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Review Article

Vitamin D deficiency and disease conditions relevant to: Orthopaedic translation

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ABSTRACT

Vitamin D, traditionally known for its role in calcium-phosphate homeostasis and bone health, is now recognised as a pleiotropic hormone with critical effects on multiple physiological processes. It exists primarily as ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), which are biologically inactive until undergoing a sequential hydroxylation in the liver to form 25-hydroxyvitamin D (calcidiol), and subsequently in kidney to form the active metabolite 1,25-dihydroxyvitamin D (calcitriol). By engaging the vitamin D receptor, it exerts immunomodulatory, neuroprotective, and anti-frailty functions. Deficiency in vitamin D has been implicated in a wide range of disorders, including musculoskeletal weakness, frailty, cognitive decline, autoimmune diseases, and respiratory infections. Vitamin D deficiency affects nearly half of the global population and remains a widespread public health challenge, and effective interventions such as food fortification and targeted supplementation should be prioritized in future strategies.

The translational potential of this article: Vitamin D deficiency represents a modifiable risk factor with implicated effects across systemic, neurocognitive and musculoskeletal systems. Epidemiological evidence links deficiency to increased risk of infection, cognitive decline, frailty and orthopaedic morbidity. In orthopaedic and geriatric populations, maintaining sufficient vitamin D supplementation may reduce fracture and fall risk as well as postoperative complications and infections. These factors are also influenced by vitamin D deficiency-related effects on neurocognition. Vitamin D status may also be relevant in the management of infectious diseases, including respiratory illnesses and COVID-19. This review also discusses mechanistic and practical rationales for clinical translation. Potential interventions include vitamin D co-supplementation, dietary fortification and optimised sun exposure. However, limitations in existing randomised trials underscore the need for consistency in dosing, appropriate formulation, targeted population, as well as baseline deficiency progression status. These insights can guide clinicians, public health policy makers and researchers in developing evidence-based protocols and interventions to reduce vitamin D deficiency-related morbidity.

1. Introduction

Vitamins are critical micronutrients necessary for numerous physiological functions of the human body. Their activities are diverse, including regulation of metabolisms, immunomodulation, and maintenance of cellular homeostasis. Among these vitamins, vitamin D is a unique fat-soluble steroid that functions as both a vitamin and a hormone, and has become one of the most studied micronutrients in modern medicine [1,2]. Vitamin D is a group of chemically related compounds, of which vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are most biologically active. Unlike traditional vitamins that are provided through dietary intake only, vitamin D can be acquired through

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endogenous synthesis induced by exposure to ultraviolet B irradiation as well exogenous dietary intake. This dual mode of acquisition of Vitamin D distinguishes it from other vitamins and reflects its evolutionary importance to human physiology [3,4].

The significance of Vitamin D exceeds far beyond its classical role in calcium and phosphate homeostasis, bone mineralisation, and muscle function. In the last two decades, the discovery that vitamin D receptors (VDRs) are expressed in nearly every type of human tissue has revolutionized our understanding of its pleiotropic actions [5,6]. Vitamin D is a master regulator of many bodily functions, including immune system regulation, inflammatory inhibition, brain and cognitive development, and muscle function [7–9]. This widespread distribution of VDRs, coupled with the extra-renal availability of the vitamin D-activating enzyme 1α-hydroxylase, suggests that a deficiency of the vitamin can have broad health consequences far beyond skeletal well-being [10,11].

Current epidemiological data indicate that vitamin D deficiency has reached pandemic levels, affecting an estimated 1 billion people worldwide across all races and ages [12]. A recent combined analysis of 7.9 million participants from 81 nations showed that 47.9% of the global population suffers from Vitamin D deficiency (<50 nmol/L), of which maximum prevalence was found for the Eastern Mediterranean region (71.8%) [13]. This widespread health issue is attributed to multiple factors, including increasing indoor lifestyle, broad use of sun protection, atmospheric pollution, geographic latitude, and inadequate dietary intake [14,15]. The problem is further complicated by the scarcity of naturally vitamin D-rich foods and the absence of comprehensive fortification programs. Paradoxically, deficiency remains common even in sun-rich regions, challenging the traditional assumptions about Vitamin D status [16,17]. Demographic data show disproportionately high deficiency among elderly, individuals with chronic disease, and orthopaedic patients. Vitamin D status of these groups may directly or indirectly affect postoperative recovery, muscle strength, fall risk and fracture and tendon healing.

The clinical implications of widespread Vitamin D deficiency are profound. Beyond the long-standing consequences of rickets in children and osteomalacia in adults, increasing evidence links inadequate Vitamin D status with increased risk of susceptibility to respiratory infection, autoimmune diseases, cardiovascular disease, some types of cancer, and neurodegeneration [18–20]. Recent studies during the COVID-19 pandemic have reignited interest in Vitamin D 's immunomodulatory properties, highlighting its potential role in infectious disease outcomes. Meta-analyses show that a deficiency of Vitamin D is associated with an 80% increased risk of COVID-19 infection, and that supplementation reduces admission to ICU by 35% and mortality by 46% [21,22]. Moreover, new studies suggest a long-term consequence of a deficiency of Vitamin D during critical periods of development on cognitive outcomes, programming of the immunological system, and subsequent life metabolic health [23,24].

This review aims to synthesize current knowledge on Vitamin D across physiology, molecular and clinical relevance. We address the complex interrelation of Vitamin D status with immunocompetence, survey neurotrophic actions of Vitamin D throughout the life span, discuss its relation to frailty in older persons, and explore the evidence for deficiency being causally linked with many diseases. Additionally, we critically evaluate current strategies including supplementation, fortification, and public health education approaches to address this global deficiency. By integrating recent advances in Vitamin D research with established knowledge, this review provides a holistic perspective on this essential nutrient and identifies key areas for future investigation. By combining mechanistic, epidemiological and translational findings, this review highlights vitamin D as a key area for future research and modifiable factor relevant in orthopaedic medicine, geriatric care, infection prevention and cognitive ageing.

2. Vitamin D and its receptor physiology and pharmacology

2.1. Vitamin D

Vitamin D exists in two main forms, D_2 and D_3 (Fig. 1). Vitamin D_2 is synthesised from yeast irradiation, while Vitamin D_3 is synthesised upon skin exposure to ultraviolet B (UVB) or from animal-based food consumption. Vitamin D_3 has a higher potency than D_2 and is the primary form of Vitamin D in humans [3]. Skin UVB exposure breaks the B ring in 7-dehydrocholesterol, forming pre-D3, which then isomerizes to D_3. Vitamin D_3 then binds to Vitamin D binding protein (DBP) or albumin and is transported in the blood. Hence, serum Vitamin D levels reflect cutaneous Vitamin D produced from UVB as well as dietary Vitamin D [4].

Vitamin D that is derived through food intake or skin UVB absorption is biologically inert. To be converted into its active form, it needs two sequential steps of hydroxylation. Vitamin D is metabolised in the liver to 25-hydroxyvitamin D [25(OH)D] by hydroxylase (CYP2R1). 25(OH)D represents the major circulatory and predominant biomarker for assessing the status of Vitamin D. Subsequently, in the kidneys, it is converted to its active form and locally regulated hormone, 1,25-dihydroxyvitamin D [1,25 (OH)2D], by acting as a substrate for the enzyme 1α-hydroxylase (CYP27B1) [25]. 1,25 (OH)2D production is stimulated by the parathyroid hormone (PTH) and inhibited by high levels of calcium, phosphate and fibroblast growth factor 23 (FGF23), while in non-renal cells, 1,25(OH)2D production is regulated by tumour necrosis factor (TNF-α) and interferon-gamma (IFN-γ). To maintain homeostasis and prevent Vitamin D toxicity, CYP24A1 catabolises Vitamin D to form inactive forms, 24,25 (OH)2D and 1,24,25 (OH)3D [26].

Despite endocrine mechanisms that suggest the role of vitamin D in calcium-phosphate regulation and bone integrity, its benefit was reported to be only present when deficient of vitamin D [27]. This demonstrates that further research needs to be done since physiological sufficiency does not completely translate to universal supplementation as a benefit. Optimization may be needed to target patients with documented deficiency rather than applied uniformly.

2.2. Vitamin D receptor

Physiological actions of $1,25(OH)_2D$ are mediated by the VDR. It is a nuclear hormone receptor that is widely distributed across different body tissues. VDR was initially discovered in cells that are involved in calcium and phosphate homeostasis such as bone, kidney, parathyroid and intestines. They are expressed in non-calcium regulating cells such as skin, immune cells and brain. Upon binding to $1,25(OH)_2D$, VDR heterodimerises with other hormone receptors, especially retinoid X receptors (RXR). Their binding complex then translocate to nucleus to regulate transcription by binding to Vitamin D response elements of DNA. Several coactivators or corepressors also bind to this complex to regulate transcriptional activity. Vitamin D also exerts non-genomic effects such as calcium metabolism *via* membrane VDRs and triggers rapid cellular signal transduction pathways [26]. Despite VDR signaling being a prominent factor in skeletal biology, its mechanistic evidence should be interpreted as biological plausibility, rather than direct clinical benefit for orthopaedic outcomes.

Dysfunctional VDR activation may reduce intestinal intake of calcium and result in the suppression of osteoblast-driven mineralisation, leading to fragility in skeletal structures. Orthopedically, disruption of vitamin D and VDR signalling has been associated with delayed healing of fracture, reduced tendon-to-bone healing capacity, and increased susceptibility to falls [28–30]. This highlights the receptor's direct translational implications in regard to surgical outcomes and orthopaedic rehabilitation. VDR signalling within skeletal muscle can contribute to reduction of fall-risk and increase fracture rehabilitation.

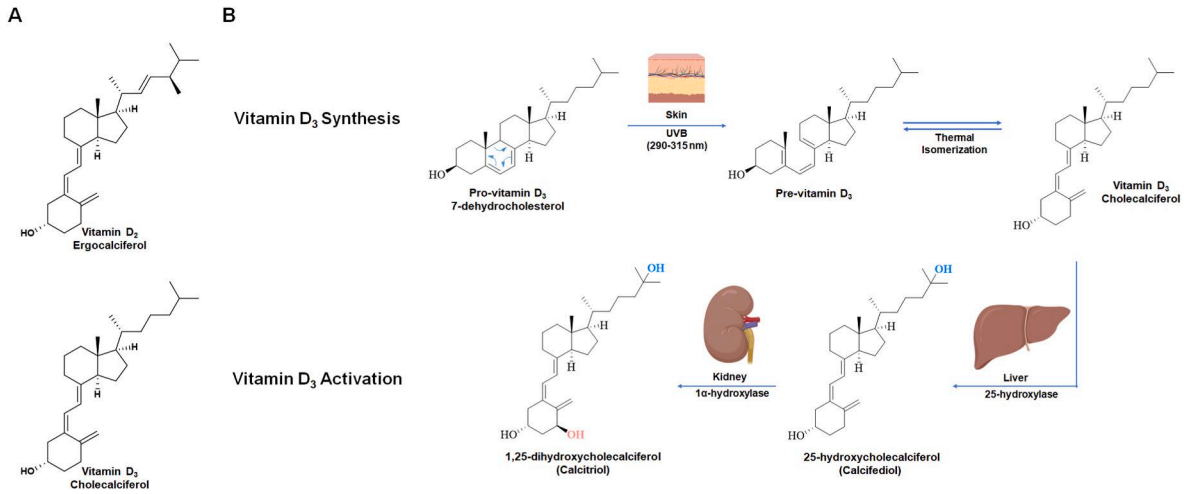

Fig. 1. Structure and synthesis of vitamin D. (A) Chemical structure of vitamin D_2 and vitamin D_3. (B) Endogenous synthesis and activation pathway of vitamin D_3.

2.3. Clinical relevance to orthopaedic physiology

Vitamin D deficiency is prevalent in orthopaedic surgical patients, and has previously been documented in orthopaedic cohorts related to impaired postoperative recovery [31]. Six studies showed that the lack of vitamin D was significantly associated with bone non-union in orthopeadic surgery. However, six other studies pointed towards no clear relationship between the two, describing vitamin D as a risk modifier instead of a determinant for clinical outcome [31]. This evidence supports a correlation of Vitamin D deficiency in orthopaedic patients rather than routine vitamin D supplementation.

Vitamin D also plays an important role in musculoskeletal stability, osseointegration and fall-risk reduction, especially within geriatric populations [31]. Altogether, these data demonstrate the potential of vitamin D in peri-operative assessments in orthopaedic optimization, while also highlighting the importance of addressing deficiency rather than universal supplementation.

3. Vitamin D immuno-modulation

3.1. Overview

Vitamin D has long been recognised for its significant role in maintaining calcium homeostasis and bone health. However, recently it has emerged as a critical immunomodulator of the immune system. Immune cells express VDR and CYP27B1, which allows for the active form of Vitamin D (1,25D) to interact with VDR [32]. Vitamin D can regulate both innate and adaptive immunity, antimicrobial defence, inflammation, and immune tolerance. Key mechanisms are the induction of antimicrobial peptides, regulation of macrophage inflammatory polarity, and modulation of T-cell tolerance. Clinically, these are pathways that may potentially influence orthopaedic infection risk, operative wound healing, and fracture inflammation. These mechanisms provide context for biological plausibility and are not guaranteed the proof of clinical outcomes.

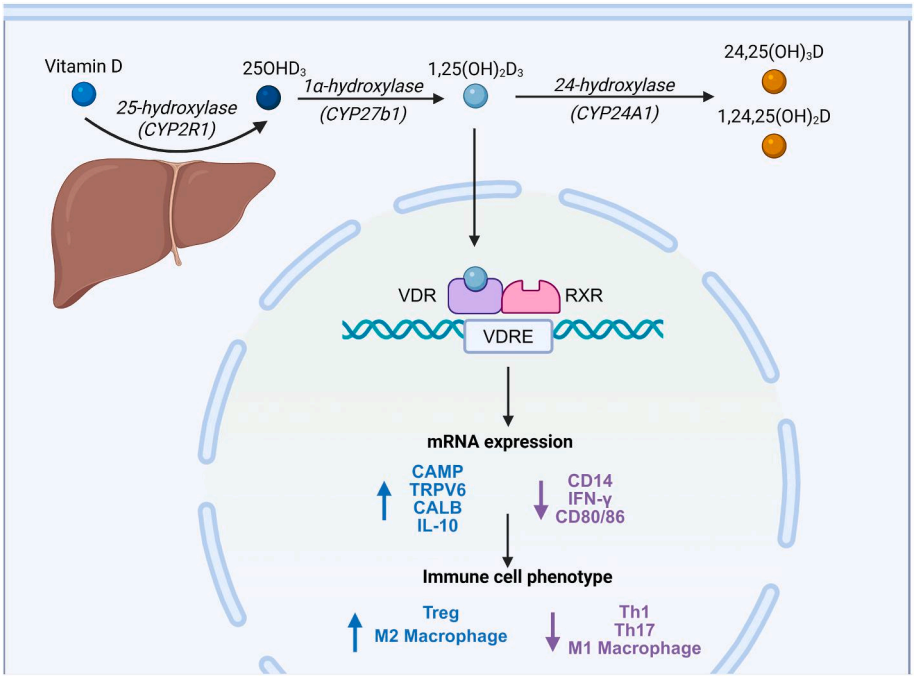

Fig. 2. Vitamin D metabolic pathway and gene expression regulation.

3.2. Vitamin D and innate immunity

Vitamin D can regulate innate immunity through genomic or VDR-mediated transcription and non-genomic pathways that include the induction of antimicrobial peptides. In terms of genomic effects, 1,25D binds to VDR and RXR to form a complex then entering the nucleus and attaching to specific areas of DNA to regulate gene expression such as the cathelicidin antimicrobial peptide gene (Fig. 2) [33]. In a study conducted on titanium surfaces, it was found that the lack of induced LL-37 levels, an active peptide derived from CAMP, inhibited *Staphylococcus aureus* biofilm formation and development to more mature biofilm stages. This study also provided implications of Vitamin D and its downstream products' influence on orthopaedic implant materials [34].

Vitamin D also modulates macrophage activity. Macrophages are the key cells in innate immune responses, exhibiting functional plasticity, being able to switch from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype. One study that assessed the effect of Vitamin D on diseased macrophages showed that increased Vitamin D suppressed M1 polarisation, while increasing M2 polarisation of macrophages [35].

Dendritic cells are critical antigen-presenting cells that play a large role in initiating immune responses. These innate immune cells bridge innate and adaptive immunity. Vitamin D can induce dendritic cells to become tolerogenic, enabling them to suppress T cell activation and proliferation. Vitamin D is able to mitigate dendritic cell maturation, which reduces molecules such as CD40/CD86 and other pro-inflammatory interleukins such as IL-23 from over-activating T cells [36]. However, the underlying mechanisms remain unclear.

3.3. Vitamin D and adaptive immunity

Vitamin D also modulates adaptive immunity through the regulation of T-cell differentiation and B-cell function. In the context of T-cells, usual infections trigger Th1 and Th17 T-cells that cause inflammation. However, evidence shows that active Vitamin D is able to reduce these inflammatory T-cells and boost regulatory T-cells (Tregs) that control T-cell inflammation [37]. The active form of Vitamin D can crosstalk between dendritic cells and T-cells as 1,25D-treated dendritic cells become tolerogenic, producing cytokines that promote the development of certain regulatory T-cells [38]. Dysregulation of T-cells due to deficiency may lead to increased inflammatory signaling and affect processes relevant to fracture signaling processes.

B-cells are another type of immune cell that is modulated by 1,25D. B-cells are important for their ability to produce antibodies that tackle bacteria and viruses. Vitamin D in its active 1,25D form prevents the differentiation of B-cells into antibody-secreting B-cells, reducing autoantibody production [38]. Furthermore, Vitamin D upregulates IL-10, a cytokine that dampens excessive immune response [38]. Although these findings support that Vitamin D promotes immune tolerance, most of the studies are done *in vitro*. Next steps to take include extending into more large-scale human trials to confirm the speculated functions of Vitamin D. Human studies could focus on causality and therapeutic dosing of Vitamin D. The influence of Vitamin D on adaptive immune effects is largely mechanistic and do not indicate direct clinical orthopaedic benefits.

3.4. Orthopaedic infection & biofilm relevance

The immunomodulatory impact of vitamin D provides context for why its deficiency is often associated with postoperative infection risk in clinical orthopaedic settings, especially periprosthetic joint infection (PJI). Lower levels of 25(OH)D were found in many arthroplasty cohorts and has been linked with increased susceptibility to PJI [39]. Arthroplasty studies showed significantly lower serum 25-hydroxyvitamin D levels in patients who had PJI when compared to patients that were undergoing primary arthroplasty [40]. This correlation provides clinical context for Vitamin D-dependent regulation of antimicrobial peptides and innate immune responses.

The biological mechanism for this vulnerability may be largely due to the translational evidence indicating that vitamin D signalling is responsible for regulating antimicrobial defense pathways. It was shown that stimulation with 1,25-dihydroxyvitamin D increased the secretion of antimicrobial peptides, such as LL-37 [41]. This shows a potential biological plausibility between vitamin D deficiency and implant infection risk but does not directly prove clinical insight.

Analyses of orthopaedic trauma also highlight vitamin D deficiency to negatively impact immune responses and cause increase post-operative vulnerability. Acute postoperative decline of vitamin D levels has been shown to persist during high levels of inflammatory stress [42]. These findings frame vitamin D deficiency to be an immunomodulatory condition that may potentially promote early immune containment and peri-implant biofilm formation.

3.5. Vitamin D and autoimmunity

Vitamin D plays a crucial immunomodulatory role in autoimmune diseases by modulating immune cell function and suppressing inflammatory pathways. Vitamin D deficiency has been associated with increased risk of autoimmune diseases, notably multiple sclerosis (MS). Recent research has shown the association among Vitamin D, Epstein–Barr Virus (EBV) infection, and immune dysregulation in Multiple Sclerosis (MS). EBV is a leading trigger for MS, and Vitamin D deficiency can exacerbate MS by limiting the control of $CD8^+$ T cells on EBV [36]. Vitamin D can promote the number and function of $CD8^+$ T cells, limiting the number of EBV-infected B cells [36]. Vitamin D may influence immune regulation that is relevant to preventing and mitigating MS.

4. Vitamin D and brain function

Vitamin D is functions as a key neurosteroid for maintaining normal brain physiology and homeostasis [43,44]. It's neurological role is supported by the co-localised expression of VDRs and 1α-hydroxylase in both neuronal and glial cells across the cerebral cortex, substantia nigra, hippocampus, thalamus and hypothalamus [45–49]. These distributions are similar in adult humans and rats [50]. Mechanistically, Vitamin D contributes to brain function and offers neuroprotection by regulating calcium signalling, neurotrophic factors, neurotransmission and synaptic plasticity [51]. Hence, cognitive and motor control necessary for balance and fall prevention may be indirectly influenced by vitamin D, with direct implications for orthopaedic outcomes.

Vitamin D affects cognitive processes across the lifespan. In the developing brain, Vitamin D exerts genomic and non-genomic effects that modulate neuronal proliferation, axonal connectivity, dopaminergic system ontology and neurotransmitter release. Maternal Vitamin D status during gestation alters offspring brain morphology and physiology. Hence, these changes can occur from as early as foetal and perinatal stages [52,53]. In neonatal brains of Sprague–Dawley rat models, Vitamin D deficiency led to increased cell proliferation but decreased neuronal differentiation [52,54,55], along with morphological changes such as longer and thinner cortices with enlarged lateral ventricles [52]. In contrast, Vitamin D deficient C57Bl/6J mice exhibited reduced lateral ventricle volumes [56–58], suggesting potential strain-specific effects of Vitamin D. These Vitamin D-induced neurodevelopmental changes may underline long-term risk for neurological disorders [53].

Vitamin D is also responsible for the development and maturation of the dopaminergic system. Cell culture SH-SY5Y/VDR + models showed enhanced neurite outgrowth, synapse number, branching and dopamine release following Vitamin D addition [59]. In Vitamin D deficient rats, foetal mesencephalon nuclear receptor related 1 protein (Nurr1) and p57kip2a expressions, key dopaminergic differentiation factors, were significantly reduced [60]. Furthermore, the ratio of Nurr1 positive cells

in the substania nigra pars compacta was higher than ventral tegmental area. Nerve growth factor (NGF) and glial-derived neurotrophic factor (GDNF), essential for cognition and neuroprotection, were also down-regulated [52,61,62]. These molecular and physiological changes are linked to neurodevelopmental disorders, including schizophrenia [63–65], Attention-Deficit/Hyperactivity Disorder (ADHD) [66], and autism [67].

4.1. Vitamin D and neurocognition

Vitamin D affects cognitive processes across the lifespan. In vitro vitamin D application increased neurite outgrowth in primary cortical and embryonic hippocampal neurons [68] and dopaminergic maturation effects [59] linked to optimal motor coordination and executive function. During neurodevelopment, vitamin D regulates neuronal proliferation, differentiation and synaptic formation. Maternal vitamin D deficiency led to increased cell proliferation but decreased differentiation in neonatal rodents [49–51]. Some studies also reported longer and thinner cortices and enlarged lateral ventricles [49,52], while others showed reduced lateral ventricle volumes [52,56–58], suggesting potential strain-specific effects of vitamin D. Restoring vitamin D at conception improved locomotor activity and interaction time with novel objects [69–71], while postnatal supplementation increased hippocampal neurogenesis and cognitive improvement [72]. Hence, beyond its cognitive implications, hippocampal dysfunction in vitamin D-deficient individuals may lead to impaired memory and spatial cognition and indirectly contribute to increased fall risk and fracture susceptibility.

Human studies similarly suggest that maternal vitamin D influences cognitive and motor outcomes. Higher gestational [73], cord [74] and prenatal Vit D levels are associated with improved language [75,76] and cognitive scores [73–75]. Lnfants born to mothers with >30ηg/ml 1,25 $(OH)_2D_3$ concentrations exhibited higher mental and psychomotor scores [77], compared to those with deficiency. These studies suggest that Vitamin D supplementation during pregnancy influences offspring cognition.

Vitamin D deficiency in early childhood has been linked to impaired neuromuscular integration, with lower cognitive-adaptive and language-social task scores [78] as well as impaired problem-solving and gross motor task [79]. Genetic variation in vitamin D binding protein further modulates these associations that influence both cognitive and motor performance in preschool children [79]. Therefore, data suggest that vitamin D supports shaping neurocognitive and psychomotor development implicated with lifelong coordination, postural control and balance.

4.2. Orthopaedic relevance of vitamin D and cognitive function in ageing

Age-related cognitive impairment contributes to falls and gait impairments, which in turn increases fracture risk. Midlife vitamin D intake is associated with improved working [80–82], learning [82] and verbal memory [82,83] as well as executive function [80–82] and attention [82,83]. In elderly adults, Vitamin D supplementation enhanced short-term memory [80] and overall cognitive performance [84–86] while mitigating depressive symptoms [85,86]. These effects are thought to be mediated by Vitamin D's anti-inflammatory or anti-oxidative properties [87]. In a 12-month randomised clinical trial in elderly individuals with mild cognitive impairment, Vitamin D supplementation reduced oxidative stress by increasing telomere length of leukocytes and also improved Full Scale Intelligence Quotient [88]. However, not all clinical studies report improved [89,90], likely reflecting heterogeneity in study design, dosage, baseline deficiency status and participant characteristics.

Although exercise combined with cognitive training has been found to improve gait performance, vitamin D supplementation of 4000 IU/day did not confer additional cognitive or gait benefit [91]. High doses have also been found to negatively affect cognitive processing [92]. This is consistent with evidence that vitamin D supplementation primarily benefits those are deficient, while effects in sufficient individuals are limited [93]. Nevertheless, studies highlight a known association between vitamin D and cognition [94].

Meta-analyses of randomised trials indicate that daily vitamin D supplementation of 800 – 1000 IUD/day [95] and ≥700 IU/day reduced fall incidence in older adults [96]. Peterson et al. [97] and Lopez et al. [98] also found an association between vitamin D and reduced falls; however, this reduction is not fully explained by muscle strength, gait or balance. Instead, these findings point to a potential cognition-mediated mechanism, where adequate vitamin D supports executive function that influences gait and fall risk. Clinically, this highlights the importance of assessing vitamin D status alongside cognitive function in older adults at risk of falls and fractures, instead of relying solely on motor function assessments.

The relationship between vitamin D, cognition and gait remains inconclusive. While some studies found that low vitamin D levels were associated with reduced gait speed [99], others demonstrate no significant effect [97,98]. Recent evidence also indicated a U-shaped relationship where both low and high vitamin D levels are associated with poorer outcomes. For example, maximum cognition score and minimum walking time was reported at 28.09 ng/mL and 31.42 ng/mL, respectively [100], suggesting an optimal physiological range rather than a maximal dosage. These findings reinforce that vitamin D may indirectly influence gait and fall risk *via* cognition, with important implications for perioperative care and fall prevention in orthopaedic patients. However, given the insufficiency of current evidence, the extent to which vitamin D supplementation improves gait and fall risk in the ageing population requires further validation through well-controlled trials integrating musculoskeletal and neurocognitive outcomes.

5. Vitamin D, frailty, and orthopaedic outcomes vitamin D and frailty

5.1. Vitamin D and frailty

Vitamin D deficiency and frailty are highly prevalent in older adults and are common signs of biological ageing (Table 1). Frailty is characterised by reduced multisystem physiological reserve, increased vulnerability to endogenous and exogenous stressors and heightened risk of falls, disability, morbidity and mortality [101,102]. The Fried Frailty Phenotype assesses weight loss, exhaustion, reduced grip strength, physical activity and gait speed, whereas the Rockwood and Mitnitski Frailty Index quantifies accumulated health deficits to include clinical symptoms, disabilities and diseases [90]. Together, these frameworks highlight the multifactorial avenunes through which vitamin D may influence frailty risk.

Vitamin D plays roles in neuromuscular, immune, metabolic and skeletal pathways that influence frailty. Decreased serum vitamin D promotes muscle wasting *via* proteolytic pathways, including ubiquitin-proteasome, autophagy-lysosomal pathways [30,103] and renin/angiotensin systems [104,105]. Although skeletal muscles express low levels of nuclear VDR expression, vitamin D/VDR signalling regulation remains essential for muscle proteostasis, calcium handling, myogenesis [106] and cell senescence [105]. *In vitro*, VDR knockdown impairs myogenic proliferation, differentiation and overall myoblast cell regulation [107], highlighting the importance of vitamin D for early-stage myogenic differentiation and myotube size [108]. VDR knockout and vitamin D-deficient mice displayed weaker grip strength, upregulated E−3 ubiquitin ligase [109,110] and heightened proinflammatory cytokine release [110]. These changes mirror hallmarks of physical decline observed in frail individuals.

In elderly, low baseline $1,25(OH)_2D_3$ (25 nmol/L) was linked with increased muscle mass loss, and after adjusting for mortality, significantly associated with sarcopenia [111]. Haemodialysis patients given

Table 1
Summary of studies investigating the effects of Vitamin D on frailty.

Type of Study	Author	Number participants	Type of subjects	Meanage	Frailty assessment	Vit D assessment	Duration	Result
Prospective cohort	Zhang et al., 202472	287926	55.9% female	58 years	Frailty index (Rockwood and Mitnitski)	Serum 1,25(OH)$_2$D Vit D levels using electro-chemiluminescence	Baseline 4 years (2006–2010) and follow-up 1 year (2012–2013)	Higher serum VitD is associated with decreased frailty.
Cross-sectional	Alvarez-Ríos et al., 201573	592	All female	72 years	Fried physical frailty phenotype	Serum 1,25(OH)$_2$D levels using electro-chemiluminescence	Approx. 3 years (June 2006-September 2009)	Frail women had lower VitD.
Cross-sectional	Gotaro Kojima et al., 201674	152	All male	70 years	34- item Frailty Index	Serum 1,25(OH)$_2$D levels using electro-chemiluminescence	1 year (2011-2012)	Frail men were more likely to be VitD deficient and had lower 25(OH)D levels
Randomized control	Gagesch et al., 202375	2157	56.5% female	74.3 years	Fried physical frailty phenotype	Randomly assigned 2000 IU/d Vit D3 and measured serum 1,25(OH)$_2$D levels using electro-chemiluminescence	3 years of follow-up	No relationship between frailty and 25(OH)D levels
Cross-sectional	Sousa-Santos et al., 201876	1447	57.8% female	74 years	Fried physical frailty phenotype	Serum 1,25(OH)$_2$D levels using electro-chemiluminescence	Approx. 6 months (December 2015 - June 2016	Frailty and obesity were both associated with low serum 25(OH)D
Randomized control trial	Cai et al., 202277	687	44% female	77.1 years	Fried physical frailty phenotype	Randomly assigned to 200, 1000, 2000 or 4000 IU/d cholecalciferol (vitamin D3) supplementation	2 years (2017-2019)	High-dose VitD supplementation did not prevent frailty progression
Longitudinal	Bolzetta et al., 201778	4421	58% female	61.3 years	Study of Osteoporotic Fracture (SOF) index	Daily VitD consumption questionnaire	8 years	VitD supplementation was not associated with reduced frailty risk
Longitudinal	Xiong et al., 202279	1944	46.8% male	85.06 years	Study of Osteoporotic Fracture (SOF) index	Serum 1,25(OH)$_2$D levels using electro-chemiluminescence	2011	Positive association between frailty and cognition (Mini-Mental State Examination scores)
Prospective cohort	Ensrud et al., 201180	1606	All male	73.8 years	Modified Fried physical frailty phenotype	Serum 1,25(OH)$_2$D levels using chromatography tandem mass spectroscopy	Approx 2 years (March 2000- April 2002) and 4.6 years follow-up	Lower serum 25(OH)D levels associated with baseline frailty at baseline but not with progression over time
Cross sectional	Gutiérrez-Robledo, 201681	331	54.1% female	79.3 years	Fried physical frailty phenotype	Serum 1,25(OH)$_2$D levels using ELISA	3-year follow-up	Low 1,25(OH)$_2$D levels increased the likelihood of frailty
Randomized control trial	Orkaby et al., 82	25057	50.7.% female	67.2 years	Frailty index (Rockwood and Mitnitski)	. Randomly assigned to 2000 IU/d cholecalciferol (vitamin D3) or omega-3 supplementation	Approx 3 years baseline (November 2011- March 2014) and 3 years follow-up to December 31, 2017.	VitD or omega-3 fatty acid supplementation did not prevent frailty
Cross sectional	Krams et al., 201683	321	60.2% female	82.94 years	Modified Fried physical frailty phenotype	Serum 1,25(OH)$_2$D levels using electro-chemiluminescence.	Approx. 8 months (January-September 2013)	No significant association between 1,25(OH)$_2$D levels and frailty
Prospective cohort	Wong et al., 201384	4203	All male	70-88 years	5-point FRAIL (fatigue, resistance, ambulation, illness and weight loss) scale	Serum 1,25(OH)$_2$D levels using electro-chemiluminescence.	5.3 years	Low 1,25(OH)$_2$D levels linked to prevalence and incidence of frailty

1,25(OH)$_2$D$_3$ showed greater thigh muscle surface area and strength compared to those receiving 1,25(OH)$_2$D$_3$ analogue [112]. Therefore, these data indicate that reduced serum 1,25(OH)$_2$D$_3$ influences muscle strength, physical activity and muscle atrophy [112–114].

5.1.1. *Muscular effects of Vitamin D in frailty*

Human studies support the link between vitamin D deficiency and muscle atrophy. Vitamin D-deficient patients with chronic low back pain had significantly increased pAkt and *Atrogin-1* but decreased FoxO3a, a key regulator of ubiquitin-proteasome degradation [115]. This demonstrates the activation of catabolic pathways central to muscle wasting. In osteoarthritis patients, quadriceps muscle biopsies from patients' individuals with lower strength showed elevated VDR, DBP, albumin and FoxO1. The increase in albumin, a circulating liver-derived protein, along with elevated DBP, suggests increased blood perfusion to the muscle as a compensatory response. This may support the muscle by supplying more vitamin D and DBP, potentially counteracting inflammatory stress, reflected by increased FoxO1 [116]. Furthermore, among patients undergoing arthroscopic rotator cuff repair, lower serum vitamin D levels correlated with lower isokinetic muscle performance in abduction and external rotation. However, there was no link between serum vitamin D levels, functional outcomes or VDR expression [117].

5.1.2. *Skeletal effects of Vitamin D in frailty*

Vitamin D is essential for bone health, and hence frailly outcomes [101]. Vitamin D/VDR signaling in small and large intestinal cells

triggers the opening of the calcium channel TRPV6, leading to increased Ca^{2+} uptake and absorption. VDR activation also stimulates Receptor Activator for Nuclear Factor κB Ligand expression and osteoclastogenesis, regulating metabolism of calcium stores in bones and release into blood. Therefore, insufficient vitamin D levels lead to bone demineralisation, calcium and phosphate loss and skeletal [118], while severe deficiency leads to rickets and osteomalacia [119].

Animal models consistently demonstrate the skeletal impact of vitamin D. Mice given 20,000 IU/kg versus 1000 IU/kg or 8000 IU/kg of Vitamin D_3 exhibited improved mechanical bone properties, including failure stress and higher post-yield strain and toughness. Vitamin D deficiency also significantly increased bone cementum resorption but decreased deposition [120]. Göttingen Minipigs fed with low calcium without Vitamin D had a negative calcium balance and exhibited significant loss in bone mineral density, higher osteoid surface and serum 1, $25(OH)_2D_3$ and increased $1,25(OH)_2D_3$ likely induced by calcium insufficiency that downregulates the biomarker of bone turnover, parathyroid hormone (PTH) [120]. Circulating $1,25(OH)_2D_3$ had also been linked to bones toughness and ductility [121].

Vitamin D deficiency also accelerates intervertebral disc degeneration through Sirt1 downregulating which in turn lowers extracellular protein synthesis and increases extracellular matrix protein degradation. Conversely, vitamin D/VDR signalling can activate Sirt1 deacetylase, which leads to NF-κB inflammatory pathway inhibition and exerts protective effects in intervertebral disc degeneration [122]. Furthermore, 1, $25(OH)_2D_3$ upregulates Sirt1 expression through VDR receptor binding, and hence vitamin D deficiency has been found to downregulate Sirt1 expression and accelerate bone loss and subsequently elevate oxidative stress and osteocyte senescence in bone marrow-derived mesenchymal cells. This evidence highlights a potential therapeutic target in treating osteoporosis [123]. Preclinical work demonstrates that the senolytic agent, ABT263, selectively targets senescent bone marrow cells. ABT263 administration in mice led to increased bone density, volume and trabecular number and thickness [124]. Emerging evidence also suggests that in osteoarthritic and osteoporosis patients, vitamin D and K indirectly reduce cartilage degradation. This exhibits a dual action in inhibiting osteoclast genesis and mitigating subchondral bone remodelling. Although these treatments alone did not give favourable results [125], these studies highlight that vitamin D and related pathway targets show therapeutic potential in frailty-related conditions such as osteoarthritis and osteoporosis.

Human evidence on the skeletal benefits of Vitamin D are more context. In prediabetic males, Vitamin D supplementation was protective against femoral neck bone mineralisation density (BMD) loss [126] and in premenopausal women, elevated serum $1,25(OH)_2D_3$ levels upregulated bone mineral mineralisation [127]. Vitamin D-fortified bread improved lumbar spine and hip BMD in older adults while lowering serum PTH [128]. Furthermore, osteopenia and osteoporosis patients demonstrated elevated femoral neck and total hip bone mineral density and reduced cross-linked C-telopeptide (β-CTX) and PTH [128]. Conversely, high-dose Vitamin D without calcium is linked to increased $1,25(OH)_2D_3$ metabolism and may reduce BMD [129]. Several studies suggest that high intermittent doses of vitamin D are linked to increased fall and fracture risk, with benefits primarily observed in vitamin D-deficient individuals [130–132].

5.1.3. Orthopaedic relevance of Vitamin D and frailty

Frailty has major orthopaedic implications, given its association with falls, fractures and sarcopenia. Observational studies link vitamin D deficiency with frailty risk, yet evidence for supplementation in frailty prevention is mixed. In a cohort of 444,382 participants, vitamin D levels below 43.618 nmol/L significantly increased the risk of frailty. Each incremental rise in vitamin D units reduced the risk of transitioning from robust to pre-frailty or frailty, while increasing the likelihood of transition from frailty to pre-frailty. Women over 60 years with low vitamin D exhibited a higher risk of developing frailty than men, likely reflecting menopause-related hormonal changes and osteoporosis [90]. Frail women with high-terminal propeptide of type I procollagen (PINP) and low 1,25(OH)2D3 had a 5.85-fold increase in frailty risk, identifying PINP and vitamin D as potential therapeutic orthopaedic targets [101]. Low baseline vitamin D levels in older men were also significantly associated with frailty [76,78], however, not a greater risk of frailty status at 4.6 years [78]. One study reported low vitamin D $<$ 52.9 nmol/L as an independent predictor of increased frailty in older men and as well as all-cause mortality up to 9.2 years [133]. These may suggest that vitamin D is a causal factor or a marker of poor health, reduced outdoor activity and sunlight exposure or underlying chronic disease.

Randomized controlled trials showed thatDaily supplementation of 2000 IU/day vitamin D alongside 1g marine omega-3 and physical activity in older adults lowered the risk of becoming pre-frail over a period of three years, though this was only observed with combined intervention [102]. Low dose vitamin D (e.g 384 IU/day), however, did not lower frailty [134,135] likely due to pre-existing supplementation, unassessed serum vitamin D or insufficient dosing. High dose vitamin D supplementation, while reducing the risk in some contexts, does not consistently prevent or attenuate frailty, falls or gait speed.

Overall, while animal and mechanistic studies strongly support vitamin D in maintaining musculoskeletal health and mitigating frailty, human clinical data reveal a context-dependent effect. This may be due to inconsistencies in baseline deficiency, dosing, co-interventions and individual characteristics. From an orthopaedic perspective, these findings emphasise the importance of vitamin D screening in older adults, particularly in those at risk of falls, fractures, osteoarthritis or low muscle strength. Clinically, optimising vitamin D within a safe physiological range may support bone healing, rehabilitation, fall prevention and recovery after orthopaedic surgery. Given the variability in trial outcomes, supplementation strategies should avoid high intermittent doses and instead prioritise daily regimens tailored to deficiency status, comorbidities and functional orthopaedic goals.

5.2. Impact of vitamin D on surgical and post-traumatic healing

5.2.1. Vitamin D and fracture prevention

Fractures are a major consequence of frailty, particularly in patients with a low bone mineral density or a history of frailty. Falls are common among the elderly and contribute to fracture risk which are also associated with mortality and morbidity. Vitamin D plays key roles in bone metabolism, muscle function and bone-tendon integrity, making it a potential modifiable factor in fracture prevention and recovery [136].

Vitamin D has been widely studied for its potential to prevent and lower fracture risk. A recent meta-analysis with over 58,000 participants found that vitamin D3 and calcium co-supplementation significantly reduced falls. This may likely be due to effects in calcium homeostasis, bone resorption and muscle function [136]. Contrarily, a study by Grant et al. [137] reported that neither alone nor combination supplementation of 800 IU/day vitamin D3 or 1000 mg calcium reduced further fractures in elderly patients [137].

Calcium and vitamin D co-supplementation has also been shown to elevate bone mineral density in osteoporosis patients [138]. However, other studies report no difference in fall outcomes with vitamin D supplementation, whether administered alone or with calcium [139,140]. Vitamin D2 and D3 have both been associated with reduced fall incidence [141], though some studies found no benefit [142]. This discrepancy may be due to differences in the ability of vitamin D3 to raise serum levels more effectively than D2. Daily vitamin D supplementation appears more effective in fall prevention compared to intermittent supplementation. High intermittent doses (over 800 IU) may increase fall incidence [136]. While most of those studies focused on primary fall and fracture incidence, evidence for secondary prevention is limited.

5.2.2. Effect of Vitamin D on fracture healing

Hypovitaminosis D is prevalent among fracture patients and may affect fracture healing [143]. Preclinical osteoporosis studies demonstrate that vitamin D supplementation improved biomechanical and fracture callus remodelling [29]. Clinical trials in patients with hip fractures indicate that vitamin D supplementation supports fracture union and functional recovery [144,145]. In a phase II randomised trial, low-dose vitamin D showed no effect on healing, while high-dose supplementation demonstrated moderate improvements in acute tibia and femoral shaft fractures, as assessed by clinical (FiX-IT) and radiological union (RUST) [146]. Other studies found no difference in fracture healing, wound issues, reoperation and infections between supplemented and placebo groups. Despite numerous studies suggesting promising preclinical results, translation of vitamin D in clinical fracture healing shows mixed results, which may be due to non-randomisation, reverse causality and unaccounted confounding factors [29]. These mixed results highlight the need for adequately powered randomised controlled trials that assess baseline serum vitamin D level and calcium supplementation and adherence.

5.2.3. Effect of Vitamin D on spinal fusion

Vitamin D deficiency has been implicated as a risk factor for pseudoarthrosis and linked to unfavourable spinal fusion outcomes [147]. Sufficient pre- and post-surgical vitamin D status may therefore support bone union following spinal fusion. Ravindra et al. [148] reported significantly longer spinal fusion times in patients with pre-existing vitamin D deficiency. Vitamin D deficiency was also found to be an independent predictor of non-union rates after multivariate adjustment [148]. Observational data also suggested a negative correlation between vitamin D levels and Cobb angle [149]. In adolescent idiopathic scoliosis, vitamin D deficiency has also been associated with increased pain and reduced function following spinal fusion surgery [150]. Randomised control trial evidence further supports these observations. Postoperative vitamin D supplementation in elective spinal surgery patients has been shown to shorten fusion time, improve spinal function and reduce pain outcomes. A significant negative correlation was also reported between fusion time and both preoperative and postoperative (3 and 6 months) vitamin D levels [147]. However, no difference in fusion rates was observed at 1-year postoperative follow up between the intervention and control groups. This finding reflects the relatively low proportion of patients who were vitamin D deficient preoperatively, with only 23.5% and 47.1 % classified as preoperative deficient and insufficient, respectively [147]. This limits the capacity to accurately detect both short and long-term differences in a largely vitamin D-deficient population. Although vitamin D supplementation in deficient patients appears to accelerate fusion following spinal surgery [151], further well-designed randomised control trials are needed to clarify its role in enhancing long-term fusion outcomes following spinal surgery.

5.2.4. Effect of Vitamin D on tendon healing

VDR are expressed in tendons and suggest a role of vitamin D in tendon biomechanics and healing. This relationship between tendon healing and vitamin D is particularly relevant to injuries such as the rotator cuff that require arthroscopic or open surgical procedures for repair. Although vitamin D deficiency may lead to poor tendon and bone healing outcomes, the evidence is limited and weakened by methodological inconsistencies across studies. Retrospective studies report that, irrespective of age and sex, vitamin D-deficient orthopaedic patients are more likely to experience rotator cuff re-tear within a year of rotator cuff repair [152]. Preoperative deficiency was also linked to a higher risk of re-tear following rotator cuff repair [28]. Furthermore, low serum vitamin D in patients who underwent rotator cuff repair was linked to low serum vitamin D one-year post-surgery [117]. Conversely, some studies reported no significant association between vitamin D levels and rotator cuff tear or repair [153] and vitamin D and revision surgery following rotator cuff repair [154]. There is a predominance of studies investigating rotator cuff repair, likely due to its high incidence, highlighting a key gap regarding other tendons and limiting generalizability. Overall, these findings suggest that optimising vitamin D status may support tendon healing, but further high-quality studies are needed.

5.2.5. Effect of Vitamin D on prosthetic osseointegration and aseptic loosening

Vitamin D plays a critical role in the biological interface between bone and orthopaedic implants, significantly affecting both the initial osseointegration and its long-term stability. Vitamin D deficiency is associated with lower baseline function and suboptimal osseointegration and has been associated with an up to fourfold increase in early implant failures [155].

The clinical impact of vitamin D status is evident in both joint arthroplasty and dental implantology. A study on patients undergoing total hip arthroplasty found its sufficiency had achieved better osseointegration (94.3%) than deficient patients (81.6%). The latter group also demonstrated more post-operative complications such as delayed healing and implant loosening [156]. A meta-analysis also reported vitamin D deficiency to be associated with a 76% increased risk of aseptic loosening [157]. Functional outcomes in deficient patients were also significantly worse at 6 and 12 months postoperatively, with the association between vitamin D deficiency and complications being the strongest in patients with serum levels <10 ng/mL [157]. Severely vitamin D deficient patients undergoing dental implantation also saw the highest implant loss rate of 11.1% [158].

Importantly, this is a modifiable risk. Presurgical vitamin D supplementation has been shown to improve implant osseointegration and bone-implant-contact (BIC), promote peri-implant bone preservation, and reduce early implant failures, even among high-risk populations, such as diabetics [155]. A review on osseointegration in dental implants reveals a similar trend, showing successful implantation following Vitamin D3 supplementation, even in severe deficiency cases [158]. Another study also domenstrated significantly improved bone density following post-surgical vitamin D supplementation for up to 12 weeks [159]. Collectively, these findings highlight that optimising vitamin D status improves implant osseointegration and the long-term success of prosthetic interventions.

5.3. Clinical management pathways for orthopaedic patients

Translating vitamin D research into better orthopaedic outcomes require assessment and management strategies that reflect its established muscular and skeletal effects. Evidence reviewed above shows that vitamin D contribute to muscle strength, postural stability and neuromuscular coordination that contribute towards frailty and fracture and fall risk. This is supported by studies that report on the biomechanical role of vitamin D in bone mineralisation, calcium-phosphate homeostasis and osteoblast function. Therefore, the routine assessment of baseline serum vitamin D level can be justified in elderly, frail and orthopaedic patients as well as individuals with fractures, tenon injuries or a history of falls. Clinical decision-making should consider baseline vitamin D deficiency, supplementation history, age, sex, comorbidities, functional status and frailty severity.

In clinical practice, structured care pathways such as Fracture Liaison Services (FLS) and perioperative care bundles help improve treatment, reduce future fractures and related comorbidities and health care burden. Patients admitted with fragility, frailty, fractures or orthopaedic injuries should undergo baseline assessment of serum vitamin D levels, using chemiluminescent microparticle immunoassay technology, as part of a comprehensive bone evaluation [160]. Incorporating vitamin D screening and supplementation into standardised admission, fracture clinic, and preoperative protocols reduces variability in care and optimises early support for musculoskeletal recovery. Within these pathways, vitamin D supplementation can be initiated according to

recommended dosing strategies and levels routinely monitored across preoperative, postoperative, discharge and follow-up stages. This approach allows management of fall risk, osteoporosis, and rehabilitation planning to provide a multidisciplinary strategy to orthopaedic practice, especially for older, frail and high-risk populations. In addition, routine data captured within FLS frameworks allow evaluation of outcomes such as fracture healing, mobility and function recovery, further strengthening evidence-based clinical implementation.

Existing evidence points towards a moderate daily supplementation of 800 – 1000 IU/day of vitamin D [95] in combination with 1000 mg calcium [137] to have positive improvements on muscle performance, falls, bone health and fracture risk. These collectively strengthen frailty and fracture outcomes. Steady daily dosing of vitamin D is further highlighted by high intermittent or bolus dosing reports showing inconsistent benefits and, in some cases, increased fall and fracture risk [136,161,162].

Some of these findings align with the recent expert consensus on vitamin D based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [163]. The report emphasised that serum vitamin D level testing is the most accurate way to determine vitamin D status, with ≥50 nmol/L considered to be sufficient and ≥75 nmol/L recommended for patients with osteoporosis. However, unlike the studies discussed, the consensus report recommends a more conservative intake of ≤400 IU/day with 1000 mg calcium. This reflects broader population safety considerations, whereas orthopaedic and frailty-focused studies emphasise functional outcomes that respond to relatively higher daily doses in the range of 800 – 1000 IU/day vitamin D. For high-risk adults over 50, the consensus report suggests ≥800 IU vitamin D and 1200 mg calcium, aligning with orthopaedic recommendations for frailty and fracture outcomes. Within the GRADE framework, the evidence supports to assess and correct vitamin D status in deficient high-risk orthopaedic patients, while evidence for routine supplementation in vitamin D-replete populations remains limited, favouring targeted rather than universal clinical recommendations.

When implementing vitamin D and calcium supplementation in orthoepic pathways, clinicians must also consider risks such as nephrolithiasis and hypercalcemia associated with calcium and vitamin D, respectively. Furthermore, high or bolus doses of vitamin D have also been linked to elevated fall and fracture risk. Taken together, integrating daily adequate vitamin D supplementation and routine serum assessment may be beneficial in frail or high-risk adults for muscle function, bone quality, fracture and fall risk, as well as post-injury recovery.

6. Vitamin D deficiency and disease conditions

6.1. Vitamin D deficiency as a disease risk factor

Apart from its classic role in calcium and bone homeostasis, Vitamin D is increasingly recognised as a potent immunomodulator [164]. Its deficiency has been linked to a wide range of conditions, including infections, Alzheimer's disease, and COVID-19, owing to its role in regulating inflammation, neuroinflammatory pathways, amyloid-beta metabolism, and oxidative stress [18,165].

Moreover, Vitamin D deficiency has important implications for orthopaedic practice. Bogunovic et al. [166] demonstrated that Vitamin D is important for bone health and muscle function and reported that 43% of patients scheduled for orthopaedic surgery had insufficient Vitamin D levels, with deficient levels common across trauma, sports, arthroplasty, and foot-and-ankle services. There low serum levels of Vitamin D within the adult orthopaedic surgery population may negatively affect surgical and functional outcomes [167]. Furthermore, postoperative respiratory complications are particularly prevalent in older orthopaedic patients. Lee and Kim found that pneumonia is a serious complication following hip fracture surgery and is associated with markedly longer hospitalisation and higher mortality [168]. Consequently, vitamin D deficiency is emerging as a significant risk factor for both systemic and neurological diseases.

6.2. Vitamin D deficiency and cognitive impairment

VDRs are expressed in multiple brain regions including the hippocampus, cortex, thalamus, hypothalamus, substantia nigra, and amygdala and are important for cognitive function [169]. Vitamin D exerts pleiotropic effects in neurons, astrocytes, and microglia, including antioxidant and anti-inflammatory actions that may influence neurotransmission and neuroprotection, all processes essential for maintaining cognitive health [7,170,171]. Furthermore, Vitamin D readily crosses the blood-brain barrier and can act directly on neurons and glial cells [172].

Epidemiological evidence strongly links Vitamin D deficiency to cognitive impairment and dementia risk. Sommer et al. [20] conducted a meta-analysis of five studies and found that individuals with severe Vitamin D deficiency had a 54% increased risk of developing dementia. Similarly, Kalra et al. [164] found that Vitamin D levels below 25 nmol/L were linked with a 33% increased risk for all-cause dementia and 87% increased risk for Alzheimer's disease. Etgen et al. [18] reported an odds ratio of 2.39 for cognitive impairment in vitamin D-deficient individuals, based on pooled data from previously published studies, thereby highlighting a consistent association across diverse populations [18,173–179]. However, there are still inconsistencies, partly because of the difference in the study designs and Vitamin D cut-off levels [180,181].

Vitamin D exerts a neuroprotective effect through several pathways. It regulates neuroinflammation by reducing pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, which are processes that are central to Alzheimer's disease pathology [172]. Rao et al. [182] note that Vitamin D inhibited activation of NLRP3 inflammasome, hence preventing excessive inflammation and promoting amyloid-β clearance. Keeney & Butterfield [183] reported that Vitamin D supplementation reduced amyloid-β production and toxicity, while enhancing its degradation and clearance by microglia. Animal studies also reveal that Vitamin D preserved synaptic proteins and memory performance in models that are exposed to amyloid-β [184,185]. Additionally, Vitamin D exerts an antioxidative effect by reducing oxidative stress and protecting mitochondrial function, preventing neurodegeneration [9].

However, despite strong biological plausibility and consistent epidemiological associations, large-scale randomized controlled trials (RCTs) have not demonstrated clear cognitive benefits from Vitamin D supplementation. The Finnish Vitamin D Trial (FIND, 2025), a 5-year double-blind RCT involving 2493 older adults randomised to 1600IU/day or 3200IU/day of Vitamin D_3, reported no significant reduction in dementia or alzheimer's disease compared with placebo [47]. Similarly, major trials including VITAL-COG and DO-HEALTH, which examined cognitive trajectories in more than 4000 older participants over 2-4 years, found no improvement in global cognition, executive function, memory, or composite cognitive scores despite adequate dosing [166].

From a clinical and orthopaedic perspective, cognitive impairment is highly relevant because it alters musculoskeletal risk and recovery profiles, especially in older adults. A systematic review by Seitz et al. demonstrated that dementia and cognitive impairment are significant risk factors for hip fractures, with most studies showing an approximate doubling of fracture risk [19]. Furthermore, cognitive impairment predicts poorer rehabilitation trajectories, greater dependence, and higher likelihood of hospitalisation after orthopaedic injury and surgery [19]. This highlights that Vitamin D deficiency, through its association with cognitive decline may indirectly contribute to orthopaedic morbidity by increasing fall risk, fracture incidence, postoperative complications, and impaired recovery. From an orthopaedic translational perspective, these findings support the role of Vitamin D deficiency as a clinical risk marker rather than a direct therapeutic target, helping to identify patients at higher risk of falls, fracture, postoperative complications, and delayed functional recovery.

Nevertheless, randomised controlled trials in humans showed mixed results, with some showing no significant cognitive benefit from Vitamin D supplementation, emphasising the need for higher-quality research to understand its therapeutic potential [180]. This area of previous research has been summarised in Table 2.

6.3. Vitamin D deficiency and respiratory infections

Vitamin D has emerged as an important modulator of both innate and adaptive immunity, with deficiency implicated in higher susceptibility to infections. 1,25D is synthesised locally in immune cells like macrophages and dendritic cells, where the gene involved regulates antimicrobial defence, including those encoding cathelicidin (CAMP/LL37) and β-defensin 2 [8,186]. In addition, Vitamin D signalling suppresses proinflammatory cytokines such as IL-6 and TNF-α, which helps to prevent excessive inflammation during infections [8,187–190]. This would enhance the pathogen clearance while modulating inflammatory responses, underlying the proposed protective role of Vitamin D in infectious diseases.

Low Vitamin D has been shown to link with increased rates of various infections, including respiratory infections. Gaudet et al. [191] reported that Vitamin D deficiency is prevalent among individuals with chronic airway diseases and that supplementation may reduce bacterial and viral colonisation of the lungs. The importance of Vitamin D deficiency in respiratory infections was highlighted in the observational studies that consistently reported an independent association between low serum concentrations of 25(OH)D and susceptibility to acute respiratory infection [192,193]. For example, Martineau et al. [194] highlighted that daily Vitamin D supplementation reduced the risk of respiratory infections, especially the risk of asthma exacerbations. However, the findings across trials remain inconsistent, with some studies showing no significant benefit, especially when the supplementation was given intermittently instead of every day.

The role of Vitamin D in tuberculosis (TB) has been widely studied. Kafle et al. [195] conducted a meta-analysis of meta-analyses, demonstrating that individuals with TB have 3.23 times higher chances of Vitamin D deficiency compared to the healthy controls. Moreover, 1, 25D improves mycobacterial killing by upregulating cathelicidin and inducing autophagy in macrophages [3,8,195]. Tabsh and Bilezikian [196] highlighted that Vitamin D is important to innate immune response to TB and emphasised social factors of health that might link to Vitamin D deficiency and TB risk, like malnutrition and limited sun exposure. The Vitamin D modulation of antimicrobial peptides like CAMP/LL37 and β-defensin 2 plays an essential role in defending against several bacterial and viral pathogens, underscoring its significance as an immune regulator in infectious diseases [8]. However, randomised trials that are investigating Vitamin D supplementation for infectious disease prevention remain inconsistent, indicating the need for more high-quality research.

During the COVID-19 pandemic, it was hypothesised that Vitamin D deficiency might contribute to increased susceptibility and severity of SARS-CoV-2 infection due to its role in regulating innate and adaptive immune responses and modulating inflammation [91]. Exposure to sunlight, which drives the endogenous Vitamin D production, was suggested as a factor in geographical differences in the COVID-19 mortality rate [197].

Epidemiological studies showed a significant association between low vitamin D levels and worse COVID-19 outcomes. Wang et al. [198] found that Vitamin D deficiency was associated with a significantly higher risk of mortality (OR 2.47, 95% CI 1.50-4.05) and a higher rate of hospital admissions (OR 2.18, 95% CI 1.48-3.21) among COVID-19 patients. Similarly, Pereira et al. [199] reported that severe cases of

Table 2
Summary of studies investigating the effects of Vitamin D on cognition.

Type of study	Author	Number of Participants	Type of Subjects	Age	Cognitive Assessment	Vit D Assessment	Duration	Results
Prospective Cohort	Afzal et al., 2014	*10,186*	General population (Denmark)	Median 57–58 (range 47–65)	ICD codes, hospital discharge records	Plasma 25(OH) D (nmol/L)	~30 years	Serious Vit D deficiency ↑ dementia risk (RR 1.27; CI 1.01–1.60)
Prospective Cohort	Graf et al., 2014	*615*	Elderly hospitalized patients	Mean 85.3	DSM-IV, clinical assessment	Serum 25(OH) D (nmol/L)	2 years	Serious Vit D deficiency ↑ dementia risk (OR 1.35; CI 0.39–4.64)
Retrospective Cohort	Knekt et al., 2014	1006	General population (Finland)	Mean 62.6	National registers (ICD)	Serum 25(OH) D (nmol/L)	29 years	Serious Vit D deficiency ↑ dementia risk (RR 2.08; CI 1.20–3.60)
Prospective Cohort	Littlejohns et al., 2014	1658	Older adults (U. S.)	Mean 73.6	DSM-IV, NINCDS-ADRDA	Serum 25(OH) D (nmol/L)	5.6 years	Serious Vit D deficiency ↑ dementia risk (RR 2.25; CI 1.23–4.12)
Prospective Cohort	Schneider et al., 2014	1174	Older adults (U. S.)	Mean 73.3	DSM-IV, NINCDS-ADRDA	Serum 25(OH) D (nmol/L)	10 years	Serious Vit D deficiency ↑ dementia risk (RR 1.44; CI 0.65–3.20)
Prospective Cohort	Annweiler et al., 2010	40	Elderly (France)	Mean 78.4	DSM-IV for dementia diagnosis	Serum 25(OH) D (nmol/L)	7 years	Non-AD dementia strongly linked to Vit D deficiency (OR 19.57; 95% CI 1.11–343.69)
Cross-sectional	McGrath et al., 2007	4809	NHANES III participants (USA)	60–90	Learning & Memory Task	Serum 25(OH) D; <25 nmol/L	Baseline	Cognitive impairment OR 1.83; 95% CI 1.45–2.29
Cross-sectional	Llewellyn et al., 2009	850	Community-dwelling elderly (UK)	~85	MMSE	Serum 25(OH) D (nmol/L)	Baseline	Cognitive impairment OR 2.03; 95% CI 1.23–3.35
Cross-sectional	Annweiler et al., 2011	80	Geriatric inpatients (France)	≥65	MMSE & DSM-IV	Serum 25(OH) D (nmol/L)	Baseline	Cognitive impairment OR 2.21; 95% CI 1.10–4.43
Cross-sectional	Llewellyn et al., 2011	4809	Reanalysis of NHANES III (USA)	60–90	Cognitive battery & MMSE	Serum 25(OH) D (nmol/L)	Baseline	Cognitive impairment OR 1.60; 95% CI 1.23–2.08
Prospective Cohort	Llewellyn et al., 2010	858	InCHIANTI study (Italy)	≥65	MMSE & TICS	Serum 25(OH) D (nmol/L)	6 years	Incident cognitive decline HR 1.60; 95% CI 1.11–2.30
Prospective Cohort	Slinin et al., 2010	1604	MrOS (elderly men, USA)	Mean 74.5	3MS & Trails B	Serum 25(OH) D (nmol/L)	4.6 years	Incident cognitive decline HR 1.25; 95% CI 1.02–1.53

COVID-19 presented 65% higher odds of Vitamin D deficiency compared to mild cases (OR 1.65, 95% CI 1.30-2.09). However, there was no significant association between Vitamin D deficiency and the risk of contracting COVID-19 itself, which shows that Vitamin D may not influence infection susceptibility but rather the disease progression. Further, Shah et al. [200] observed that Vitamin D supplementation decreased the chances of mortality by 52% (OR 0.48, 95% CI 0.346-0.664) and reduced the need for ICU care and mechanical ventilation. However, Wang et al. [198] concluded that evidence for supplementation reducing severity or mortality remains inconclusive due to heterogeneity and potential confounding factors. Pereira et al. [199] also highlighted that low Vitamin D levels were showed to link to increased proinflammatory cytokines, including IL-6 and C-reactive protein, which were strongly associated with COVID-19 progression.

Randomised controlled trials evaluating Vitamin D supplementation for respiratory infections have produced mixed and often inconclusive results, despite strong observational associations. A meta-analysis of RCTs by Martineau et al. [19] showed that Vitamin D supplementation moderately reduced the risk of acute respiratory infections, with the greatest benefit observed among individuals receiving daily or weekly dosing rather than large bolus doses. However, these protective effects have not translated to viral respiratory infection such as COVID-19. In a double-blind RCT involving 240 hospitalized patients with moderate to severe COVID-19, Murai et al. [201] found that a single high dose of Vitamin D_3 (200 00 IU) failed to reduce hospital length of stay compared with placebo, and showed no significant differences in mortality, ICU admission, or need for mechanical ventilation. Together, these findings demonstrate substantial heterogeneity across trials, suggesting that while Vitamin D may influence respiratory immune responses, current RCT evidence does not support its consistent therapeutic benefit in acute respiratory infections or COVID-19, especially when administered as intermittent high-dose supplementation.

Beyond infection risk, respiratory illnesses create downstream consequences that are highly relevant to orthopaedic outcomes. Pneumonia commonly results in rapid loss of mobility and functional autonomy. In a cohort of older adults, 67.4% death or functional decline within 30 days of pneumonia hospitalisation, with substantial increases in disability across activities such as walking [202]. Such hospitalisation-associated disability is frequently prolonged or irreversible. Chronic or recurrent respiratory disease contributes to accelerated sarcopenia, with studies showing that hypoxic and inflammatory environments impair muscle metabolism, reduce skeletal muscle mass, and weaken functional capacity in conditions like Chronic Obstructive Pulmonary Disease (COPD) [203]. This respiratory-driven musculoskeletal decline directly elevates risks of falls, fractures, and prolonged rehabilitation needs. Therefore, the link between Vitamin D deficiency and respiratory infections carries indirect orthopaedic implication: Vitamin D deficient individuals experience more frequent or severe infections, which in turn precipitate mobility loss, sarcopenia and fall-related orthopaedic morbidity. In orthopaedic populations, particularly older adults, respiratory illness-associated deconditioning is an important contributor to fracture risks, delayed rehabilitation, and prolonged hospitalisation. Thus, vitamin D deficiency may have indirect orthopaedic relevance by identifying patients' vulnerability to infection-related functional decline rather than serving as a stand-alone intervention for respiratory infection related disease.

In addition, although observational data consistently link low Vitamin D status to worse COVID-19 outcomes, randomised controlled trials remain inconclusive, and further high-quality research is required to determine whether Vitamin D supplementation can be recommended as an adjunctive treatment for COVID-19 [198–200].

Overall, Vitamin D deficiency has been increasingly linked to various disease conditions, ranging from cognitive impairment to infectious diseases. While epidemiological studies highlight compelling associations, mechanistic insights provide biological plausibility for these links. However, the inconsistency of findings across interventional trials underscores the need for further rigorous research to determine whether Vitamin D supplementation can be clinically recommended for these conditions. This area of previous research has been summarised in Table 3.

7. Preventing and managing vitamin D deficiency in orthopaedic practice

Vitamin D deficiency is highly prevalent in orthopaedic patients and has direct relevance to bone healing, neuromuscular function, and postoperative recovery. While epidemiologic studies strongly associate low 25(OH)D levels with increased fall and fracture risk, this is not reflected in large randomised clinical trials (RCTs). This section summarises the biological basis of sourcing vitamin D, clarifies the discrepancy between observational and trial data, provides clinical pathways for addressing deficiency in orthopaedic care, and also outlines the roles of diet and sunlight exposure.

7.1. Sourcing vitamin D

Vitamin D_3 is synthesised in the skin from 7-dehydrocholesterol upon ultraviolet B (UVB) exposure and is also found in animal-based foods such as fatty fish, egg yolks, and liver. In contrast, Vitamin D_2 is plant-derived, occurring mainly in mushrooms, yeast, and lichen [204]. Following either endogenous production or dietary intake, Vitamin D (D_2 and/or D_3) is biologically inactive and must undergo two hydroxylation steps: first in the liver to form 25-hydroxyvitamin D (25(OH)D or calcidiol) – the major circulating and storage form – and subsequently in peripheral tissues to produce the active hormone 1,25-dihydroxyvitamin D ($1,25(OH)_2D$ or calcitriol) The latter has a shorter half-life and acts *via* intracrine, autocrine, and paracrine signalling mechanisms, regulating gene expression in tissues such as bone, intestine, kidney, and immune cells [1,205].

Serum 25(OH)D concentration is considered to be the gold-standard biomarker for assessing Vitamin D status [1]. Current clinical thresholds classifies values $<$ 50 nmol/L ($<$20 ng/mL), 50-75 nmol/L (20-30 ng/mL) as insufficient, and $\geq$75 nmol/L ($\geq$30 ng/mL) as sufficient. Measuring total 25(OH)D does not usually differentiate between D_2 and D_3 forms [206].

Under optimal environmental and behavioural conditions, cutaneous synthesis accounts for the majority of vitamin D supply [207]. However, individuals with acute orthopaedic injury or major surgery tend to have limited UV exposure, mobility and nutritional intake. Hence, deficiency is highly prevalent in hip-fracture admissions, fragility-fracture patients, and those recovering from orthopaedic procedures [31,208,209]. In these populations, maintaining adequate vitamin D status becomes clinically relevant for fracture healing, neuromuscular recovery, and postoperative rehabilitation.

7.2. Epidemiology versus randomised trails: reconciling the evidence

Epidemiological research consistently shows low serum 25(OH)D to be strongly associated with an increased risk of bone and functional complications, including higher rates of falls, fractures, sarcopenia, and impaired postoperative recovery [210–212]. Observational studies also link deficiency with increased morbidity and mortality [213]. On the other hand, large RCTs in generally healthy adults with sufficient vitamin D intake, demonstrate little to no benefit of routine supplementation on musculoskeletal status or mortality. For instance, the VITAL trial reported no reduction in total, nonvertebral, or hip fractures under daily vitamin D_3 supplementation in midlife and older adults [214].

Several factors may help reconcile why associations appear strong in epidemiology while RCT findings remain largely neutral. Firstly, baseline deficiency plays a critical role. Meta-analytical data indicates vitamin D supplementation reduces fall risk primarily in individuals

Table 3
Summary of studies investigating the effects of Vitamin D on respiratory infections and COVID-19 outcomes.

Type of study	Author	Number of Participants	Type of Subjects	Age	Respiratory/ Clinical Assessment	Vit D Assessment	Duration	Results
Observational (Cohort)	De Smet et al., 2020	186	Hospitalized COVID-19 patients (Belgium)	Mean 69	Mortality, ICU admission, disease severity	Serum 25(OH)D at admission	Hospital course	Severe Vit D deficiency associated with higher mortality and ICU admission.
Observational (Cohort)	Carpagnano et al., 2020	42	ICU COVID-19 patients (Italy)	Mean 65	Mortality and need for mechanical ventilation	Serum 25(OH)D	Hospital course	81% of ICU patients were Vit D deficient; deficiency linked to worse prognosis.
Observational (Cohort)	Baktash et al., 2020	105	Hospitalized older adults with COVID-19 (UK)	Mean 81	Disease severity, oxygen need, mortality	Serum 25(OH)D at admission	Hospital course	Vit D deficiency strongly associated with increased disease severity.
Retrospective Multicenter	Alipio, 2020	212	PCR-confirmed COVID-19 patients (Philippines)	Mean ~60	Clinical severity (mild/moderate/ severe)	Serum 25(OH)D	Hospital course	Higher Vit D levels linked to milder COVID-19 and lower progression risk.
Randomized Controlled Trial	Entrenas Castillo et al., 2020	76	Hospitalized COVID-19 patients (Spain)	Mean 53	ICU admission, mortality	Calcifediol (0.532 mg on day 1, then 0.266 mg on days 3 & 7)	Hospital course	High-dose calcifediol significantly reduced ICU admission; trend toward lower mortality.
Randomized Controlled Trial	Rastogi et al., 2020 (SHADE)	40	Mild-moderate COVID-19 (India)	Mean 50	Disease severity, viral clearance	60,000 IU/day oral cholecalciferol × 7 days	2 weeks follow-up	High-dose cholecalciferol led to faster viral clearance and fewer severe progressions.

with a baseline 25(OH)D of below 50 nmol/L, namely those with insufficient baseline levels [215]. In fact, in these individuals, pooled analyses report a relative risk reduction of approximately 23%. In contrast, RCTs recruiting generally healthy patients with largely replete vitamin D, such as VITAL, show minimal effect. Dosing regimen also influences the outcome. While intermittent or high-dose bolus strategies have been shown to be ineffective for preventing fall risk, potentially even increasing the risk; daily supplementation, particularly in combination with calcium, produces more stable serum levels and better biological responses [130,215,216]. Dose-response studies have demonstrated that intakes within the range of around 1000-4000 IU vitamin D_3 is more reliable for reaching target 25(OH)D concentrations in deficient adults than lower doses [217,218]. Effect modifiers, including obesity, age, institutionalisation, chronic disease burden, mobility limitations, and co-nutrient status, also influence both the baseline vitamin D level and response to supplementation [219]. Since routine supplementation shows benefit for deficient individuals but offers little benefit in replete populations, a test-and-treat strategy is the most appropriate approach in orthopaedic pathways [208,220].

7.3. Clinical pathways for preventing and treating vitamin D deficiency in orthopaedic patients

Orthopaedic patients require timely correction of deficiency to align with the fracture-healing and perioperative window. Hence, serum 25 (OH)D test should be performed at key decision points, including at admission for hip or fragility fracture, preoperative screening for arthroplasty or spinal fusion, and evaluation of delayed or non-union [210–212,221]. Patients found to be deficient should undergo treatment to correct for their deficiency.

The vitamin D dose required to address deficiencies varies depending on the severity of the deficiency and the patient's own underlying risk factors. However, in any case, Vitamin D_3 is preferred as it produces higher and more sustained serum concentrations than Vitamin D_2, supporting a more reliable correction [222]. As previously mentioned, daily dosing is recommended and for deficient adults, doses between 1000 and 4000 IU per day if able to effectively raise serum 25(OH)D into the sufficient range in adults [130,215–218]. However, in the case of severely deficient patients with a serum level <30 nmol/L (<12 ng/mL), initial supplementation for 8 weeks with a daily dosage of 6000 IU or 25,000–50,000 IU weekly is recommended. Once serum 25(OH)D levels exceed 75 nmol/L (30 ng/mL) and is considered sufficient, a daily maintenance dose of 1000-2000 IU is recommended. For high-risk patients who are deficient, such as those with obesity, undertaking medication or with malabsorption syndrome, a higher daily dose of 10,000 IU and a maintenance dose of 3000-6000 IU may be necessary [223].

Operationalising vitamin D repletion in acute post-fracture inpatient settings necessitates more intensive dosing strategies to ensure repletion within the perioperative window. An example is the protocol followed by the Massachusetts General Hospital (MGH) FLS for patients with osteoporotic fractures and a vitamin D deficiency of ≤19 ng/mL. Patients are given doses of 50,000 IU vitamin D_2 orally daily for 3-7 days, followed by maintenance vitamin D_3 of 1000-1500 IU daily. This approach was shown to effectively raise 25(OH)D levels, highlighting that the acute setting may need significantly higher loading doses [160].

Adequate calcium and dietary protein intake should also be ensured, particularly in frail or sarcopenic patients, in order to support musculoskeletal outcomes. Monitoring may include reassessment of 25(OH)D at 8–12 weeks and checks of calcium and renal function. In cases of malabsorption or hepatic impairment, calcidiol may be considered as an alternative formulation. However, the evidence of better clinical outcomes remains limited, and vitamin D_3 should remain the primary therapy for most orthopaedic patients [224].

7.4. Role of food fortification and sun exposure

Food fortification and sunlight exposure both contribute to baseline vitamin D status at the population level. The systematic fortification of dairy and select staple foods has shown increased average serum 25(OH) D concentrations as demonstrated by countries such as the United States, Canada, and the Nordic nations [225–229]. However, fortified foods typically only provide 100-200 IU/day, this is insufficient for correcting the deficiency in orthopaedic patients who generally require at least 1000 IU/day or structured high-dose regimens for timely repletion [230–235]. While cutaneous synthesis of Vitamin D_3 *via* UVB exposure is a major physiological source of vitamin D, it is also rather unreliable as its effectiveness is variable and substantially reduced by ageing, darker skin pigmentation, seasonal variation, and limited time outdoors – a common situation for fragility-fracture and postoperative patients [225, 236–238]. Hence, both fortification and sun exposure should be

considered to be supportive public-health measures rather than therapeutic strategies (Fig. 3).

7.5. Health economics and equity in vitamin D management

The financial burden of orthopaedic complications represents a significant portion of modern healthcare expenditure and the integration of vitamin D management into standard orthopaedic care serves as a critical healthcare opportunity. Five million surgical procedures are performed annually in the United Kingdom's (UK) National Health Service (NHS), and postoperative complications increase expenditure by approximately 200% [239]. Vitamin D deficiency (<30 ng/mL) was found up to 90% of orthopaedic patients and closely correlated with greater infection rates. Notably, postoperative vitamin D levels have been shown to decline by as much as 40%, exacerbating existing deficiency at a time when infection risk is increasing [42]. Data from the MGH FLS revealed vitamin D deficiency to be associated with longer hospital stays and higher 30-day-readmission risk [160]. A previous study found that almost 22% of patients with serum 25(OH)D levels ≤11 ng/mL develop at least one complication after periacetabular osteotomy [240]. Another study on patients undergoing total shoulder arthroplasty, reported the associations between vitamin D deficiency and a high rate of periprosthetic fractures at 90 days, with similar trends persisting a year later [241]. Given that for most surgical procedures, regardless of complications, expenditure exceeds income, addressing modifiable risk factors that influence hospital stay and readmission, such as vitamin D deficiency, is a fiscal necessity.

Economic modelling demonstrates that targeted supplementation is a high-value strategy. Using a Markov health state transition model shows that treating adults aged ≥60 with 800 IU/day of vitamin D3 is estimated to save approximately £420 million over 5 years [242]. This is achieved by preventing 190,000 major falls, avoiding 84,000 person-years of long-term care, and reducing mortality, with the greatest gains seen in those aged ≥75 years [242]. In Ireland, a study investigating the cost-effectiveness of vitamin D3 supplementation in adults aged ≥50 with year-round vitamin D deficiency, showed cost-per-QALY (Quality-Adjusted Life Year) below the usually acceptable threshold of €20, 000/QALY. The intervention was most cost-effective in adults ≥70 years, with a cost/QALY of approximately €5400 [243].

From an equity perspective, vitamin D status is a modifiable determinant of health outcomes that disproportionately affects vulnerable groups. While therapeutic measures are essential in the hospital setting, population-wide strategies such as food fortification can better address broader social disparities. An economic evaluation of a population-wide vitamin D and calcium food fortification programme in Germany concluded an annual net cost saving of €315 million by preventing over 36,000 fractures in the German female population aged ≥65 years, alone [244].

Integrating vitamin D optimization into orthopaedic care pathways allows for a transition from reactive treatment to proactive risk mitigation. While public health measures such as food fortification raises the population baseline, targeted therapeutic intervention is necessary to safeguard patient outcomes. Addressing vitamin D deficiency as a surgical priority not only improves clinical recovery but also helps to reduce socioeconomic health disparities and ensure long-term fiscal sustainability although further GRADE-informed evidence is needed.

8. Conclusion

Vitamin D deficiency is a significant public health concern linked to frailty, cognitive impairment and increased risk of infection, fractures and falls, particularly among the ageing population. As such, its role extends beyond calcium and bone metabolism to include regulation of immune response, neuroprotection and bone-muscle function.

Vitamin D plays a crucial role in innate and adaptive immunity. Through promoting antimicrobial peptide production, supporting tolerogenic dendritic cells, and regulating T-cells, Vitamin D modulates inflammation and immune tolerance [33,35,36]. Vitamin D deficiency has been linked to heightened pro-inflammatory states [199], impaired pathogen clearance [46], and increased risk of autoimmunedisease [36], highlighting its importance for immune health. Lower preoperative vitamin D levels are repeatedly reported with higher postoperative infection risk, likely due to reduced LL-37-mediated antimicrobial activity and impaired biofilm control at implant surfaces [39,41]. Host defence may also be compromised due to an acute postoperative decline in vitamin D status during inflammatory stress [42]. These highlight the orthopaedic translation of sufficient vitamin D in infection prevention and inflammation control and determine postoperative outcomes.

Beyond immunomodulation, Vitamin D deficiency is associated with impaired cognition [69], language development [75,76] and increased risk of neurodegenerative and psychiatric disorders [20,164,245–249]. As such, evidence demonstrates that Vitamin D influences neuronal growth, synaptic plasticity [59], neurotransmitter regulation [60] and neuroprotection [172]. Evidence from both human and animal studies links Vitamin D deficiency to altered brain morphology [52–55],

Common ways of Vitamin D Intake and their Advantages and Disadvantages

	Description	Advantages	Limitations	Public Health Impact
Food Fortification 	Direct addition of VitD to foods (e.g. milk, bread, oils) and biofortification (e.g. UV-irradiated yeast/mushrooms)	• Passive & population wide • Proven historical efficacy • Scalable & cost effective	• Limited food variety • Regulatory challenges in some regions	High: WHO and FAO-endorsed long-term strategy
Supplementation 	Oral intake of VitD or 25(OH)D₃ in tablets, capsules, drops, or sprays	• Targeted correction • Rapid effect in deficient individuals	• Adherence issues • Quality control concerns • Not suitable for broad population-level prevention	Moderate: effective in clinical scenarios
Sunlight Exposure 	Cutaneous VitD₃ synthesis under UVB radiation	• Natural & self-regulating • No dietary intake required	• Influenced by latitude, season, skin pigmentation, sunscreen use	Variable: dependent on geography & lifestyle

Fig. 3. Comparison of three primary vitamin D intake strategies, their advantages and disadvantages, and impact on public health.

dopaminergic system development [60] and increased risk of dementia [164] and Alzheimer's disease [20,245]. However, randomised trials yield mixed results, underscoring the need for high-quality, standardised clinical studies to validate the therapeutic potential of Vitamin D.

Vitamin D deficiency is highly prevalent in older adults and contributes to key components of frailty, such as sarcopenia and increased risk of fractures. Vitamin D/VDR signalling regulates muscle proteostasis, calcium handling, and myogenesis [106], while supporting bone mineralisation through calcium absorption and osteoblast activity [118]. Vitamin D deficiency leads to increased muscle protein degradation and inflammation. Although animal models robustly support these mechanisms, human studies show inconsistent results, likely due to variability in Vitamin D status, dosing and population differences. These factors may also explain the context-dependent results seen in clinical studies that highlight the role of vitamin D in influencing falls, fractures and functional capacity. Maintaining sufficient daily vitamin D intake appears more clinically beneficial than high intermittent dosing, reinforcing its relevance in frailty management, musculoskeletal health and orthopaedic care [136,250,251]. Vitamin D deficiency is also linked to increased susceptibility and severity of infectious diseases, particularly respiratory tract infections such as tuberculosis [195] and COVID-19 [199]. Vitamin D induces antimicrobial peptides like cathelicidin and defensin and mitigates excessive inflammation by suppressing IL-6 and TNF-α, proinflammatory cytokines [8,187–190]. Although meta-analyses have found reduced acute respiratory infection risk with vitamin D supplementation, translation of these effects is limited. These may be attributed with inconsistencies among intervention trials highlighting the need for further validation before clinical recommendations for Vitamin D supplementation can be made.

Vitamin D deficiency is common in orthopaedic patients and has important implications for fracture healing, neuromuscular function, and postoperative recovery [210–212]. While epidemiological studies consistently associate low serum 25(OH)D levels with adverse musculoskeletal outcomes, large, randomized trials in largely vitamin-D-replete populations show limited benefit from routine supplementation [214,215]. These findings underscore the importance of a targeted, test-and-treat approach in orthopaedic practice, with selective testing at key clinical decision points and individualized repletion for patients with documented deficiency [208,220]. Diet, food fortification, and sun exposure contribute to baseline vitamin D status but are insufficient to achieve timely correction in high-risk orthopaedic populations and should, therefore, be regarded as supportive public-health measures rather than definitive therapeutic strategies.

Author contributions

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Declaration of generative AI in scientific writing

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