathways that process nociceptive information (i.e., pain sensitization) is an important contributor to knee OA clinical symptoms. Furthermore, low levels of vitamin D have been found to be associated with the presence of pain sensitization, as well as the overall experience of clinical pain severity in knee OA. African–Americans with knee OA may be at increased risk for poor clinical outcomes given evidence of lower vitamin D levels as well as greater pain sensitization compared with non-Hispanic whites. Whether vitamin D supplementation is effective for alleviating knee OA clinical symptoms is an important topic to be addressed in future research with racially diverse samples that include sufficient numbers of African–Americans.

[1]University of Florida, College of Nursing, Biobehavioral Nursing Science, Gainesville, FL 32610, USA
[2]University of Florida, Pain Research & Intervention Center of Excellence (PRICE), Gainesville, FL 32610, USA
[3]University of Florida, College of Dentistry, Department of Community Dentistry & Behavioral Science, Gainesville, FL 32610, USA
[4]University of Alabama at Birmingham, Departments of Psychology & Anesthesiology & Perioperative Medicine, Birmingham, AL 35294, USA
*Author for correspondence: Tel.: +1 205 934 8743; Fax: +1 205 975 6110; bgoodin1@uab.edu

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KEYWORDS
• African–Americans
• healthcare disparities
• knee osteoarthritis • pain sensitization • vitamin D status

Osteoarthritis (OA) is the most common of the arthritic conditions, with the knee being the most commonly affected joint. Symptomatic knee OA affects roughly 16% of the American population over 45 years of age (>10 million) and produces significant functional impairment of the lower extremities [1]. Knee OA can be accompanied by experiences of intense pain that is severe enough to produce significant emotional distress [2]. However, why some people with knee OA report greater pain intensity than others, even when radiographic evidence of disease severity is comparable, remains unclear. The clinical presentation of knee OA pain symptoms is often heterogeneous, varying from a dull ache to sharp, stabbing pains [2]. Activity-related pain in knee OA is common but pain during rest and spontaneous pain flares sometimes occur. Until recently, mechanisms that help explain the differential intensity and clinical presentation of knee OA pain symptoms have received surprisingly little attention. It seems probable that a variety of different mechanisms contribute to the experience of pain in knee OA, and that the relative importance varies among individuals and over time. The purpose of this review is to address two mechanisms that have quickly become the focus of cutting-edge research in recent years on the topic of painful knee OA – pain sensitization and vitamin D status. Each mechanism appears to have broad relevance to the pain experiences of many people living with knee OA; however, evidence will be presented suggesting that older African–Americans with knee OA may be particularly at risk for the deleterious effects of pain sensitization and low vitamin D levels.

Knee OA is an active disease process characterized by joint space narrowing, subchondral sclerosis and osteophyte formation [3]. Diagnosis has traditionally relied upon radiographic evidence because x-ray can generally identify the effects of these pathological processes [4]. Along this line, knee OA has historically been considered a localized disease process, with nociceptive damage at the joint presumed to account primarily for the experience of pain. It is important to mention, however, that radiographic evidence of knee OA has variable predictive validity as a marker of clinical pain experiences. Several population-based studies have reported weak associations between radiographic evidence obtained from x-ray and knee OA pain [5,6], while others have reported stronger associations [7,8]. Taken together, the mixed nature of these findings suggests that radiographic knee OA is an imprecise marker of whether knee pain will be present, and if pain is present, how intense it will be. The use of more advanced imaging techniques such as MRI has proven helpful for clarifying the origins of pain in knee OA. MRI findings suggest that bone marrow lesions and synovitis are probable pain generators [9]; however, these pathological processes still do not fully account for the wide variability in pain intensity experienced by people with knee OA. Due to the relatively modest concordance between diagnostic images of disease severity and the clinical presentation of knee OA pain, it seems likely that factors above and beyond local tissue damage contribute to the intensity of pain experienced.

Pain sensitization

Recently, it has been suggested that sensitization of the peripheral and central pathways that process nociceptive information (i.e., pain sensitization) is also an important contributor to the clinical presentation of pain in knee OA [10]. Pain may result when nociceptors located deep within the knee become sensitized as a result of local inflammation (peripheral sensitization), as well as when nociceptive signals from the knee joint cause CNS changes that augment the perception of pain (central sensitization) [11]. Initial support for the role of sensitization in painful knee OA comes from animal research showing that continuous and intense input from afferent nociceptive pathways originating in the OA-damaged knee joint potentiates central sensitization [12]. To examine peripheral and central aspects of pain sensitization in humans, studies have incorporated quantitative sensory testing to examine sensitivity to experimental pain stimuli including mechanical, thermal and electrical pain [13]. Indeed, recent findings have demonstrated generalized alterations of peripheral and central pain processing suggestive of sensitization in people with knee OA [14]. Specifically, people with knee OA show enhanced sensitivity to experimental pain stimuli via quantitative sensory testing at both symptomatic (knee) and asymptomatic (nonknee) body sites compared with age-matched controls without knee OA [15,16]. This enhanced experimental pain sensitivity appears to be greatest among people with knee OA who have more severe clinical pain as indicated by the Western Ontario and McMaster Universities Index of Osteoarthritis [17], particularly in the

presence of mild radiographic evidence of disease severity [18]. Findings further support that central sensitization prospectively predicts future reports of clinical pain severity in people with knee OA [19]. Moreover, brain imaging studies have demonstrated functional and structural changes in brain regions that process pain-related information among patients with OA, providing further evidence of central contributions to OA pain [20]. As emerging evidence continues to build a case for the involvement of peripheral and central sensitization in painful knee OA, the role of pathophysiological mechanisms that may help explain how this sensitization arises remains unclear.

The role of vitamin D status

One candidate mechanism that may help explain the emergence of peripheral and central sensitization, as well as the overall experience of clinical pain more broadly, in knee OA is vitamin D status. The basis for considering that vitamin D status might influence the course of knee OA and related pain seems to have arisen from its known role in bone health [21], the importance of systemic and local bone changes in OA-related pain [22,23] and epidemiological observations suggesting slower rates of OA progression among people with higher vitamin D levels [24,25]. Low serum levels of vitamin D have already been implicated in other chronic pain conditions besides knee OA [26]. The optimal serum concentration of vitamin D for adults is believed to be between 30 and 60 ng/ml [26]. Clinical practice guidelines define vitamin D levels <30 ng/ml as inadequate [27]. More specifically, vitamin D levels between 29 and 21 ng/ml are defined as insufficient, levels <20 ng/ml as deficient and levels <10 ng/ml as severely deficient [27]. These guidelines are important for arguing that low vitamin D is a particular concern for the development of chronically painful conditions like knee OA. In a previous study of patients with persistent, nonspecific musculoskeletal pain syndromes, 93% had deficient levels of vitamin D (<20 ng/ml) and 23% were found to be severely deficient (<10 ng/ml) [28]. These findings demonstrate that the overall prevalence rate of vitamin D deficiency in people with chronic musculoskeletal pain (93%) is much greater than the rate observed in the general population of USA, which has been estimated to be ~40% [29]. Low vitamin D appears to be an important problem specifically in the context of knee OA as well. A recent observational study of obese individuals with painful knee OA found that people with adequate levels of vitamin D (>30 ng/ml) reported significantly less severe knee pain and demonstrated better lower extremity functional performance compared with their obese counterparts with insufficient or deficient levels [30]. These results suggest that adequate levels of vitamin D may attenuate knee OA pain severity and preserve lower extremity functional performance, particularly among obese individuals. Given the cross-sectional nature of the data in this study, alternative explanations cannot be ruled out. For instance, higher levels of pain may lead to reduced outdoor activity, which may contribute to both obesity and vitamin D deficiency. Future longitudinal studies will likely be helpful for clarifying this matter.

It has been suggested that low vitamin D levels might enhance pain sensitization, particularly through pathways that promote centrally mediated sensitivity [31]. This notion is supported by animal research whereby low levels of vitamin D caused muscle hypersensitivity for mechanical stimuli together with increased nociceptive skeletal muscle innervation, even before muscle or bone pathology occurred [32]. Low vitamin D levels might also promote peripheral and central pain sensitization in people with painful knee OA. A recently completed study of people with painful knee OA subjected to quantitative sensory testing found low levels of vitamin D to be predictive of increased heat and mechanical pain sensitivity when tested locally at the most affected knee as well as distally at the ipsilateral forearm [33]. Vitamin D has anti-inflammatory properties [34]; therefore, proinflammatory cytokine proliferation can occur when vitamin D levels are low. In turn, augmented proinflammatory cytokine production might alter peripheral and central processing of nociceptive information [35], which could account for the increased heat and mechanical pain sensitivity seen in people with knee OA. Furthermore, pain suppression by the CNS, including the top–down inhibition of nociceptive information, might also become compromised when vitamin D levels are low [36].

African–Americans seem to be at greater risk

The burden of knee OA and its symptoms, particularly pain, appears to disproportionately affect African–Americans in comparison to

non-Hispanic whites [37,38]. Specifically, previous studies have reported greater OA prevalence and associated pain severity for African–Americans relative to non-Hispanic whites (see [39] for review). Greater knee OA prevalence and pain severity often result in higher levels of pain-related physical and psychosocial disability for African–Americans [40]. Pain sensitization and low vitamin D levels may be particularly relevant to the high pain severity and poor physical functioning commonly reported by African–Americans with knee OA.

Healthy African–Americans and those with chronic pain often demonstrate evidence of increased pain sensitivity compared with non-Hispanic whites when subjected to quantitative sensory testing [41,42]. A recent study of people with knee OA provided evidence of augmented peripheral and central sensitization in African–Americans compared with non-Hispanic whites when painful heat and mechanical stimuli were applied locally at the most affected knee as well as other distal body sites [43]. Furthermore, in this study, augmented peripheral and central sensitization was shown to differentially predict reports of greater clinical pain severity on the Western Ontario and McMaster Universities Index of Osteoarthritis and Graded Chronic Pain Scale for African–Americans and non-Hispanic whites according to the type of pain stimulus used. Increased sensitivity to mechanical stimuli was generally more strongly predictive of clinical pain severity for African–Americans, while sensitivity to thermal stimuli (hot and cold) was a stronger predictor for non-Hispanic whites. These findings support the idea that there are likely distinct pathophysiological mechanisms beyond cultural and socioeconomic factors contributing to differences in knee OA pain symptoms between these two racial groups. The challenge for future research is to better understand why pain sensitization generally appears to be more prevalent and severe in African–Americans, as well as the extent to which pain sensitization is a clinically meaningful predictor of knee OA pain severity in racially diverse groups.

Inadequate vitamin D levels (<30 ng/ml) are highly prevalent in African–Americans and non-Hispanic whites alike; however, it appears that the most severely deficient levels (<10 ng/ml) are apparent in African–Americans [44]. Although the overall prevalence rate of vitamin D deficiency (<20 ng/ml) in the general population of the USA has been reported to be ~40% of people; however, estimates indicate 30% of non-Hispanic whites and 80% of African–Americans are vitamin D deficient [29]. Greater vitamin D deficiency in African–Americans may, in part, explain the increased prevalence and severity of many chronic health conditions including knee OA in this racial group. Vitamin D is synthesized through the skin with adequate exposure to sunlight, particularly ultraviolet-B light. Vitamin D synthesis requires longer periods of sun exposure for those with dark skin pigmentation [45]. African–Americans likely have low vitamin D levels because increased melanin in skin melanocytes absorbs ultraviolet-B rays and slows vitamin D synthesis [46]. In the context of knee OA, it may also be that the greater pain intensity and poorer physical functioning observed in African–Americans lead to reduced physical activity, including outdoor activity, which would limit sunlight exposure and opportunities to synthesize vitamin D. This possibility remains speculative at present, and future research is needed to address this hypothetical chain of events. Furthermore, socioeconomic status, healthcare access, lifestyle and cultural factors are all known contributors to racial disparities in health outcomes, including pain [47]. Moving forward, it will be important for researchers to consider the role of socioeconomic disadvantage when investigating the associations among pain intensity, physical functioning and vitamin D levels in African–Americans with knee OA.

Initial evidence suggests that African–Americans with knee OA have lower vitamin D levels and are more pain sensitive compared with their non-Hispanic white counterparts [33]. There are vitamin D receptors in nucleated cells throughout the peripheral and CNS. Low levels of vitamin D could impact both the transmission and modulation of painful stimuli, which could pave the way for pain sensitization to occur. Taken together, low vitamin D levels and pain sensitization may be important inter-related mechanisms that help to explain racial differences in painful knee OA between African–Americans and non-Hispanic whites.

Conclusion

The goal of this article was to review a select literature addressing the newly recognized roles of pain sensitization and low vitamin D levels as mechanisms of chronic pain in knee OA.

Pain sensitization appears to be an important component of knee OA pain severity; however, it is important to note that not all people with knee OA experience pain sensitization. In a recent review of the literature, it was suggested that a select subgroup of people with OA, or ~30%, will experience pain sensitization that contributes to their clinical symptoms including pain [14]. This begs the question of why some people with knee OA will experience pain sensitization and others will not. It may be that the subgroup of people with knee OA at greatest risk for developing pain sensitization are African–Americans with low levels of vitamin D. African–Americans tend to have lower vitamin D levels [44], demonstrate a higher degree of pain sensitization [41,42] and report greater knee OA pain severity compared with non-Hispanic whites [43]. Furthermore, recent evidence has demonstrated an association between low levels of vitamin D and pain sensitization [30,32]. An interesting avenue for future research will be to investigate whether low vitamin D levels play a causal role in the development of pain sensitization, and whether low vitamin D and pain sensitization together prospectively predict the severity of knee OA pain, particularly in African–Americans.

Future perspective

Given that vitamin D insufficiency and deficiency is widespread, and low vitamin D levels may be a key contributor to the progression and severity of painful knee OA, it stands to reason that vitamin D supplementation could be a simple and relatively inexpensive therapy for people with knee OA. Thus far, the research addressing this topic has been sparse and produced mixed findings. There is evidence from two placebo-controlled trials that vitamin D supplementation may be modestly useful for decreasing pain, improving physical function and generally slowing the progression of bone marrow lesions in knee OA [48,49]. Conversely, another trial showed that vitamin D supplementation does not significantly reduce knee pain or the progression of knee OA disease severity compared with placebo [50]. Thus far, the evidence supporting the efficacy of vitamin D supplementation for knee OA has not been very compelling. However, it should be noted that in these previous clinical trials, African–American participants have been underrepresented and the sample sizes have been too small to allow for meaningful subgroup analyses to determine whether effects may have varied according to participants' racial background. Given that African–Americans represent the population subgroup most likely to be adversely affected by both knee OA and low levels of vitamin D, it seems necessary for a future clinical trial on vitamin D supplementation to enroll adequate numbers of racially diverse participants to fully characterize the impact of improved vitamin D status on pain severity and knee OA disease progression.

Disclaimer

The contents are solely the views of the authors and do not necessarily represent the official views of the NIH.

Financial & competing interests disclosure

This work was supported in part by NIH/NIA Grant R37AG033906-12. TL Glover received support from the John A Hartford Foundation (2011–2013) as a Building Academic Geriatric Nursing Capacity Scholar and a Mayday Fund grantee (grant number AAN 11-116). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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