RESEARCH PAPER

Vitamin D Deficiency And Its Role In Cnmp Associated With Osteoporosis And Radiological Assessment - A Narrative Review

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Abstract

Background: Vitamin d deficiency is a widely prevalent global public health concern with significant musculoskeletal and extra skeletal consequences. Beyond its classical role in calcium-homeostasis and bone mineralization, vitamin d plays a critical modulatory role in neuroimmune responses, nociception, and inflammatory pathways implicated in chronic non-specific musculoskeletal pain (cnmp).

Aim & objectives: This narrative review aims to examine the biological interplay between vitamin d deficiency, neuroimmune mechanisms in cnmp and global burden, and the role of radiological assessment and fracture prediction tools in clinical practice.

Methods: A comprehensive narrative literature search was conducted using pubmed/medline, scopus, and embase for articles published up to january 2026. Core search terms included: "vitamin d deficiency", "chronic musculoskeletal pain," "neuroimmune mechanisms," "osteoporosis," "bone mineral density," "dxa," "dual-energy x-ray absorptiometry," "radiological assessment," and "frax." Priority was given to high-quality observational studies, clinical trials, meta-analyses, and global osteoporosis reports, including data aligned with the world health organization.

Results: Emerging evidence suggests that hypovitaminosis d contributes to persistent musculoskeletal pain through elevated pro-inflammatory mediators, central sensitization and impaired neuromuscular function. Simultaneously, chronic deficiency promotes secondary hyperparathyroidism, accelerates individuals to decrease bone mineral density (bmd), microarchitectural deterioration and increased fracture risk culminating in osteoporosis. Radiological assessment remains central to diagnosis, with dual-energy x-ray absorptiometry (dxa) serving as the gold standard for bmd measurement. Conventional radiography, vertebral morphometry, and fracture risk assessment tools such as frax provides prognostic evaluation of individuals 10-year fracture probability.

Conclusion: Vitamin d deficiency represents a interconnected pathways linking chronic pain syndromes and osteoporosis. Integrated evaluation incorporating biochemical markers, radiological assessment, and clinical risk stratification may boost the early detection and management, prevention of risk fractures and improves the individual's quality of life.

Keywords: Vitamin D Deficiency, Chronic Non-Specific Musculoskeletal Pain, Osteoporosis, Radiological Assessment Tools, Frax.

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Introduction :

Chronic non-specific musculoskeletal pain (CNMP) is a common clinical condition characterized by persistent pain involving bones, muscles, ligaments, and joints without a clearly identifiable pathological cause. Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".It is frequently associated with degenerative skeletal changes, muscle weakness, muscle wasting, and diffuse bone pain, significantly affecting quality of life and functional ability (1). Emerging evidence suggests that vitamin D deficiency plays an important role in the development and persistence of CNMP (2).Vitamin D is essential for maintaining calcium and phosphorus homeostasis and for normal bone mineralization. Deficiency of Vitamin D can result in hypocalcemia, hypophosphatemia, secondary hyperparathyroidism, bone loss, and skeletal fragility, which may contribute to osteomalacia and osteoporosis (3).

Hypovitaminosis D is widely prevalent world wide and is particularly common among postmenopausal women and elderly men due to decreased sun exposure, inadequate dietary intake, and reduced cutaneous synthesis (4). Patients with vitamin D deficiency often present with pain in the lower back, spine, hips, knees, and ribs. Studies report that vitamin D insufficiency is present in approximately 30-90% of individuals with chronic musculoskeletal pain (1). Serum 25-hydroxyvitamin D [25(OH)D] is the most reliable biomarker for assessing vitamin D status. Early evaluation and achieving optimum levels of it may help in the management of chronic musculoskeletal pain (CNMP) (2,5).

The aim of this narrative review is to summarize current evidence on the association between vitamin D deficiency and CNMP. It focuses on recent clinical and scientific data highlighting the role of vitamin D in bone health, pain mechanisms, and musculoskeletal function. In addition, this review emphasizes the importance for clinicians to evaluate patients at risk of vitamin D deficiency using appropriate diagnostic approaches, including biochemical analysis of serum vitamin D and calcium levels, radiological assessment of bone changes, and fracture risk prediction tools such as the FRAX model (14). Early identification and proper evaluation may help in the prevention of osteoporosis, reduction of fracture risk, and improvement in the overall quality of life in individuals suffering from chronic musculoskeletal pain.

1) Vitamin D Sources & Metabolism :

1.1. Sunlight : sunlight is the primary natural source of vitamin D. when the skin is exposed to sunlight with wavelength of 290 – 315nm UVB radiation, converts 7-dehydrocholesterol in the epidermis into previtamin D_3. Subsequently the active of vitamin D is synthesized in liver and kidney. The adequate sunlight is essential for the optimal vitamin D synthesis however factors such as increased skin pigmentation, aging, air pollution, sedentary & indoor lifestyle, clothing habits, sunscreen use eventually reduce cutaneous production. Further more when Vitamin D_3 synthesized in the skin easily diffuses into the capillary bed in the dermis and binds 100 % to the Vitamin D binding protein (DBP). In contrast VitaminD_3 obtained through the dietary sources or supplements is incorporated into chylomicrons and transported via the lymphatic system before entering the venous circulation. The ingested Vitamin D_3 approximately 60% binds to DBP and remaining 40% is rapidly cleared in the lipoprotein- bound fraction (6).

1.2. Metabolism in liver & kidney : vitamin D exists in two forms D2(Ergocalciferol) from plant based foods like fungi, yeast etc., & D3 (Cholecalciferol) via sunlight and animal based foods like fish liver oil, egg yolk etc. The DBP facilitate its transport to the Liver and hydroxylated by Vitamin D hydroxylase to form 25 hydroxy Vitamin D [25(OH) D]. This metabolite represents the vitamin D and the most reliable biomarker for assessing the Optimal concentrations which are generally considered to be 30 – 60 ng/ml as per many laboratories in clinical practice.

25(OH) D is biologically inactive and undergoes further hydroxylation in the kidneys by 25 -hydroxyvitamin D-1α- hydroxylase to generate the biologically active form 25 – dihydroxyviamin D [$1,25\ (OH)_2D$]. Renal synthesis is strictly regulated by serum calcium, phosphorus, fibroblast growth factor -23 (FGF -23), parathyroid hormone and feedback inhibition by $1,25(OH)_2D$ itself. Functionally, $1,25(OH)_2D$ enhances intestinal calcium absorption by binding to the Vitamin D receptor –

retinoid X receptor (VDR-RXR) complex, upregulating epithelial calcium transport proteins such as $TRPV_6$ and calbindin -D9k, a calcium binding protein (CaBP) (7).

1.3. Action in Bone : vitamin D promotes bone health by regulating bone remodeling and by metabolism of calcium and phosphorous, osteoblast-osteoclast interactions. osteoblasts receives the active form of vitamin D [1,25(OH)D] and stimulates the expression of receptor activator of nuclear factor – κB ligand (RANKL) for converting the preosteoclasts to mature osteoclasts there by promoting osteoclast differentiation and activation. This controlled osteoclastic bone resorption is essential for maintaining normal bone turnover and for releasing the calcium and phosphate to into circulation when it is required (6).

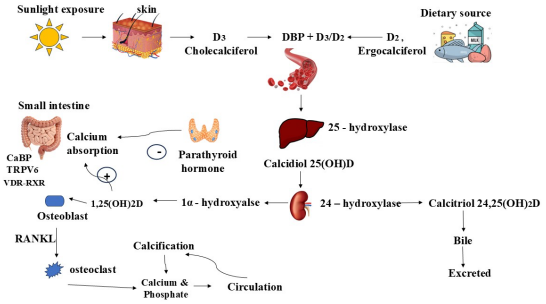

Fig 1: Schematic representation of vitamin D synthesis on exposure to sunlight and thermodynamically it is converted to previtamin D3 and from dietary sources the D2 & D3 diffuses into the capillary bed where it is binding with vitamin D binding protein (DBP) which is transported into liver and converted into Calcidiol 25(OH)D by an enzyme 25 – hydroxylase. 25(OH)D is converted to Calcitriol 24, 25 (OH)D and 1,25-dihydroxyvitaminD [1,25-(OH)2D]. The [1,25-(OH)2D] regulates its own synthesis decreases the synthesis & secretion of parathyroid hormone and the biologically inactive calcitriol is excreted in the Bile. [1,25-(OH)D] enhances the calcium absorption in small intestine by stimulating proteins such as Calcium binding protein (CaBP) , Transient receptor potential cation channel ,subfamily V, member 6 (TRPV6) and Vitamin D receptor - retinoic acid X-receptor complex (VDR-RXR). [1,25(OH)2D] is recognized by the receptor present in the osteoblasts and stimulates the Receptor activator of nuclear factor -κB ligand (RANKL) which induces the preosteoclast to become mature osteoclast. Mature osteoclasts resorb bone and release calcium and phosphate into the circulation. The adequate concentrations of Ca^{2+} & HPO_4^{2-} promote calcification and bone mineralization.

2) CNMP & Vitamin D : The international association for the study of pain (IASP) defines chronic pain as " pain that has persisted beyond normal tissue healing time ". It can be generated after tissue damage or inflammation, nerve damage & after alteration of normal neural function. Chronic pain is considered as 3 months. Among the various types of chronic pain the chronic non-specific musculoskeletal pain is an idiopathic pain which is associated with decreased physical health, mental well – being, social life, work ability and overall quality of life. The aetiology of CNMP is not well understood therefore it is difficult to diagnose, prevent & treat. However research studies have highlighted the link between vitamin D and CNMP because Vitamin D is involved in numerous regulatory biological processes such as calcium homeostasis, and modulation of immune and inflammatory pathways, which may influence nociceptive processing and contribute to the chronification of pain. (Bonanni et al., 2022)

A clear understanding of the pathophysiological mechanisms involved in nociceptive stimulation & central nervous sensitization is essential for effectively approaching the musculoskeletal pain. The study of pain is complex, as it is involved by multiple comorbidities. There are several scales & questionnaires are commonly used to assess the pain intensity such as, Visual analogue scale (VAS), Numeric pain rating scale (NPRS), Orebro musculoskeletal pain screening questionnaire, McGill pain Questionnaire. The 11th edition of International classification of diseases (ICD-11) conceptualizes pain as an experience resulting from the integration of biomedical, psychological & social factors involved in the CNMP (8).

2.1. Pathophysiology of CNMP : The perception of pain is initiated by the peripheral nociceptors. Nociceptive neurons originate from neural crest stem cells of the neural tube during neurogenesis. Their cell bodies are located in the dorsal root ganglion (DRG) from which a peripheral axon innervates target tissues while the central axon enters the central nervous system (CNS), to synapse with second - order nociceptive neurons. Among these fibres, Aδ fibres are thinly myelinated sensory nerve fibres that conduct impulses at velocities ranging from 2 to 30 m/s, they predominantly innervate the ligaments, capsules, menisci & muscles and are responsible for fast well-localized pain. In contrast, TrKA – positive C fibres are unmyelinated nerve fibres with conduction velocities

of <2m/s. These fibres express the tropomyosin receptor kinase A (TrKA) and release neuropeptides such as Calcitonin gene - related peptide (CGRP). They include sympathetic adrenergic & cholinergic nerve fibres which contribute to sustained nociceptive signaling and pain transmission (8).

2.2. Interaction of Immune cells & Nociceptive neurons in CNMP : chronic non-specific musculoskeletal pain involves complex bidirectional communication between the nervous and immune systems. Inflammation plays a major role in pain sensitization by activating and lowering the threshold of peripheral nociceptors through the release of proinflammatory mediators such as TNF-α, IL-1β, IL-6, prostaglandin E_2 (PGE_2), Histamine. sustained nociceptive input subsequently triggers neuroimmune activation within the spinal cord and brain, leading to central sensitization and persistent pain. However, it is important to recognise that systemic inflammatory responses are not inherently harmful. Acute inflammation represents a normal adaptive process that initiates and facilitates tissue repair following injury. For example, IL-6, CRP (C-reactive protein) are elevated early during tissue healing but resolve rapidly after an acute episode of back pain typically within 2 weeks of onset, in individuals who recover favourably. Notably, IL-6 and CRP exhibit both pro- and anti-inflammatory properties supporting the clearance of damaged cells and the regulation of inflammatory mediators essential for tissue repair. In contrast persistent dysregulation of inflammatory responses promotes neuroimmune sensitization, driving the transition from acute to chronic non-specific musculoskeletal pain.

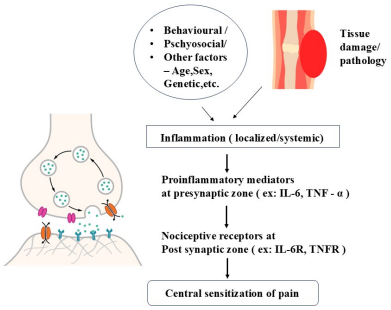

Fig.2: Basic model explaining the interactions of neuroimmune responses in pain sensitization.

3) Osteoporosis associated with Vitamin D : Osteoporosis is a systemic skeletal disease characterized by reduced bone mass, microarchitectural deterioration of bone tissue, resulting in increased bone fragility and susceptibility to fractures. Osteoporosis remains a major global public health problem affecting more than 200 million people over worldwide, the disease burden raises as the population age(10). According to recent estimates up to 9-10 million fragility fractures occur annually, the majority due to osteoporosis, and the number of hip fractures exceeds 10 million in people aged 55 and above in recent global reports. The life time risk of sustaining an osteoporotic fracture remains high: approximately 1 in 3 women and 1in 5 men over the age of 50 will experience atleast 1 osteoporotic fracture including Hip, Vertebral or Wrist fractures as reported by the international osteoporosis foundation (IOF).

3.1. Classification of Osteoporosis : Osteoporosis is classified into primary and secondary types based on factors affecting bone metabolism and remodeling.

- Primary osteoporosis occurs without an identifiable underlying cause and is mainly associated with aging and hormonal changes. It is again subdivided into

Type I (Post menopausal OP) : occurs in women following menopause due to estrogen deficiency, leading to increased bone resorption and predominant loss of trabecular bone. It most commonly results in vertebral compression fractures and distal forearm (colle's) fractures.

Type II (Senile OP) : Affects both men & women in older age due to age related decline in osteoblast function, reduced calcium absorption and decreased Vitamin D synthesis. It involves both cortical and trabecular loss, increasing the risk of Hip and vertebral fractures.

- Secondary osteoporosis arises from identifiable medical conditions, life style factors, that disrupt normal bone remodelling and bone metabolism. Life style related factors including physical inactivity, smoking, excessive alcohol consumption and inadequate intake or absorption of calcium and vitamin D, contribute significantly to reduce bone mass and increased risk fracture. underlying medical conditions such as hyperthyroidism, hyperparathyroidism, Cushing's syndrome, Diabetes mellitus and hypogonadism accelerate bone resorption through hormonal imbalances that adversely affect osteoblast and osteoclast activity. Gastrointestinal disorders, including malabsorption syndromes, celiac

disease, inflammatory bowel disease, and chronic liver disease, impair calcium and vitamin D absorption, leading to defective bone mineralization. Haematological disorders, such as multiple myeloma, leukaemia, and chronic anaemia, promote bone loss through marrow infiltration and increased osteoclastic activity. Neurological and Musculoskeletal conditions, including stroke, spinal cord injury, Parkinson's disease, prolonged immobilization and chronic neuromuscular disorders, contribute to OP primarily through reduced mechanical loading and disuse bone loss. Additionally, rheumatologic and autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis, are associated with OP due to chronic inflammation, cytokine-mediated bone resorption, and long-term use of glucocorticoids (11).

Among these diverge aetiologies, Vitamin D deficiency emerges as a common and modifiable pathway, impairing calcium absorption, secondary hyperparathyroidism, and bone mineralization, thereby playing a central role in the development and progression of osteoporosis.

4) Diagnostic Approach: Early diagnosis is essential for the appropriate management of osteoporosis (OP), as timely detection enables preventive strategies and reduces fracture risk. To date, dual – energy X-ray absorptiometry (DXA) remains the most widely used and validated technique for assessing bone mineral density (BMD) in clinical practice. According to the world health organization (WHO) criteria, Osteoporosis (OP) is defined as a BMD that is 2.5 standard deviations (SD) or more below the mean peak bone mass of young, healthy women (T-score $\leq$ -2.5). Severe OP is defined as a T- score $\leq$ -2.5 SD in the presence of one or more fragility fractures. Although DXA is considered the gold standard for the diagnosis of bone densitometry, it is not always suitable as a screening tool in primary health care settings. Factors such as exposure to ionizing radiation (albeit low dose), the large size of the equipment relatively high costs and limited availability restrict its widespread use. These limitations prevent DXA from serving as a practical population-based screening benchmark for OP management. Consequently, increasing attention has been directed toward the development of reliable pre-screening modalities for OP assessment, particularly quantitative ultrasound (QUS) devices (12,13).

4.1. Radiological assessment : To improve the accuracy of osteoporosis diagnosis beyond BMD assessment, additional imaging modalities have been developed, particularly for detecting vertebral fractures, which are frequently asymptomatic yet clinically significant. Vertebral morphometry has emerged as a valuable quantitative method that involves measuring anterior, middle, and posterior vertebral body heights and calculating relative reductions or ratios to identify compression deformities. These measurements can be obtained from conventional lateral spine radiographs (morphometric X-ray radiography, MXR) or from dual-energy X-ray absorptiometry (DXA) – based images, also known as vertebral fracture assessment (VFA) (13). Accurate identification and labelling of vertebral levels prior to measurement are essential to ensure consistency and reliability, especially in longitudinal follow-up studies.

4.2. Quantitative and semiquantitative evaluation : A combined approach incorporating semiquantitative visual (conventional radiography) assessment (e.g., the Genant grading system) and quantitative morphometric analysis is considered the most reliable strategy for defining vertebral fractures, as it integrates clinical judgment with objective measurement and reduces interobserver variability. However, as highlighted by Kanis et al., the National Osteoporosis Foundation (NOF), and the International Osteoporosis Foundation (IOF), this imaging- based strategy is primarily intended for accurate fracture identification rather than for preventive purposes. (Pisani, 2013)For prevention and risk stratification, emphasis should remain on clinical risk factor assessment and BMD evaluation, often integrated through validated tools such as FRAX.

4.3. Fracture assessment tool : FRAX is a simple screening tool developed in 2008 by the World Health Organization (WHO) collaborating centre, estimates an individual's 10-year probability of major osteoporotic and hip fractures. It incorporates seven readily available dichotomous clinical risk factors – prior fragility fracture, parental history of hip fracture, current smoking, systemic glucocorticoid use, excessive alcohol intake, rheumatoid arthritis, and secondary osteoporosis – entered as "yes" or "no" responses. In addition, FRAX includes age, sex, and body mass index (BMI) in its calculation. Importantly, the tool can estimate fracture

probability even in the absence of bone mineral density (BMD) measurements (14,15).

Conclusion : Vitamin D deficiency represents a significant yet often underrecognized contributor to chronic non-specific musculoskeletal pain (CNMP) and progressive degenerative alterations in bone. Radiological evaluation, supported by clinical and laboratory investigations, provides valuable insights into the structural and metabolic consequences of hypovitaminosis D. The growing global prevalence of Vitamin D deficiency highlights its substantial impact on individuals quality of life, including both physiological and psychological health. Integrating diagnostic approaches with risk assessment tools such as the FRAX model may enhance early identification of individuals at increased risk of osteoporosis-related fractures and falls. Therefore, timely recognition and appropriate management of vitamin D deficiency are essential for improving musculoskeletal health outcomes and reducing long-term skeletal complications.

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