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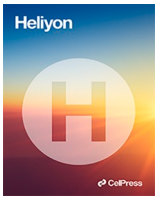

Review article

# The interplay between vitamin D status, subclinical inflammation, and prediabetes

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ABSTRACT

Vitamin D's role extends beyond classical calcium and phosphate homeostasis to encompass a pivotal influence on immune modulation and metabolic health. The mechanisms by which vitamin D exerts these effects involve its conversion to hormonally active calcitriol, which binds intracellular vitamin D receptors, initiating various downstream cascades. In this review, we tease out the evidence showing the relationship between vitamin D deficiency and prediabetes within the context of subclinical inflammation, with a special focus on the novel monocyte-to-HDL ratio (MHR), a novel inflammatory marker reflecting subclinical inflammation. This was based on a thorough literature review using reputable databases covering the period from 1980 to 2024. In light of this, we discuss calcitriol's anti-inflammatory effects and consequently link vitamin D deficiency to both overt and subclinical inflammation. Additionally, the utility of several biomarkers, notably MHR, in investigating this association is also discussed. We further reviewed the role of vitamin D deficiency in precipitating prediabetes and type 2 diabetes mellitus (T2DM) via insulin resistance, decreased insulin synthesis and secretion, and subclinical inflammation. Taken together, this mini review highlights that vitamin D deficiency is significantly associated with subclinical inflammation, playing a critical role in the development of prediabetes and the progression to T2DM. Addressing vitamin D deficiency through appropriate interventions may serve as a preventative measure against the development of prediabetes and T2DM.

## 1. Introduction

Vitamin D, a fat-soluble vitamin encompassing a primary cholesterol ring structure, is known to modulate phosphate and calcium homeostasis [1,2]. Besides vitamin D's fundamental role in skeletal health, the hormonally active metabolite of vitamin D, calcitriol (1α, 25-dihydroxyvitamin D), has a pivotal immune modulatory function [1]. Other extra-skeletal functions encompass cell proliferation, immune modulation, muscular functionality, skin differentiation and reproduction, safeguarding against insulin resistance, and the mediation of vascular and metabolic properties [3,4].

Given the significance of these well-established extra-skeletal immune-modulatory and metabolic functions of vitamin D, it is

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unsurprising that a deficiency in this vital nutrient is implicated in various abnormalities and disorders [3,4]. Notably, vitamin D deficiency has been identified in the literature as an important risk factor for numerous cardiometabolic and inflammatory diseases, such as cardiovascular disease, hypertension, susceptibility to infections and autoimmune disorders [5–10]. The implications of vitamin D deficiency in metabolic diseases become particularly critical given the alarming global prevalence of low vitamin D [11–13]. Among the myriad of disorders associated with vitamin D deficiency, the relationship with insulin resistance and type 2 diabetes mellitus (T2DM) stands out due to its complexity and intricacy, involving an interplay of genetic, environmental, and lifestyle factors [14].

While the literature has extensively explored the relationship between vitamin D and T2DM in the context of overt inflammation, it has been relatively silent on stages preceding overt inflammation, better known as subclinical inflammation, and T2DM manifestation. Thus, this review aims to provide a better understanding of the early inflammatory changes associated with vitamin D deficiency and their potential impact on the progression to prediabetes and subsequently to T2DM. We aim to investigate the relationship between vitamin D deficiency and prediabetes within the context of subclinical inflammation, with a special focus on monocyte-to-High-density lipoprotein ratio (MHR), a novel inflammatory marker capable of reflecting subclinical inflammation [15,16].

## 2. Methods

A comprehensive literature review was conducted on January 29, 2024, to investigate the relationship between vitamin D status, subclinical inflammation, and prediabetes. Databases searched included PubMed and Google Scholar. Keywords and search terms were developed based on the main concepts of the research question. The following keywords and their combinations were used: "vitamin D," "subclinical inflammation," "immune-modulation," "prediabetes," "Monocyte-to-High-Density-Lipoprotein Ratio (MHR)," "insulin resistance," and "type 2 diabetes mellitus (T2DM)." Additionally, Boolean operators (AND, OR, NOT) were used to create effective search strings. Inclusion criteria comprised peer-reviewed articles published in English, from 1980 to 2024, focusing on the specified relationships. Each result was screened initially by title, then by abstract, to assess relevance, and filtered against exclusion criteria such as studies unrelated to the research focus, non-peer-reviewed articles, opinion pieces, and inaccessible full texts.

### 2.1. Vitamin D metabolism

Vitamin D, as a nutritional element, has two distinctive types that vary in terms of sources and chemical structure: ergocalciferol (vitamin $D_2$) and cholecalciferol (vitamin $D_3$). Ergocalciferol, derived from plant-based sources and supplements, is distinct from cholecalciferol due to its C22–C23 double bond and C24 methyl group (Fig. 1). Conversely, cholecalciferol originates from animal-derived sources and supplements and is also endogenously synthesized in the epidermis [17]. This synthesis involves the conversion of provitamin $D_3$ (7-dehydrocholesterol), a cholesterol synthesis intermediate, to previtamin $D_3$ upon exposure to ultraviolet B radiation (UVB). Following this, thermal isomerization of previtamin $D_3$ produces vitamin $D_3$ [2,17,18]. Once in circulation, vitamin $D_2$, vitamin $D_3$ and their metabolites bind with high affinity to vitamin D-binding protein (VDBP) for transportation, with vitamin $D_3$ metabolites having a higher affinity than vitamin $D_2$ metabolites (Fig. 2) [2,19].

The activation of vitamin D involves an enzymatic hydroxylation process, which takes place in two phases [20]. The initial phase transpires in the liver, where both vitamin $D_3$ and vitamin $D_2$ undergo hydroxylation by 25-hydroxylases (CYP2R1 and CYP27A1), leading to the formation of calcidiol (25-hydroxyvitamin D (25(OH)D)) [2,18]. Subsequently, 25(OH)D is hydroxylated by 1α-hydroxylase (CYP27B1), facilitated by cubilin and megalin, resulting in the production of the active vitamin D hormone, calcitriol (1α, 25-dihydroxyvitamin D (1,25$(OH)_2$D)) as depicted in Figs. 1 and 2. Although it was originally believed that CYP27B1 is only present in kidneys, it is now suggested that it is also found in macrophages, keratinocytes, and other cells across the body [1]. While calcitriol has a short half-life of 4–8 h, calcidiol, has a half-life of 2–3 weeks. This notably longer half-life makes calcidiol a reliable biomarker for serum vitamin D assessment [2,21].

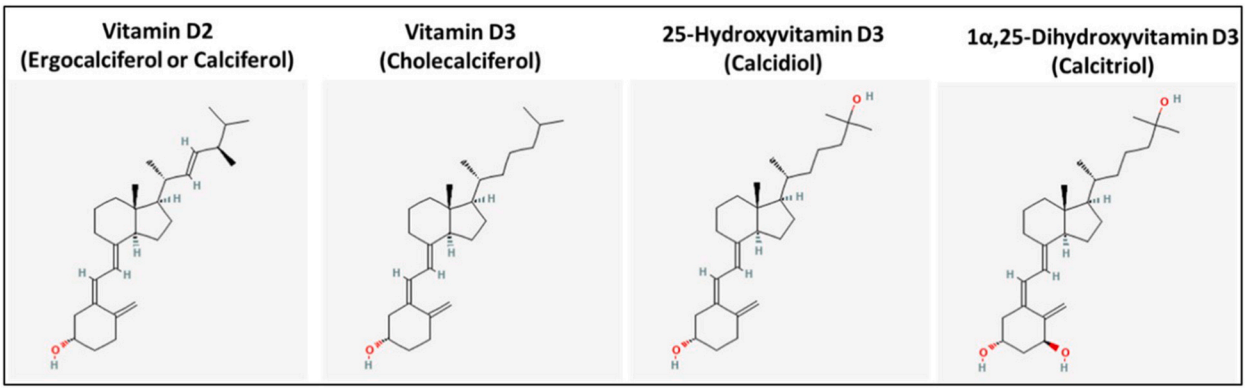


**Fig. 1.** Chemical structures of vitamin $D_2$, vitamin $D_3$, and metabolites produced mainly by liver 25-hydroxyvitamin $D_3$ and by kidney 1α,25-dihydroxyvitamin $D_3$ (source: https://pubchem.ncbi.nlm.gov/).

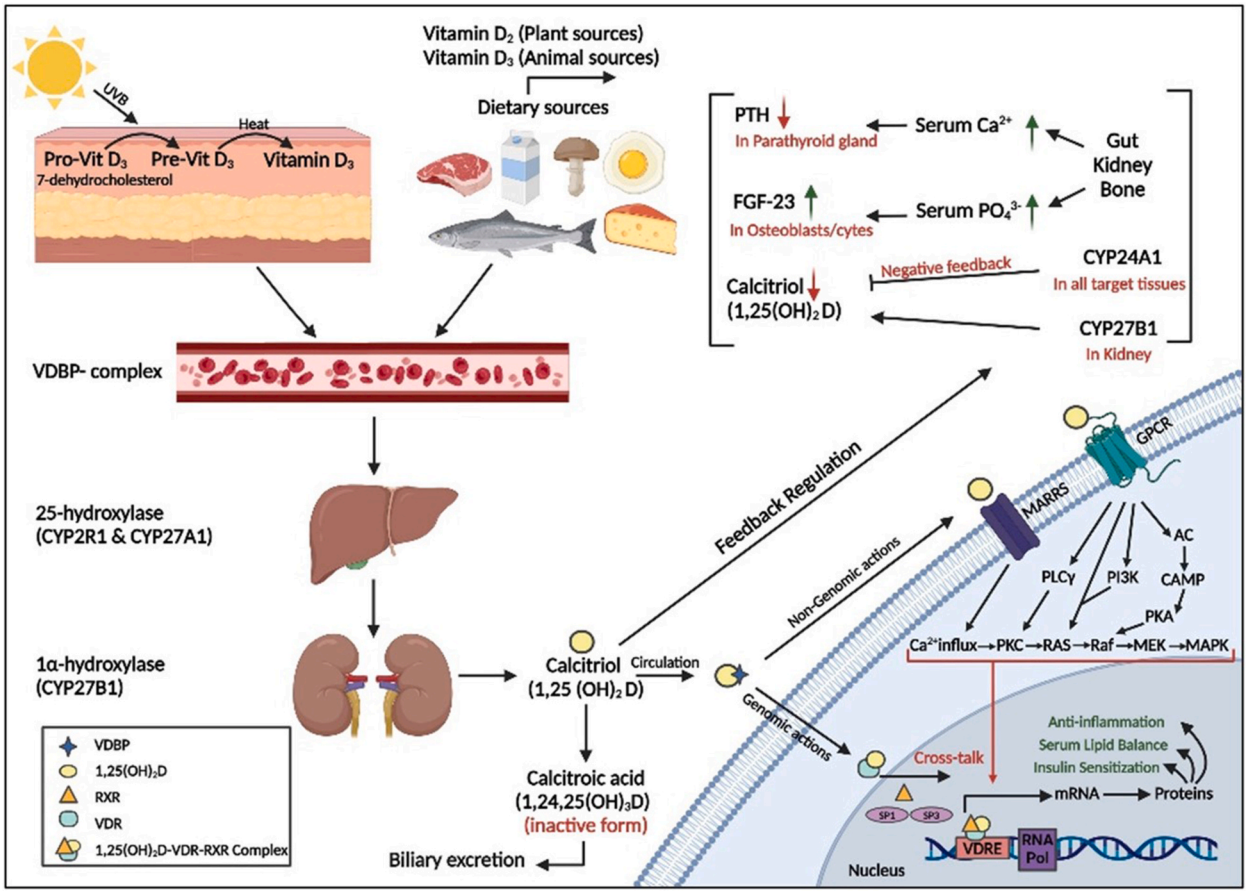


**Fig. 2. Overview of vitamin D metabolism:** UVB radiation converts 7-dehydrocholesterol in the skin to pre-vitamin $D_3$, which transforms into vitamin $D_3$ with heat. Once in the bloodstream, vitamin D binds to VDBP and is transported to the liver, where it undergoes hydroxylation. This process results in the formation of 25(OH)D, which is subsequently converted to the active metabolite, $1,25(OH)_2D$ in the kidney. The synthesis of $1,25(OH)_2D$ is influenced by PTH stimulation and is inhibited by high levels of calcium, phosphate, and $1,25(OH)_2D$ itself. Created with BioRender.com.

Both vitamin $D_2$ (ergocalciferol) and $D_3$ (cholecalciferol) undergo analogous hydroxylation processes, yielding the same active metabolite, calcitriol ($1,25(OH)_2D$). However, evidence suggests that vitamin $D_3$ supplementation has a pronounced superiority in enhancing serum 25(OH)D levels compared to vitamin $D_2$ supplementation [20]. The variances in their potencies may be attributed to cholecalciferol being the preferred substrate for liver 25-hydroxylase [22]. This phenomenon can be elucidated by the structural disparities of the side chains between the two vitamin D types, directly affecting ergocalciferol's hydroxylation rate into calcidiol (25 (OH)D) and its affinity for VDBP [22–24]. Furthermore, a critical distinction delineating the impact of ergocalciferol from that of cholecalciferol is the occurrence of a third hydroxylation step in the kidney at C24, yielding 1 α,24,25-trihydroxyvitamin D (1,24,25 $(OH)_3D$) (Fig. 2) [24]. This divergence between the two vitamin D types emanates from the irreversible deactivation of ergocalciferol once $1,24,25(OH)_3D_2$ is formed [25]. Conversely, cholecalciferol, in the form of $1,24,25(OH)_3D_3$, retains its ability to bind to the vitamin D receptor (VDR) and necessitates an additional side-chain oxidation step for deactivation [24,25]. This confers a significant advantage and potential for vitamin $D_3$ to persist in a biologically active state, thereby maintaining serum 25(OH)D status [24]. [20]. The intricate mechanism of vitamin D activation is stimulated by parathyroid hormone (PTH) and is inhibited via a negative feedback loop mediated by several factors, including $1,25(OH)_2D$ itself, phosphate, calcium, and notably, fibroblast growth factor 23 (FGF23), which is synthesized predominantly by osteocytes and osteoblasts (Fig. 2) [2,18,26]. $1,25(OH)_2D$ later interacts with VDR, a ubiquitous nuclear binding protein present in nearly all cells, to execute its multifaceted roles and self-regulates its serum concentration (Fig. 2) [2].

### 2.2. Vitamin D immune modulatory effects

There is accumulating evidence that the hormonally active form calcitriol plays a pivotal role in immunity [27]. This has been proven through animal studies [28,29], observational studies [30,31], and randomized controlled trials (RCTs) [32,33]. The immune modulatory role of vitamin D can be explained by the fact that VDR and CYP27B1 are expressed in various immune cells including

monocytes, macrophages, activated T and B lymphocytes, and dendritic cells [1]. This indicates that the autocrine function of calcitriol is modulated by its binding to VDR, which is described as high-affinity binding resulting in $1,25(OH)_2$D-VDR complex. In turn, this will start a unique cascade depending on the trigger or type of cell [19,34,35]. Many studies suggest that $1,25(OH)_2$D-VDR complex further binds to retinoid X receptor (RXR), a nuclear receptor, forming a heterodimer that will additionally recruit co-regulators, leading to gene expression in a ligand-dependent fashion [19,35–37]. The VDR/RXR heterodimer then either promotes or inhibits DNA transcription by binding to vitamin D response element (VDRE) on the promotor region of the targeted gene [19,35]. The outcome of this cascade will vary with different stimuli and immune cell types.

Monocytes and macrophages are activated in settings of infection through toll-like receptors (TLRs) and other pattern recognition receptors (PRRs) [1]. Signaling through TLRs upregulates the production of VDR and CYP27B1, allowing calcitriol to carry out its function [1,38,39]. The consequent VDR/RXR heterodimer binding to VDRE results in the production of defensin $\beta_2$ and cathelicidin (also known as LL-37), both of which are antimicrobial peptides [1,27,38]. Additionally, it upregulates the expression of TLRs, which initiates a positive feedback loop to enhance the antibacterial effect and it stops when the stimulus is no longer available [38,40]. This is especially beneficial in granulomatous inflammation including tuberculosis and sarcoidosis given the ability of cathelicidin to neutralize capsular polysaccharides and endotoxin [1,27,41].

In the absence of infection, calcitriol shifts antigen presenting cells function, including monocytes and dendritic cells, from immunogenic to tolerogenic [42]. This is marked by the reduction in expression of major histocompatibility complex class two (MHC-II) and co-stimulatory molecules, such as CD40, CD80 and CD86, on their surfaces [38]. Subsequently, their antigen presentation capacity decreases leading to impairment in the activation of T lymphocytes [38]. Moreover, a reduction in secretion of proinflammatory cytokines is noted from both antigen presenting cells and T lymphocytes. This includes IL-6, IL-1β, and IL-12 from macrophages and monocytes as well as IFN-γ and IL-17 from dendritic cells and various types of T lymphocytes [1,34,35,43]. This anti-inflammatory effect is further augmented through shifting to the tolerogenic phenotype, evidenced by the upregulation of FoxP3, which increases the production of regulatory T cells ($T_{reg}$). This is also accompanied with increased production of the anti-inflammatory cytokine IL-10 [34,44]. Thus, calcitriol exerts an anti-inflammatory role by both inhibiting the production of pro-inflammatory cytokines and stimulating the production of anti-inflammatory cytokines. Such anti-inflammatory properties of calcitriol are postulated to be potentially associated with the susceptibility to autoimmune diseases [44].

Since the hormonally active metabolite of vitamin D, calcitriol, has a significant modulatory role in both innate and adaptive immunity, deficiency or inadequacy of vitamin D poses a risk on health [19]. Vitamin D levels are reflected by serum levels of 25-hydroxyvitamin D; however, there is controversy around the cutoff value for deficiency [45]. According to the Institute of Medicine classification, vitamin D inadequacy is defined as 25-hydroxyvitamin D serum level between 12 and <20 ng/mL (30–50 nmol/L), whereas vitamin D deficiency is defined as 25-hydroxyvitamin D serum level less than 12 ng/mL (<30 nmol/L) [46]. A recent study revealed that the global prevalence of vitamin D deficiency stood at 15.7 % between 2000 and 2022 [12]. In the United States, the prevalence of vitamin D inadequacy among adults ranged from 34 % to 37 % [47].

An association between vitamin D deficiency and the occurrence and severity of multiple chronic inflammatory diseases has been established [27]. This includes cardiovascular events [48], inflammatory bowel disease [30], and respiratory conditions like asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD) [49–51]. Given this evidence, there has been an increased interest to explore the potential benefits of vitamin D supplementation for afflicted patients and its possible prophylactic effects. Grossmann et al. conducted an RCT to assess the effect of high-dose vitamin D supplementation as compared to placebo in hospitalized patients with cystic fibrosis by measuring changes in serum concentrations of inflammatory markers. They detected 50.4 % reduction in tumor necrosis factor-α (TNF-α) and 64.5 % reduction in IL-6 in the supplementation group [52]. Moreover, Niroomad et al. carried out an RCT in which adults with prediabetes and vitamin D deficiency were randomized to vitamin $D_3$ and placebo groups. Although there was no statistically significant difference in fasting plasma glucose (FPG), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score as well as the rate of progression toward diabetes were significantly lower in the intervention group [32]. Thus, vitamin D supplementation is associated with decreased inflammatory markers and reduced severity of chronic inflammatory diseases [27,32,52,53].

### *2.3. Vitamin D and subclinical inflammation*

Apart from overt inflammation, vitamin D deficiency has also been linked to subclinical inflammation [54–56], a condition characterized by mild and chronic systemic inflammation which features the absence of overt clinical symptoms [57]. This form of inflammation is mediated by the innate immune system, which in turn is modulated by inflammatory signaling pathways. These intracellular signaling pathways are regulated by various mediators including nuclear factor kappa B (NFκB) and activator protein-1 (AP-1), along with their anti-inflammatory counterparts such as peroxisome proliferator activated receptor-γ (PPAR-γ). Extracellularly, pro-inflammatory cytokines such as TNF-α and IL-6 play a role in transmitting inflammatory signals [58]. Various biomarkers have been identified and used to indicate the presence of subclinical inflammation such as high-sensitivity C-reactive protein (hs-CRP), ferritin, albumin, IL-6, sialic acid, and complete blood count-derived indices including neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) [57,59,60].

There are diverse examples of pathologies where subclinical inflammation plays a significant role. One example is primary hypertension in children and adolescents, where the subclinical inflammation of endothelial cells leads to the formation of atherosclerotic plaques, which in turn results in premature vascular aging [61,62]. Familial Mediterranean Fever (FMF) is another prominent example, where the presence of subclinical inflammation in FMF patients increases the likelihood of complications, including anemia, heart disease, and amyloidosis [54]. Metabolic syndrome is also illustrative; where increased metabolic risk factors, such as impaired

FPG and high-density lipoprotein cholesterol (HDL) levels, were associated with elevated hs-CRP levels in individuals with normal body weight, indicating a state of subclinical inflammation [63]. In the same context, existing literature has also established links between different subclinical inflammation biomarkers such as IL-6 and TNF-α and nerve conduction velocity in individuals who have recently been diagnosed with either type 1 or type 2 diabetes [57,64]. Furthermore, in individuals with obesity, an association was observed between hs-CRP, increased waist circumference, and high blood pressure [63]. It was further identified that obesity correlates with persistent, localized low-grade inflammation, predominantly in visceral fat and liver regions [65].

The precise mechanism by which the deficiency in vitamin D is linked to subclinical inflammation is a subject of ongoing research, and several hypotheses have been proposed. On the one hand, one hypothesis suggests that subclinical inflammation may result from the deficiency in vitamin D. This notion stems from the multiple anti-inflammatory properties possessed by vitamin D as previously stated. On the other hand, another hypothesis is that subclinical inflammation may lead to vitamin D deficiency. A study suggests that the decrease in calcidiol can be an outcome of the inflammatory process when cells are parasitized by intracellular bacteria [66]. The proposed mechanism is that infection induces the production of inflammatory cytokines. This, in turn, upregulates CYP27B1 that converts more 25(OH)D into calcitriol. Notably, the excess calcitriol binds to the pregnane X receptor (PXR), resulting in the inhibition of the conversion of the dietary vitamin D3 to calcidiol, leading to calcidiol deficiency. Additionally, calcitriol inhibits the hepatic synthesis of calcidiol, further contributing to the decreased calcidiol levels [66]. Another study observed a reduction in serum calcidiol levels after an acute inflammatory event, such as orthopedic surgery [67]. These findings led to the conclusion that low vitamin D levels might result from chronic inflammatory diseases rather than being their initial cause. Fundamentally, the literature highlights a strong association between vitamin D deficiency and subclinical inflammation, regardless of which event precedes the other.

A number of biomarkers can be used to study the relationship between subclinical inflammation and vitamin D deficiency. Notably, ferritin and hepcidin, which primarily serve as indicators for iron deficiency anemia, are two important biomarkers recognized for subclinical inflammation, given that they both are acute phase reactants [68]. In the presence of inflammation, elevated serum calcidiol levels were found to be associated with reduced ferritin levels [69]. Additionally, hepcidin's relationship with vitamin D has been researched, revealing that vitamin D is involved in regulating cellular iron balance via the hepcidin-ferroportin-NRAMP1 pathway within macrophages, particularly to support iron release during inflammation [43]. Although numerous studies reported a negative correlation between serum calcidiol levels and serum hepcidin levels, some studies reported no significant correlation [43,70, 71]. Another inflammatory biomarker that has been found to correlate with vitamin D status is C-reactive protein (CRP). A comprehensive genetic analysis revealed a causal link between vitamin D levels and CRP, indicating that vitamin D status influences CRP [72]. The connection between vitamin D and CRP was predominantly significant in cases of deficiency, where individuals with low serum calcidiol levels displayed elevated serum CRP. A systematic review determined that vitamin D status is linked to biomarkers of oxidative stress and inflammation, including CRP, IL-6, cathepsin S, vascular cell adhesion molecule-1 (VCAM-1), malondialdehyde (MDA), myeloperoxidase, 3-nitrotyrosine, and superoxide dismutase (SOD), which further elucidates the relationship between vitamin D status and markers of subclinical inflammation [73]. Notably, according to the systematic review, the majority of studies with children and adolescents found an association between vitamin D status, oxidative stress and inflammation [73]. In summary, the elucidated data on the inflammatory biomarkers help illustrate and quantify the correlation between vitamin D levels and subclinical inflammation.

Monocyte-to-High-Density-Lipoprotein Ratio (MHR) has been proposed by recent research as a novel biomarker reflecting subclinical inflammation. The rationale behind using MHR is based on the fact that monocytes are a type of white blood cells of the innate immunity that play a critical role in cellular homeostasis and immune responses to inflammation, where they regularly screen for pathogens and initiate immune reactions by secreting pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α [74]. Accordingly, an increase in monocytes percentage is often associated with subclinical inflammation. On the other hand, HDL exhibits an anti-inflammatory effect by inhibiting the activity of monocytes as well as the differentiation of monocytes into macrophages [75]. MHR is elevated in cases of systemic inflammation and oxidative stress, and has been found to have a higher sensitivity at predicting the prognosis of inflammation as compared to other markers including CRP [76]. MHR has been proposed to have an association with vitamin D deficiency, given the known anti-inflammatory properties of vitamin D, including the downregulation of cytokine production by monocytes, as well as the established positive correlation between vitamin D and serum HDL levels [77–79].

### *2.4. Vitamin D, prediabetes and type 2 diabetes mellitus (T2DM)*

In addition to the examples previously outlined, subclinical inflammation was found to be linked to abnormal glucose metabolism by promoting insulin resistance, suggesting a strong link with prediabetes [57,80,81]. The term "prediabetes" was introduced by the American Diabetes Association (ADA) and is defined as a multifactorial metabolic disorder characterized by impaired glucose homeostasis, resulting in blood glucose concentration that exceeds normal baseline values, yet not reaching the diagnostic thresholds of diabetes [82]. According to their criteria, prediabetes is defined by a hemoglobin A1C (HbA1c) of 5.7 %–6.4 %, a FPG of 100 mg/dl to 125 mg/dL, or an Oral Glucose Tolerance Test (OGTT) of 140–199 mg/dL [83].

Other health organizations, such as the World Health Organization (WHO) and the International Diabetes Federation (IDF), refer to the same condition as "intermediate hyperglycemia" and "impaired glucose tolerance", respectively. The diagnostic criteria of the aforementioned organizations are also slightly different. While these organizations concur on the lower and upper levels for OGTT, they exhibit variations concerning FPG. Additionally, the guidelines from the WHO and IDF do not consider HbA1C a suitable diagnostic criterion [83]. Globally, the prevalence of prediabetes is both substantial and on the rise. In 2021, approximately 9.1 % of the global adult population was diagnosed with prediabetes through OGTT, whereas 5.8 % were diagnosed through FPG. Projections suggest a rise in the global prediabetes burden to 20.0 % (OGTT-diagnosed) and 6.5 % (FPG-diagnosed) by 2045. Notably, high-income

countries reported the highest prevalence of prediabetes in 2021. Nevertheless, the most marked relative increase in cases by 2045 is predicted to occur in low-income countries. It is crucial to highlight that reliable data on prediabetes prevalence is currently lacking for approximately two-thirds of countries globally. Therefore, there is a need for initiatives to reduce the global prediabetes burden given the fact that unmanaged prediabetes can lead to a range of serious complications [82,84]. These include nephropathy, chronic kidney disease, small-fiber neuropathy, retinopathy, cognitive dysfunction, macrovascular disease, and infertility in both men and women [82]. The relationship between vitamin D deficiency and the pathophysiology of prediabetes is multifaceted and can be elucidated via a plethora of mechanisms. These mechanisms encompass insulin resistance, diminished insulin synthesis and secretion, and subclinical inflammation.

- **Vitamin D Deficiency, Insulin Resistance, and Prediabetes:**

Vitamin D is integral to blood glucose regulation by modulating insulin secretion and enhancing insulin sensitivity. This is achieved by promoting glucose metabolism through the upregulation of the SIRT1/IRS1/GLUT-4 signaling cascade and increasing glucose uptake in muscle cells, particularly in hyperglycemia [85]. Conversely, in the setting of vitamin D deficiency, there is reduced activation of VDR by calcitriol, leading to impairments in the insulin signaling pathway. This decreases the expression of insulin receptors (IRs) on the surface of insulin-responsive cells and deactivates peroxisome proliferator-activated receptor delta (PPAR-δ) [86,87]. PPAR-δ is a transcription factor that plays a pivotal role in the mobilization and breakdown of fatty acids in both muscle and adipose tissue. It also has the capacity to mitigate insulin resistance induced by free fatty acids (FFAs), ultimately averting cellular insulin resistance. Consequently, glucose uptake by the skeletal muscles, liver, and adipose tissue is compromised, resulting in chronic hyperglycemia which induces a surge in reactive oxygen species (ROS) production and oxidative stress [85]. Moreover, a hampered insulin response in adipocytes amplifies FFA release into the circulation, where they get predominantly absorbed by the liver. In essence, both glucotoxicity and lipotoxicity catalyze chronic inflammation, further exacerbating insulin resistance, and leading to prediabetes (Fig. 3a) [85].

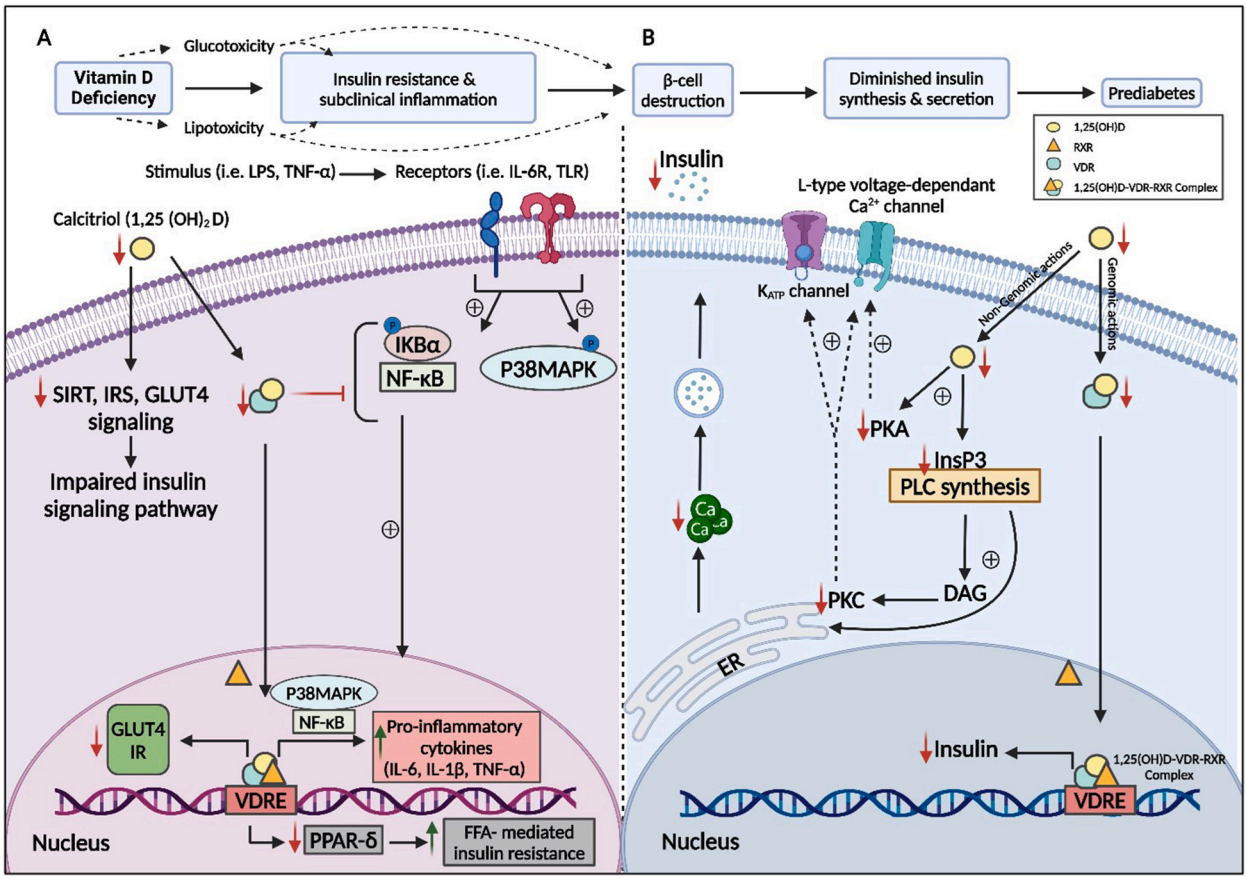


**Fig. 3. 3a:** Vitamin D deficiency hampers insulin signalling pathway, decreases GLUT4 and IR expression, and diminishes calcitriol's anti-inflammatory effects, ultimately resulting in insulin resistance and subclinical inflammation. **3b:** Vitamin D deficiency negatively affects insulin synthesis and secretion through a combination of genomic and nongenomic actions. Created with BioRender.com.

- **Vitamin D Deficiency, Diminished Insulin Synthesis and Secretion, and Prediabetes:**

Glucose enters pancreatic β-cells via glucose transporter 2 (GLUT-2) and undergoes catabolism through diverse metabolic pathways, resulting in the production of adenosine triphosphate (ATP). Increased ATP levels suppress ATP-sensitive $K^+$ channels, leading to pancreatic β-cells membranes depolarization and the activation of L-type voltage-operated calcium channels, which generate localized calcium ($Ca^{2+}$) pulses crucial for insulin secretion [88]. Vitamin D hereby influences insulin secretion by regulating intracellular $Ca^{2+}$ concentration and modulating various signaling pathways, such as protein kinase A (PKA) and phospholipase C (PLC). Furthermore, vitamin D has an impact on calbindin, a calcium-binding protein, and other proteins involved in maintaining low resting $Ca^{2+}$ levels within pancreatic β-cells [89]. Vitamin D deficiency can both directly and indirectly impact insulin synthesis and secretion, ultimately affecting glucose regulation. In an indirect fashion, vitamin D deficiency alters insulin secretion by disrupting calcium homeostasis within pancreatic β-cells, potentially leading to their dysfunction. This also results in disturbances in glucose metabolism and insulin sensitivity (Fig. 3b) [85,90].

In a more direct manner, the deficiency of vitamin D results in reduced levels of calcitriol available for interaction with VDRs located on pancreatic β-cells. This interaction plays a crucial role in activating the genomic pathway through binding to the VDRE in the insulin gene promoter region, leading to the stimulation of insulin synthesis (Fig. 3b) [85,91]. Therefore, both direct and indirect effects of vitamin D deficiency eventually culminate in the decreased synthesis and secretion of insulin, ultimately leading to prediabetes.

- **Vitamin D Deficiency, Subclinical Inflammation, and Prediabetes:**

Subclinical inflammation associated with vitamin D deficiency is characterized by the low-level release of pro-inflammatory cytokines and acute phase reactants as previously demonstrated [54–60]. Therefore, subclinical inflammation is linked to abnormal glucose metabolism and the promotion of insulin resistance. This can be explained by the significant role of adipose tissues in this process, given the established connection between obesity and vitamin D deficiency [92]. Essentially, certain stimuli such as over-nutrition and obesity stimulate adipose cells to release various proinflammatory cytokines that directly impede insulin signaling. These adipocytokines exert their effects through key inflammatory pathways like NFκB and the c-Jun NH2-terminal kinase (JNK)/AP-1 signaling pathways [81]. This modulation affects the expression of genes responsible for multiple inflammatory cytokines and disrupts insulin signaling. Furthermore, acute phase reactants such as CRP, which can be elevated due to vitamin D deficiency, can serve as predictors of insulin resistance in various ethnic groups (Fig. 3a) [93,94].

Prediabetes, frequently identified in scholarly work as a "High Risk State of Developing Diabetes" [95], exhibits a noteworthy progression rate to type 2 diabetes mellitus (T2DM), serving as an early indicator of the disease [96]. Annually, 5 %–10 % of prediabetic individuals progress to diabetes [97], and an ADA expert panel posits that approximately 70 % of those with prediabetes will manifest diabetes during their lifetime [98]. A meta-analysis conducted in 2018 revealed the relative hazards of diabetes development in prediabetic patients as 4.32 for FPG-diagnosed prediabetes per ADA criteria, 5.47 for FPG-diagnosed prediabetes as per WHO, 5.55 for HbA1C levels above 5.7 %, and 10.10 for HbA1C levels exceeding 6.0 % [99].

T2DM is a prevalent metabolic disorder globally [100]. According to the ADA criteria, T2DM is characterized by an HbA1c $\geq$ 6.5 %, FPG $\geq$126 mg/dl, OGTT $\geq$200 mg/dl, or a Random Plasma Glucose Test $\geq$200 mg/dl (in presence of classic hyperglycemic symptoms or crisis) [83]. Additionally, similar to prediabetes, T2DM is distinguished by elevated blood markers associated with the acute-phase response and important proinflammatory cytokines like IL-6 [101]. These observations emphasize the connection between vitamin D deficiency, subclinical inflammation, and the development of type 2 diabetes [57,64,102]. In 2021, global data indicated that 529 million individuals across all age groups were living with diabetes, reflecting an age-standardized prevalence of 6.1 %; notably, 96 % of these cases were attributed to T2DM [103]. Within the U.S., the combined prevalence of diagnosed and undiagnosed diabetes from 1988 to 1994 to 2017–2020 surged from 6.8 % to 14.2 % [104]. Moreover, if left untreated and uncontrolled, T2DM can lead to various acute and chronic complications. These encompass diabetic ketoacidosis and diabetic coma, macroangiopathy, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, diabetic foot, and cardiovascular diseases [105].

Prediabetes is identified as a pivotal juncture, given the empirical evidence suggesting the condition's reversibility at this stage, providing a feasible avenue to mitigate and prevent the onset of diabetes mellitus [106,107]. Timely interventions during this crucial phase can preclude associated prolonged complications. Strategies targeted at reversing prediabetes encompass lifestyle modifications, pharmacological interventions, and surgical procedures [108]. Emerging literature identifies serum vitamin D levels as a notable risk factor for prediabetes and T2DM, warranting its potentiality for consideration in preventative and interventional strategies for prediabetes. Nevertheless, existing literature presents inconsistent findings [106]. Emerging literature indicates an inverse relationship between serum vitamin D levels and prediabetes risk [109–114], further corroborated by multiple investigations demonstrating the efficacious role of vitamin D supplementation in prediabetes reversal [115–117]. Conversely, in some studies, neither serum vitamin D levels nor supplementations were found to have an association with prediabetes risk [113,118,119].

## 3. Conclusion

In summary, vitamin D plays crucial roles in immunity and blood glucose homeostasis. This is facilitated through the effects of its hormonally active metabolite, calcitriol, which include suppressing proinflammatory cytokines, promoting anti-inflammatory cytokines, and regulating insulin secretion and sensitivity. Hence, it follows that an inadequacy or deficiency in this vital compound would lead to counterproductive effects linked to subclinical inflammation, for which sensitive biomarkers, such as the novel MHR can be

used. This subclinical inflammation can further be linked to prediabetes, which subsequently could develop into T2DM if left unmanaged. Given the severity of the complications and the expected global rise in prediabetes prevalence, thorough exploration of the association of vitamin D levels with subclinical inflammation and prediabetes is imperative. This exploration could potentially provide new insights into preventive approaches and remedies for prediabetes.

## Disclosure statement

Authors declare no conflict of interests.

## Data availability statement

No dataset was used for the research described in the article.

## CRediT authorship contribution statement

**Ahmed Arabi:** Writing – review & editing, Writing – original draft, Conceptualization. **Dima Nasrallah:** Writing – review & editing, Writing – original draft, Conceptualization. **Sara Mohsen:** Writing – review & editing, Writing – original draft. **Lana Abugharbieh:** Writing – review & editing, Writing – original draft. **Dana Al-Hashimi:** Writing – original draft. **Shaikha AlMass:** Writing – original draft. **Shahd Albasti:** Writing – original draft. **Saeed A. Al-Ajmi:** Writing – original draft. **Susu M. Zughaier:** Writing – review & editing, Validation, Supervision, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Abbreviations

| | |
|---|---|
| UVB | Ultraviolet B Radiation |
| VDBP | Vitamin D-Binding Protein |
| 25(OH)D | 25-Hydroxyvitamin D |
| 1,25(OH)2D) | 1α,25-Dihydroxyvitamin D |
| 1,24,25(OH)3D | 1 α,24,25-Trihydroxyvitamin D |
| VDR | Vitamin D Receptor |
| PTH | Parathyroid Hormone |
| FGF23 | Fibroblast Growth Factor 23 |
| RCTs | Randomized Controlled Trials |
| RXR | Retinoid X Receptor |
| DNA | Deoxyribonucleic Acid |
| VDRE | Vitamin D Response Element |
| TLRs | Toll-Like Receptors |
| PRRs | Pattern Recognition Receptors |
| LL-37 | Cathelicidin |
| MHC-II | Major Histocompatibility Complex Class Two |
| CD | Cluster of Differentiation |
| IL | Interleukin |
| IFN-γ | Interferon Gamma |
| FoxP3 | Forkhead Box P3 |
| Treg | Regulatory T Cells |
| COPD | Chronic Obstructive Pulmonary Disease |
| FPG | Fasting Plasma Glucose |
| HOMA-IR | Homeostatic Model Assessment of Insulin Resistance |
| NFκB | Nuclear Factor Kappa B |
| AP-1 | Activator Protein-1 |
| PPAR-γ | Peroxisome Proliferator Activated Receptor-γ |
| TNF-α | Tumor Necrosis Factor-α |
| hs-CRP | High-Sensitivity C-Reactive Protein |
| NLR | Neutrophil to Lymphocyte Ratio |
| PLR | Platelet to Lymphocyte Ratio |
| FMF | Familial Mediterranean Fever |
| HDL | High-Density Lipoprotein Cholesterol |

| | |
|---|---|
| PXR | Pregnane X Receptor |
| NRAMP1 | Natural Resistance-Associated Macrophage Protein 1 |
| CRP | C-Reactive Protein |
| VCAM-1 | Vascular Cell Adhesion Molecule-1 |
| MDA | Malondialdehyde |
| SOD | Superoxide Dismutase |
| MHR | Monocyte-to-High-Density-Lipoprotein Ratio |
| T2DM | Type 2 Diabetes Mellitus |
| ADA | The American Diabetes Association |
| HbA1c | Hemoglobin A1C |
| OGTT | Oral Glucose Tolerance Test |
| WHO | The World Health Organization |
| IDF | The International Diabetes Federation |
| SIRT1 | Sirtuin 1 |
| IRS1 | Insulin Receptor Substrate 1 |
| GLUT | Glucose Transporter |
| IRs | Insulin Receptors |
| PPAR-δ | Peroxisome Proliferator-Activated Receptor Delta |
| FFAs | Free Fatty Acids |
| ROS | Reactive Oxygen Species |
| ATP | Adenosine Triphosphate |
| $K^+$ | Potassium Ion |
| $Ca^{2+}$ | Calcium Ion |
| PKA | Protein Kinase A |
| PLC | Phospholipase C |
| JNK | c-Jun NH2-Terminal Kinase |

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