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The bone–muscle–brain axis: Vitamin D deficiency as a sensitization amplifier in headache chronification

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Abstract

Vitamin D deficiency has been associated with migraine and tension-type headache, particularly chronic forms, but the biological basis remains uncertain. We propose the bone–muscle–brain axis, a hypothesis-generating multisystem framework in which vitamin D deficiency acts as a sensitization amplifier rather than a primary cause of headache. In the bone domain, defective mineralization and osteomalacic physiology may increase periosteal nociception; in the muscle domain, vitamin D–related muscle dysfunction, mitochondrial dysfunction, impaired calcium handling and myofascial trigger-point biology may increase peripheral nociceptive drive; and in the brain domain, vitamin D signalling may influence neuroinflammation, neuronal excitability, endothelial function, neurotransmission and descending pain modulation. These domains may interact through peripheral–central nociceptive amplification rather than a proven anatomical or endocrine axis. The model also proposes increasing musculoskeletal involvement during migraine chronification but does not imply progression from migraine to chronic tension-type headache, which remains a distinct disorder. Current evidence is predominantly observational or indirect, and causality remains unestablished. The framework does not support changes in clinical practice but generates falsifiable mechanistic and interventional predictions. Prospective mechanistic studies and adequately powered randomized trials are required to validate or refute the proposed model.

Keywords

vitamin D, migraine, tension-type headache

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Introduction

Migraine and tension-type headache (TTH) are common neurological disorders, and their chronic forms – chronic migraine (CM) and chronic TTH (CTTH) – are major causes of disability.[1] Although trigeminovascular activation, neurogenic inflammation, cortical hyperexcitability and central sensitization are key to headache pathophysiology, they do not fully explain several clinical observations.[2] CM may have bilateral, pressure-like headache resembling CTTH, while neck pain, pericranial tenderness, fatigue and musculoskeletal pain occur across chronic headache disorders.[3,4]

Vitamin D deficiency (VDD) has emerged as a modifiable factor in this overlap.[5] Vitamin D influences skeletal muscle, bone metabolism, immune regulation, vascular function and the central nervous system.[6] Vitamin D receptors (VDRs) and vitamin D–metabolizing enzymes are distributed throughout pain-processing structures, including hypothalamus, thalamus, cortex, limbic system and periaqueductal gray matter (PAG).[7]

VDD is prevalent in migraine and TTH, and supplementation may reduce headache frequency.[8] Nevertheless, the underlying mechanisms remain uncertain. Proposed hypotheses include neuroinflammation, endothelial dysfunction, nitric oxide signalling or trigeminovascular activation,[2] but these do not explain the musculoskeletal phenotype frequently accompanying chronic headache. Increased pericranial tenderness in migraine and CTTH suggests that musculoskeletal abnormalities may represent more than coincidental comorbidity.[9]

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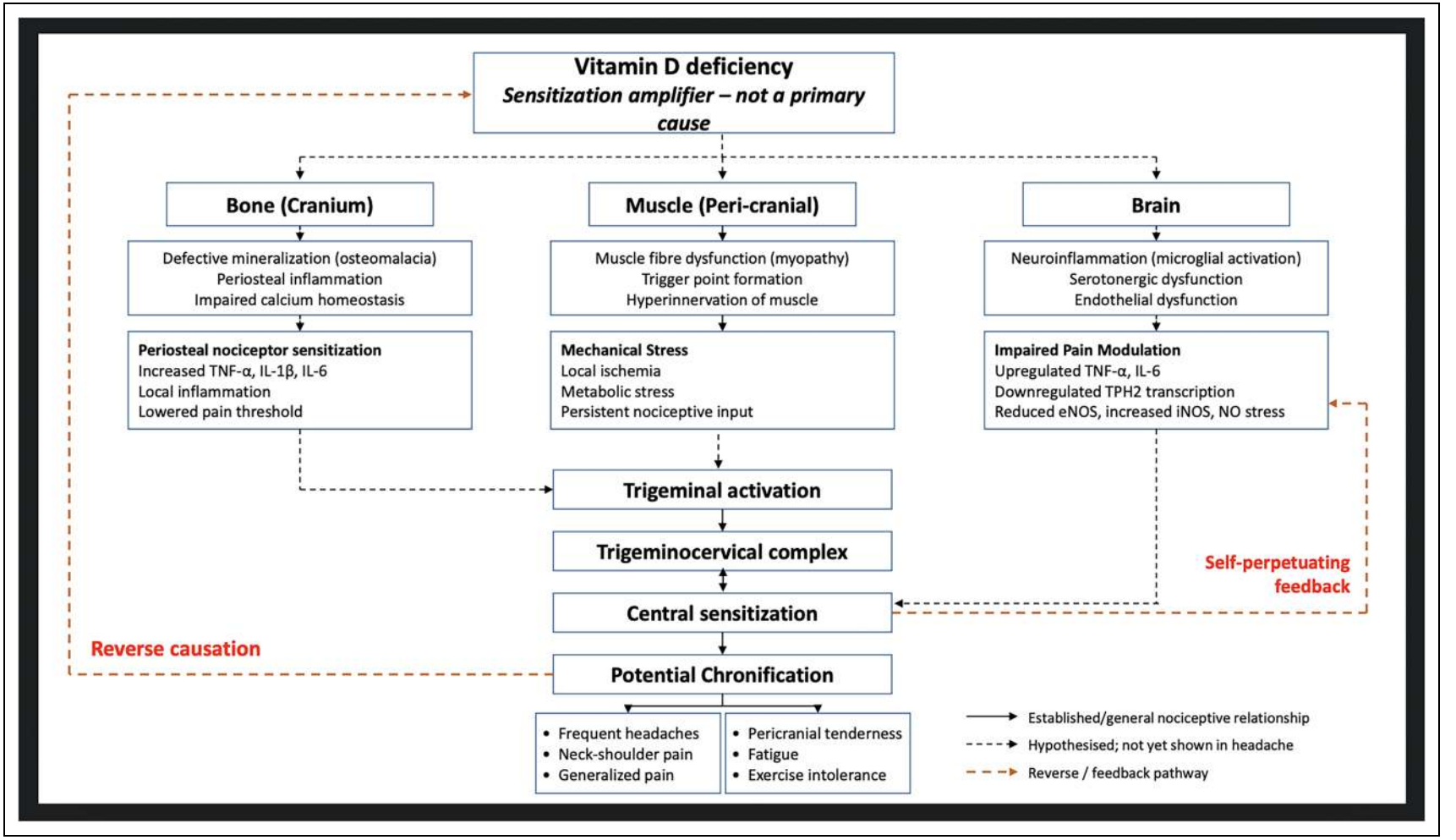


Figure 1. Proposed bone–muscle–brain axis and sensitization amplifier hypothesis. Vitamin D deficiency is proposed to act as a sensitization amplifier through parallel and potentially interacting effects on skeletal, muscular and central pain-processing mechanisms rather than as a primary cause of headache. Peripheral nociceptive mechanisms may interact with central sensitization and potentially contribute to headache persistence or chronification. Solid arrows indicate established or generally recognized nociceptive relationships; dashed arrows indicate hypothesized relationships not yet demonstrated in headache; and orange dashed arrows indicate potential reverse-causation or feedback pathways. The model is hypothesis-generating and does not establish causality or directionality.

Table 1. Shared features of myofascial trigger-point biology and vitamin D–related muscle dysfunction.

Feature	Myofascial trigger points	Vitamin D–related muscle dysfunction
Mitochondrial function	ATP depletion at the motor endplate (energy crisis model)	Reduced ATP production, mitochondrial dysfunction, reduced oxidative capacity
Calcium handling	Impaired ATP-dependent calcium reuptake, sustained sarcomere contraction	Impaired excitation–contraction coupling
Microvascular status	Local ischaemia from sustained contraction	Endothelial dysfunction, impaired microvascular perfusion
Inflammatory milieu	Elevated bradykinin, substance P, CGRP, prostaglandins, cytokines	Pro-inflammatory shift (TNF-α, IL-6, IL-1β)
Sensitization	Nociceptor sensitization	Enhanced pain sensitivity
Clinical phenotype	Tenderness, taut bands, referred pain	Diffuse pain, tenderness, fatigue, and occasionally proximal weakness

Abbreviations: ATP: adenosine triphosphate; CGRP: calcitonin gene-related peptide; IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumour necrosis factor-α.

We therefore propose an integrative hypothesis – the bone–muscle–brain axis – in which VDD simultaneously affects skeletal tissue, skeletal muscle and central pain-processing networks (Figure 1). Within this framework, osteomalacic bone, vitamin D–related muscle dysfunction and myofascial trigger points (TrPs) generate persistent peripheral nociceptive input interacting with central mechanisms to facilitate sensitization and headache chronification (Table 1). We use 'axis' as shorthand for a multisystem hypothesis involving parallel and convergent effects on bone, muscle and brain. Direct biological communication among all three domains has not been demonstrated in headache disorders. Muscle–bone–brain crosstalk has been proposed in ageing and degenerative disorders.[10,11] Our model is narrower and headache-specific, focusing on potential nociceptive interactions.

This viewpoint is not a systematic review, and no formal quality appraisal or risk-of-bias assessment was performed. Relevant literature was identified through MEDLINE and Google Scholar through July 2026, using combinations of terms including 'vitamin D', 'migraine', 'tension-type headache', 'headache chronification', 'osteomalacia', 'myofascial trigger points', 'central sensitization' and 'musculoskeletal pain'. Searches were supplemented by reference-list screening of relevant articles.

Historical evolution of the vitamin D–headache hypothesis

Early ecological observations showed higher prevalence of migraine and TTH with increasing distance from the equator, paralleling VDD.[12] Prakash and Shah described patients with CTTH, VDD and biochemical osteomalacia whose headaches improved following supplementation, introducing osteomalacic cephalalgia.[13] Subsequent studies demonstrated VDD with muscle and bone tenderness in CTTH.[14,15] Evidence extended to migraine: reviews reported a possible benefit of supplementation,[8] while increased pericranial tenderness was demonstrated in migraine and CTTH.[9] A recent study reported lower vitamin D levels and greater musculoskeletal tenderness in chronic than episodic migraine.[16] Experimental studies identified VDRs in headache-relevant brain regions.[7,17]

The bone domain: osteomalacic cephalalgia as a hypothesis

Severe and prolonged VDD can lead to osteomalacia, causing bone pain and tenderness.[18] Unlike osteopenia and osteoporosis, osteomalacia reflects defective bone mineralization. Although cranial osteomalacia has not been systematically investigated in adults, cranial abnormalities in childhood rickets indicate that the skull is susceptible to impaired mineralization.[19] Given that the cranial periosteum is richly innervated by trigeminal and upper cervical afferents projecting to the trigeminocervical complex (TCC), skull may represent an underrecognized source of nociceptive input. This hypothesis is supported by similarity between osteomalacic musculoskeletal pain and the pericranial (and extracranial) tenderness observed in CTTH, leading to the proposal of skull osteomalacia as a potential mechanism.[13,14] The hypothesis of osteomalacic cephalalgia emerged from observation that patients with chronic headache, severe VDD and biochemical osteomalacia improved following vitamin D supplementation.[13,14]

Subsequent studies demonstrated lower vitamin D concentrations with increased bone tenderness, musculoskeletal pain and osteomalacic features in patients with CTTH and CM, with bone tenderness correlating inversely with serum vitamin D concentrations.[15,16] These observations suggest that skeletal nociception may contribute to headache chronification.

Bone pain in osteomalacia is generally attributed to poorly mineralized collagen-rich osteoid, which increases mechanical stress on periosteum and activates periosteal nociceptors.[18] We speculate that a similar process may

occur in cranial bones. Physiological forces – including mastication, scalp and cervical muscle contraction as well as prolonged head posture – may activate sensitized periosteal nociceptors when cranial biomechanics are altered by defective mineralization.

Mechanical stress alone is unlikely to explain the proposed mechanism. VDD may permit local periosteal inflammation through increased production of pro-inflammatory cytokines.[20] This inflammatory milieu could lower periosteal nociceptor thresholds.

Persistent nociceptive input from osteomalacic bone may activate trigeminal afferents projecting to the TCC, facilitating central sensitization and lowering pain thresholds. Central sensitization may further amplify cephalic and extracephalic pain through altered descending pain modulation.

Bone tenderness has been reported in vitamin D–deficient patients with chronic headache and correlates inversely with serum vitamin D concentrations.[15,16,18] However, tenderness is non-specific and may reflect central sensitization or nociception arising from adjacent soft tissues rather than bone.

The muscle domain: vitamin D–related muscle dysfunction and myofascial TrPs

Muscular abnormalities represent the most clinically apparent component of the proposed bone–muscle–brain axis. Neck pain, pericranial tenderness, fatigue, reduced exercise tolerance and musculoskeletal pain are common to chronic headaches and VDD.[3,18] VDRs are expressed in skeletal muscle fibres, and deficiency is associated with proximal myopathy, impaired muscle regeneration, altered calcium homeostasis and selective type II muscle fibre atrophy.[20] In this viewpoint, 'vitamin D–related muscle dysfunction' encompasses potential functional and subclinical muscular abnormalities associated with VDD, whereas 'vitamin D–related myopathy' refers to clinically demonstrable muscle dysfunction, particularly proximal weakness. Muscle pain, tenderness and fatigue alone do not establish myopathy. These abnormalities provide a biologically plausible basis for persistent muscular nociception in chronic headache.

Clinical observations support this relationship. Patients with CTTH exhibit increased pericranial tenderness, lower serum vitamin D concentrations and greater muscle tenderness.[14,15] Castien et al. demonstrated increased pericranial tenderness in migraine, indicating that muscular tenderness is not unique to CTTH.[9] More recently, muscle tenderness increased progressively from healthy controls to episodic migraine and CM, with serum vitamin D concentrations correlating inversely with tenderness score,[16] suggesting increasing muscular abnormalities as headache frequency increases.

Several biological mechanisms may underlie this association. VDD impairs muscle calcium handling, disrupts ATP production, reduces microvascular perfusion and promotes inflammatory cytokine release. Together, these abnormalities reduce muscle endurance, delay recovery following contraction and increase susceptibility to persistent muscular pain.[21,22] Clinically, this may contribute to neck pain, fatigue, exercise intolerance and diffuse muscle tenderness.

Experimental evidence strengthens the proposed muscular pathway. In a rat model, Tague et al. demonstrated that VDD produced selective deep muscle mechanical hypersensitivity, without altered cutaneous sensitivity.[23] Muscle hypersensitivity developed before overt muscle atrophy or bone pathology. Vitamin D–deficient animals also exhibited selective hyperinnervation of skeletal muscle. Sensory neurons expressed VDRs within growth cones, and vitamin D regulated sensory neurite outgrowth.[23] These findings link VDD with muscle hypersensitivity and sensory hyperinnervation.

Myofascial TrPs provide a mechanistic bridge between VDD and headache chronification. *TrPs* are hyperirritable foci within taut muscle bands associated with sustained sarcomere contraction, local ischaemia, ATP depletion, impaired calcium reuptake and inflammatory mediators.[24] Active TrPs occur in CTTH and CM, and mechanical stimulation can reproduce typical headache.[25,26] TrPs pathophysiology shares features with vitamin D–deficient muscle dysfunction, including mitochondrial dysfunction, disturbed calcium homeostasis, reduced ATP availability, oxidative stress and increased inflammatory mediator activity.[27,28] VDD also impairs muscle regeneration, potentially increasing susceptibility to persistent trigger-point formation.[21,22] These parallels do not establish causality but suggest that deficiency may lower the threshold for TrPs. TrP may provide input to the TCC, facilitating central sensitization. The proposed sequence is as follows: VDD → muscle fibre dysfunction → mitochondrial energy deficit → impaired calcium homeostasis → local ischaemia and metabolic stress → trigger-point formation → persistent nociceptive input → trigeminocervical activation → chronic headache.

Within the proposed bone–muscle–brain axis, pericranial and cervical muscles may contribute to nociceptive drive rather than simply reflect chronic headache. Their nociceptive input may reach the TCC and interact with central pain-processing networks. VDRs and metabolizing enzymes are also expressed in nociceptive neurons, suggesting a potential additional influence of vitamin D on peripheral pain processing.[29]

Importantly, a muscular contribution does not imply that muscle contraction or spasm is the primary mechanism. Muscle relaxants are not established primary therapies for migraine or TTH. The muscular domain proposed here instead involves altered muscle metabolism, nociceptor sensitization, TrP biology and peripheral–central interactions. Muscle abnormalities are therefore potential amplifiers rather than primary causes of headache.

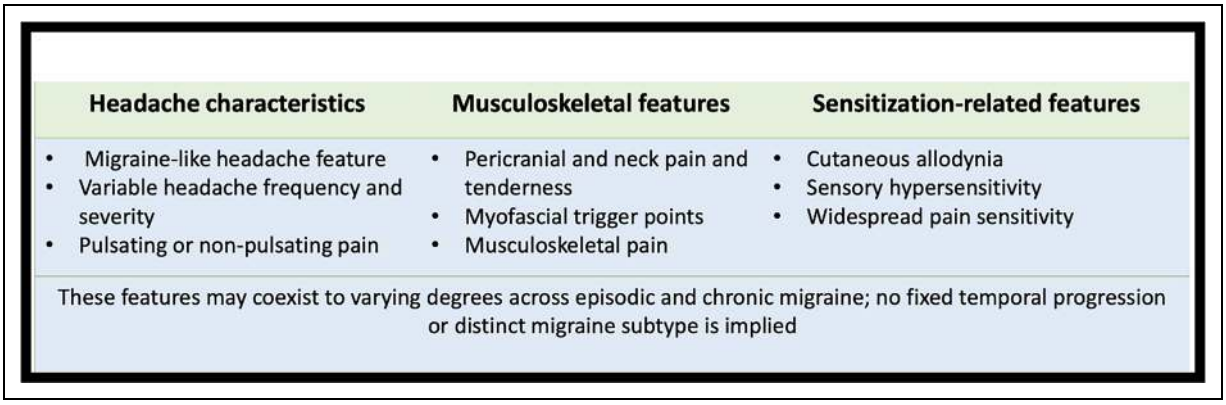


Figure 2. Proposed changes in musculoskeletal involvement during migraine chronification. The figure illustrates potentially overlapping headache characteristics, musculoskeletal manifestations and sensitization-related features across episodic and chronic migraine. Chronic migraine may include migraine-like and tension-type-like headache features, as recognized by ICHD-3. The proposed model does not imply a fixed temporal progression, distinct migraine subtype or established causal relationships.

Brain domain, including VDRs

Vitamin D influences central pain-processing pathways through widespread expression of VDRs and metabolizing enzymes within the brain, including headache-related regions such as the hypothalamus, trigeminovascular system, thalamus and PAG.[17,30] Although not directly established in headache, this distribution provides a biological basis for vitamin D to influence headache-related network.

The hypothalamus, a key regulator of migraine initiation, circadian rhythm, autonomic function and energy homeostasis, exhibits abundant VDR expression.[17] Hypothalamic dysfunction may underlie premonitory symptoms such as fatigue, yawning, food craving, sleep disturbance and neck discomfort – features that overlap with manifestations of VDD.[3,6] Within the trigeminovascular system, VDD may lower neuronal activation thresholds by altering calcium homeostasis, neuronal excitability and inflammatory signalling, thereby facilitating neurogenic inflammation and CGRP-mediated nociception, although direct evidence is limited.[21,22,30,31]

Vitamin D may also influence central pain modulation. The thalamus amplifies nociceptive transmission, whereas the PAG mediates descending pain inhibitory pathways. Abnormalities of both regions are well recognized in migraine, particularly CM.[17,32] VDD may impair endogenous pain inhibition through reduced serotonergic activity, enhanced neuroinflammation and increased neuronal excitability, thereby facilitating central sensitization and headache chronification.[20,30] Vitamin D regulates calcium homeostasis, glutamatergic neurotransmission, mitochondrial function and neuroprotection, providing a biologically plausible mechanism through which deficiency could increase cortical excitability and susceptibility to cortical spreading depression, although direct experimental evidence remains limited.[7,30] Limbic structures involved in the emotional and cognitive dimensions of pain also express VDRs,[17,30] potentially linking deficiency with associated neuropsychiatric symptoms.

Several complementary molecular mechanisms may underlie these effects. Vitamin D exerts immunomodulatory actions, suppressing pro-inflammatory cytokines and inhibiting nuclear factor kappa B (NF-κB) signalling. Deficiency may therefore facilitate microglial activation, oxidative stress and neuroinflammation.[30,33] Vitamin D has also been proposed to regulate tryptophan hydroxylase-2, involved in neuronal serotonin synthesis, potentially influencing descending pain inhibition.[34] Additionally, VDD has been associated with endothelial dysfunction and altered nitric oxide synthase signalling,[20,35] providing another possible influence on trigeminovascular activity.

These mechanisms are unlikely to operate independently. Neuroinflammation, trigeminovascular excitability, impaired pain modulation and endothelial dysfunction may interact with central pain-processing networks. We therefore propose that VDD acts as a central sensitization amplifier, influencing multiple interacting pathways rather than a single molecular target. Within the proposed bone–muscle–brain axis, these central effects may interact with peripheral nociceptive input from cranial and upper cervical structures, facilitating sensitization and headache chronification. This model remains hypothetical and requires validation.

Migraine chronification: the bone–muscle–brain continuum

Central sensitization is the dominant model of migraine chronification,[2,32] but may not fully explain the variable musculoskeletal manifestations in some patients with CM. International Classification of Headache Disorders, 3rd

Table 2. Epidemiological and longitudinal evidence showing associations between musculoskeletal disorders and primary headache disorders.

First author	Musculoskeletal disorder	Study design	Main findings	Interpretation
Hagen et al.[36]	Chronic musculoskeletal symptoms	Population-based cross-sectional	Chronic headache strongly associated with widespread musculoskeletal symptoms; association strengthened with increasing headache frequency	Headache and musculoskeletal pain commonly coexist in the general population
Hagen et al.[37]	Chronic musculoskeletal symptoms	11-year prospective cohort	Bidirectional relationship between headache and chronic musculoskeletal complaints	A bidirectional association was observed between headache and chronic musculoskeletal complaints.
Scher et al.[38]	Multiple pain disorders	Population cohort (CaMEO)	Comorbid pain disorders were associated with progression from episodic to CM	Greater comorbid pain burden is associated with migraine chronification; causality is not established.
Vivekanantham et al.[39]	Low back pain	Systematic review	Consistent association between headache and low back pain across studies	Strong evidence links spinal pain with headache disorders
Al-Khazali et al.[40]	Neck pain	Systematic review & meta-analysis	Confirmed markedly increased prevalence of neck pain among migraine patients	Robust pooled evidence supports the migraine–neck pain association
Jacob et al.[41]	Arthritis	National cross-sectional study	Arthritis independently associated with migraine	Degenerative joint disease is linked with migraine
Kim et al.[42]	Rheumatoid arthritis	National longitudinal cohort	Bidirectional association between migraine and RA	Migraine and rheumatoid arthritis were each associated with a higher subsequent risk of the other condition.
Kang et al.[43]	Rheumatoid arthritis	National retrospective cohort	RA patients had significantly higher incidence of migraine	Rheumatoid arthritis is associated with a higher incidence of migraine; shared inflammatory or other mechanisms may contribute.
Mathieu et al.[44]	Rheumatic diseases	Cross-sectional study	Migraine prevalence increased across several inflammatory rheumatic disorders	Migraine is common in inflammatory musculoskeletal diseases
Marino et al.[45]	Psoriatic arthritis & axial spondyloarthritis	Cohort study	Migraine/headache prevalence significantly higher than expected	Spondyloarthropathies are associated with migraine
de Tommaso et al.[46]	Fibromyalgia	Cross-sectional study	Fibromyalgia occurred more frequently in patients with primary headaches, especially chronic migraine	Fibromyalgia and migraine frequently coexist; central sensitization is a possible shared mechanism, but confounding and directionality remain uncertain.
Penn et al.[47]	Fibromyalgia	Retrospective cohort	Bidirectional association between migraine and fibromyalgia	A bidirectional association between migraine and fibromyalgia was observed.
Réus et al.[48]	Temporomandibular disorders	Systematic review & meta-analysis	Primary headaches strongly associated with TMD	TMD is associated with primary headache disorders; the direction and causal basis of the association remain uncertain.

(continued)

Table 2. Continued.

First author	Musculoskeletal disorder	Study design	Main findings	Interpretation
Byun et al.[49]	Temporomandibular disorders	National longitudinal cohort	TMD significantly increased future migraine risk	TMD was associated with subsequent migraine development; causality is not established.
Bendik et al.[50]	Joint hypermobility syndrome	Case–control study	Women with joint hypermobility had increased migraine prevalence	Joint hypermobility syndrome was associated with a higher prevalence of migraine in women.

Abbreviations: CM: chronic migraine; RA: rheumatoid arthritis; TMD: temporomandibular disorder(s).

edition (ICHD-3) recognizes that CM may include migraine-like or tension-type-like headache features.[4]

The bone–muscle–brain axis proposes that trigeminovascular activation and musculoskeletal nociception may contribute to phenotypic heterogeneity across migraine (Figure 2). Pericranial tenderness, myofascial TrPs, neck pain, fatigue and sensory hypersensitivity may coexist without a fixed temporal sequence or distinct stages. Tension-type-like features within CM do not imply transformation into CTTH, which remains a distinct disorder. The differential efficacy of onabotulinumtoxin A in CM and CTTH further supports this distinction.

The bone–muscle–brain axis: an integrated model

The bone–muscle–brain axis proposes that VDD influences headache through effects on skeletal tissue, muscle and central pain-processing networks (Figure 1). The bone domain involves defective mineralization and potential periosteal nociception; muscle domain comprises vitamin D–related muscle dysfunction, mitochondrial dysfunction, impaired calcium homeostasis and myofascial trigger-point formation and the brain domain includes neuroinflammation, altered serotonergic and glutamatergic signalling, endothelial dysfunction, cortical hyperexcitability and impaired descending pain modulation.

These domains may interact through peripheral–central nociceptive mechanisms. Nociceptive input from cranial and upper cervical structures may facilitate central sensitization, while altered central pain processing may increase peripheral pain sensitivity, potentially creating a self-perpetuating cycle. Central to this framework is the sensitization amplifier hypothesis.

Extension beyond VDD

If musculoskeletal abnormalities contribute to headache chronification, associations between chronic musculoskeletal disorders and primary headaches would be expected. Epidemiological and longitudinal evidence supports this association (Table 2), although causality remains unestablished.

Population-based studies, including the Norwegian HUNT Study, demonstrated associations between chronic headache and widespread musculoskeletal pain, with an 11-year follow-up confirming a bidirectional relationship.[36,37] The CaMEO study linked increasing musculoskeletal pain burden with migraine chronification, while other studies identified low back pain and neck pain as common headache comorbidities.[38–41] Comparable associations occur with osteoarthritis, inflammatory rheumatic disorders, fibromyalgia, temporomandibular disorders and joint hypermobility[42–50] (Table 2).

These associations may reflect central sensitization, systemic inflammation, depression, sleep disturbance, obesity, shared biological susceptibility, reduced physical activity or reverse-causation. Fibromyalgia is particularly important because of its frequent coexistence with migraine and widespread tenderness. Whether VDD independently associates with tenderness and headache chronification after adjustment for fibromyalgia remains unknown.

These observations support shared musculoskeletal–headache mechanisms rather than causality. Nociceptive input from distant structures such as the low back should not be assumed to converge directly on the TCC such as cranial and upper cervical afferents. Such associations may instead reflect broader pain amplification and central sensitization. VDD is proposed as one potential modifier of musculoskeletal and central nociceptive mechanisms rather than a disease-specific cause of headache.

Clinical implications and future research

The bone–muscle–brain axis is a hypothesis-generating framework and does not justify routine vitamin D testing or supplementation for headache outside established indications. Its value lies in generating falsifiable predictions. Prospective and interventional studies should determine whether vitamin D repletion reduces bone and muscle

tenderness, myofascial trigger-point burden and headache frequency or chronification. Studies should examine whether vitamin D status correlates with quantitative sensory testing, cranial skeletal abnormalities, neuroimaging or neuroinflammation biomarkers, while controlling for confounders. Demonstrating that VDD correction modifies these mechanisms alongside headache outcomes would strengthen the bone–muscle–brain hypothesis.

Limitations of the hypothesis

Most evidence supporting the bone and muscle domains originates from a single research group, with limited independent validation. Supplementation evidence is largely uncontrolled, and no adequately powered randomized trial has evaluated effects on musculoskeletal tenderness, TrPs or headache chronification. Confounding and reverse-causation remain plausible, while the brain domain is based largely on indirect evidence. Prospective mechanistic and interventional studies are therefore required to establish causality.

Conclusion

VDD may influence skeletal, muscular and central pain mechanisms beyond bone health. The proposed bone–muscle–brain axis integrates these effects into a hypothesis-generating framework for headache chronification. This model provides a plausible explanation for the overlap between VDD and chronic headache, including fatigue, musculoskeletal tenderness and widespread pain. Central to this framework is the Sensitization Amplifier Hypothesis, whereby VDD lowers the threshold for peripheral and central nociceptive activation rather than directly causing headache. Although the current evidence is insufficient to establish causality or justify changes in clinical practice, it provides a biologically plausible foundation for prospective mechanistic studies and adequately powered randomized clinical trials.

Highlights

- We propose the bone–muscle–brain axis, linking VDD to headache chronification via skeletal, muscular and central mechanisms converging on the trigeminocervical complex.
- VDD is hypothesized to act as a sensitization amplifier.
- This hypothesis-generating model requires mechanistic, imaging and randomized interventional validation.

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Ethical considerations

It is a view point; ethical permission is not required.

Consent to participate

Not applicable.

Consent for publication

Both authors have agreed to publish with Cephalalgia reports.

Author contributions

Sanjay Prakash contributed to conceptualization; methodology; writing – original draft; writing – review and editing; project administration; and supervision. Manju Yadav contributed to conceptualization; writing – original draft; writing – review and editing; and visualization.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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