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VITAMIN D DEFICIENCY AND RELATED DISORDERS & EXTRA-MUSCULOSKELETAL ROLES

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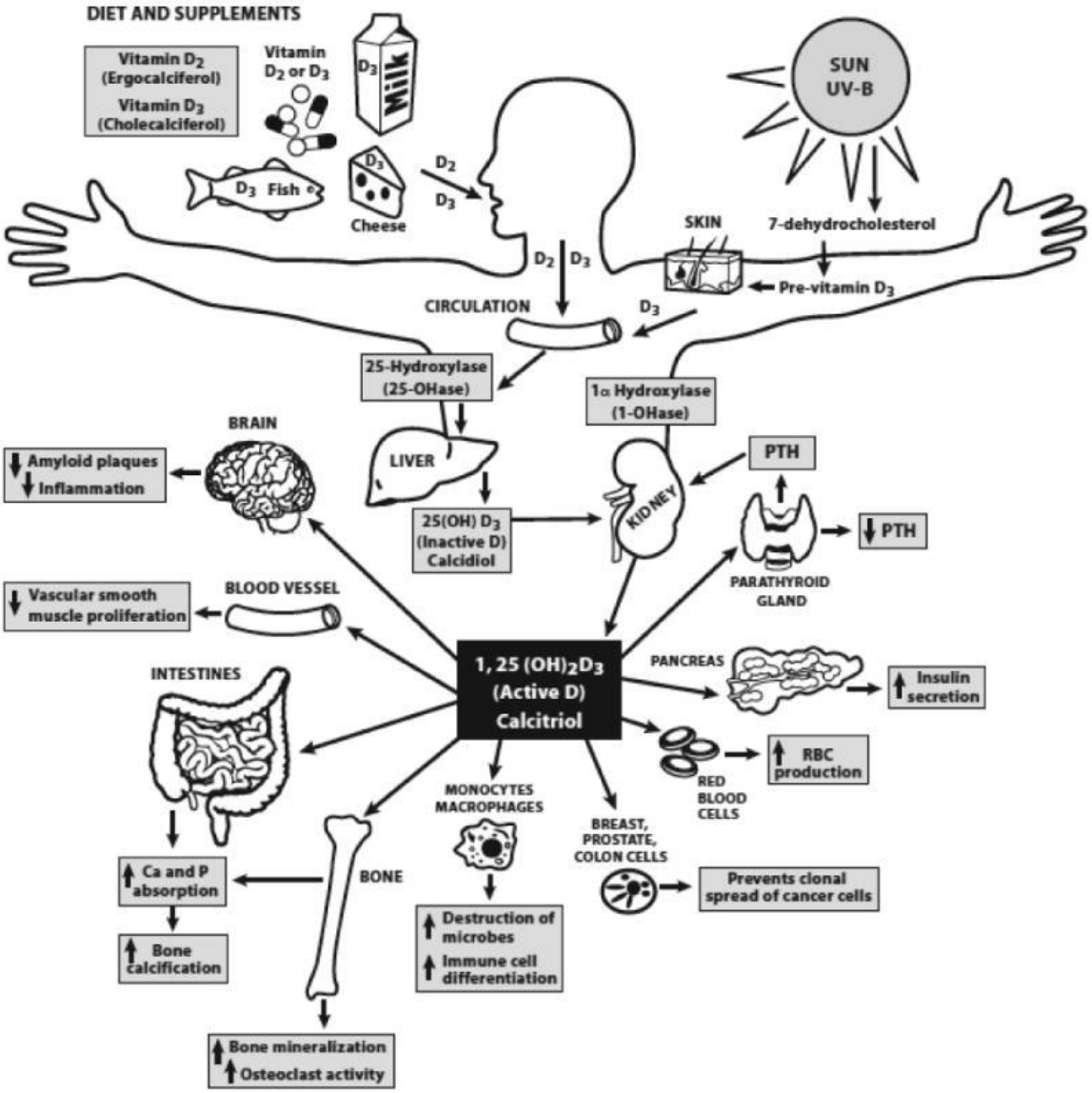
Abstract:
Vitamin D is a versatile, multifaceted micronutrient with far-reaching implications for human health, making it crucial for maintaining overall health and preventing various diseases and conditions. Its roles extend beyond traditional functions in musculoskeletal health to encompass a broad spectrum of physiological processes across multiple organ systems. The intricate interplay of vitamin D in immune modulation, anti-inflammatory responses, reproductive health, cardiovascular risk, and mental well-being. Further research is warranted to elucidate its precise mechanisms and optimize its therapeutic applications across diverse medical domains. The present review aims to understand the various effects of Vitamin D on the body system.

Keywords: vitamin D deficiency; osteoporosis type 2 diabetes mellitus; autoimmune diseases; cardiovascular diseases; infectious diseases

Introduction:

Vitamin D plays a crucial role in various aspects of human health. It maintains bone health by promoting calcium absorption and regulating bone growth and reorganization[1]. It has been linked to non-communicable diseases such as respiratory tract infections, osteoporosis, obesity, type 2 diabetes, cancer, rheumatoid arthritis, obesity, cardiovascular disease (CVD), and inflammatory bowel disease. Additionally, vitamin D plays a crucial role as an immunomodulatory hormone, regulating the innate and acquired immune cell responses and contributing to the production and release of antimicrobial substances, enhancing the body's defense against pathogens [2]. Also, it is a key element in regulating the body's inflammatory response, making it important in preventing and treating autoimmune diseases and skin diseases such as atopic dermatitis and psoriasis [3]. Vitamin D plays a significant role in the reproductive system. It has been shown to modulate metabolic and hormonal indicators of women's fertility, from menarche to menopause, pregnancy, and lactation, besides male fertility [4]. In addition, vitamin D is involved in mood regulation and mental health [5]. (Figure 1) summarizes the role of active vitamin D in the body.

Figure (1): active vitamin D role in the body

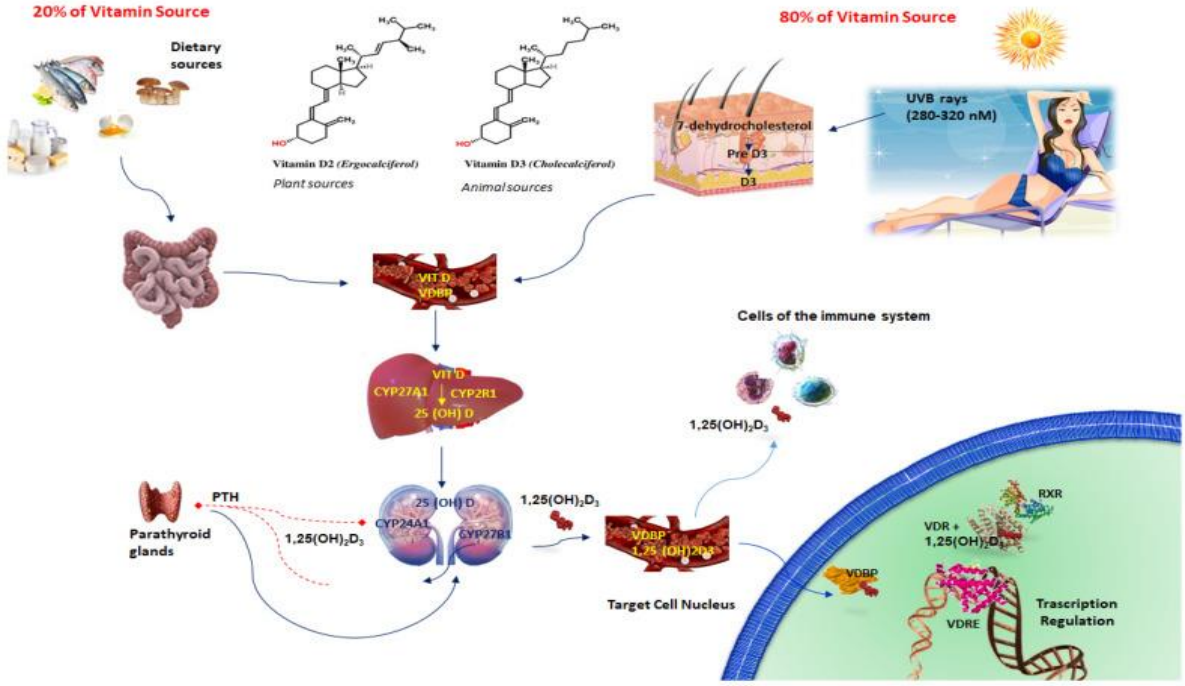


Sources of Vitamin D:

Vitamin D can be obtained from both endogenous synthesis and dietary sources. Still, vitamin D supplements are usually recommended due to the difficulty of achieving an adequate vitamin D intake through diet alone [6]. Vitamin D is mainly found in D3 (cholecalciferol) and D2 (ergocalciferol). These two forms differ in their sources, how they are synthesized, and their effectiveness in raising and maintaining vitamin D levels in the body. Vitamin D2 is primarily obtained from plant sources. It is produced when ergosterol, a compound found in fungi and yeast, is exposed to ultraviolet (UV) light. Fortified foods, such as milk, yogurt, fat spreads, orange juice, and breakfast grains, contribute to dietary vitamin D2 intake. In addition, Vitamin D2 is also available in supplement form and is sometimes prescribed to individuals with vitamin D deficiency. On the other hand, Vitamin D3 is the form of vitamin D produced in endogenous synthesis that occurs when the skin is exposed to ultraviolet B radiation, which triggers the activation of a cholesterol derivative called 7-dehydrocholesterol, which is converted into cholecalciferol in the body. It can also be found in dietary products such as fatty fish (salmon, mackerel, and tuna) and egg yolks. Vitamin D3 is also used to fortify animal-derived products like cow's milk. Additionally, vitamin D3 as a supplement is considered more effective at raising and maintaining vitamin D levels in the blood.

Vitamin D2 and D3 are two forms of vitamin D metabolized into 25-hydroxyvitamin D (25OHD) in the liver. 25OHD is then converted to 1,25-dihydroxyvitamin D (1,25(OH)2D), which is the active form of vitamin D. Vitamin D2 and vitamin D3 differ in their side chains, leading to differences in their affinity for vitamin D binding protein (VDBP) (Figure 2) [7]. Overall, vitamin D2 and D3 affect various physiological processes and may have other implications in different disease conditions. Vitamin D2 levels were higher in diabetics, particularly in females, and were associated with hypertension and dyslipidemia. In comparison, vitamin D3 levels were lower in diabetics, particularly females, and were associated with retinopathy [8].

Figure (2): Activation of vitamin D [9].



MUSCULOSKELETAL ROLES OF VITAMIN D:

as mentioned previously, vitamin D plays a crucial role in musculoskeletal health by enhancing calcium absorption, promoting bone mineralization, and maintaining muscle function. It is also involved in maintaining calcium homeostasis and neuromuscular activity. Adequate serum 25-hydroxyvitamin D concentrations are important for bone homeostasis and the prevention and treatment of osteoporosis when combined with sufficient calcium intake [10]. However, there is still a lack of consensus on optimal vitamin D status, thresholds for deficiency, and recommended intake levels. Recent studies have shown conflicting results regarding the efficacy of vitamin D supplementation in preventing fractures and falls in older adults. While some trials found no benefit of high-dose vitamin D supplementation on musculoskeletal outcomes. Vitamin D deficiency is also known to cause rickets in children, leading to hypomineralization of bone [11]. Additionally, low vitamin D status triggers secondary hyperparathyroidism, increases bone loss, and leads to muscle weakness. Further research is needed to establish realistic recommendations regarding musculoskeletal health, vitamin D status, and supplementation in different population groups.

EXTRA- MUSCULOSKELETAL ROLES OF VITAMIN D:

- **Anti-inflammatory response of vitamin D:**

Vitamin D has been shown to have anti-inflammatory effects in various conditions. In patients with cancer or pre-cancerous lesions, vitamin D supplementation (VID3S) significantly lowered serum levels of tumor necrosis factor (TNF)-α, suggesting a reduction in tumor-promoting inflammatory response [12]. In skin aging, vitamin D administration has been found to reduce inflammation in the skin by decreasing collagen breakdown, inhibiting inflammatory cytokines, and modulating immune

response activity [3,13]. Moreover, Vitamin D also has anti-inflammatory and anti-proliferative actions, making it a potential therapeutic option for other dermatologic conditions like atopic dermatitis, acne, and vitiligo, and supplementation with vitamin D or its analogs has shown beneficial effects in reducing the severity of psoriasis and promoting remissions. In patients with rheumatoid arthritis, vitamin D supplementation did not significantly reduce inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Still, it did reduce pain and disease activity scores [14]. In ulcerative colitis, vitamin D3 was found to suppress NOD-like receptor protein 6 (NLRP6) inflammasome activation, leading to a reduction in inflammation and disease development [15].

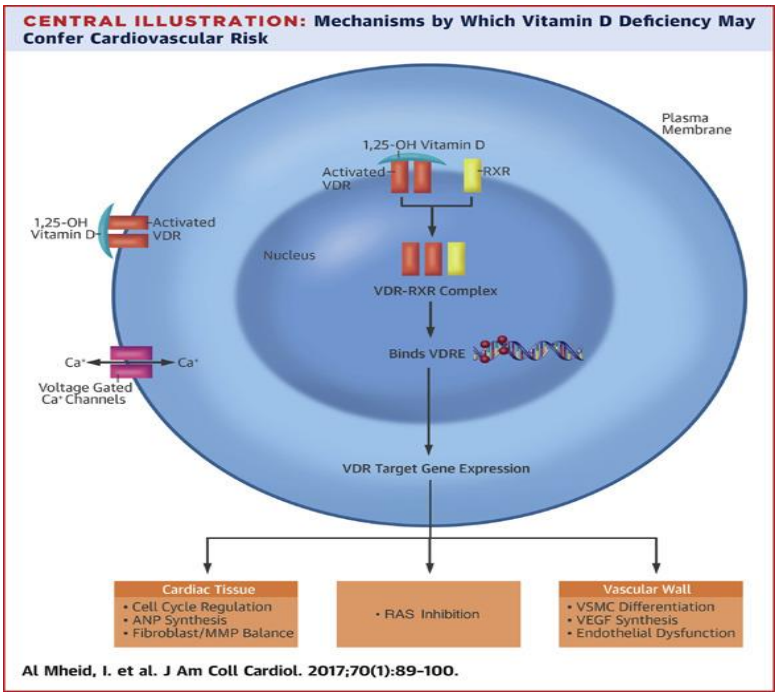
- **Vitamin-D role in diabetes:**

Vitamin D plays a significant role in managing diabetes mellitus, particularly in type 2 diabetes. It has been shown to enhance the activity of anti-diabetic drugs, such as Glibenclamide and metformin, and Improved Traditional Medicine by improving glycemic control and preventing complications like nephropathy [16]. Studies have demonstrated that vitamin D can improve glucose homeostasis by enhancing insulin secretion, reducing inflammation, preserving beta cell mass, and sensitizing insulin action. Furthermore, vitamin D has shown Reno-protective effects in diabetic nephropathy, reducing proteinuria and urinary albumin excretion.

- **Vitamin-D role in CVD:**

It contributes to promoting and preserving cardiovascular health by modulating immune and inflammatory functions, regulating cell proliferation and migration, endothelial function, renin expression, and extracellular matrix homeostasis. It has also been shown to have anti-inflammatory and antioxidant effects, decreasing cardiometabolic risk (Figure 3). It has been found that vitamin D deficiency is associated with adverse vascular remodeling, endothelial dysfunction, vascular inflammation, and increased risk for cardiovascular and cerebrovascular such as obesity, hypertension, diabetes, and metabolic syndrome, leading to significant morbidity and mortality. Vitamin D acts as a co-hormone in the body, affecting insulin sensitivity, lipid profiles, and inflammatory mediators, all of which are important factors in cardiovascular health [2,17].

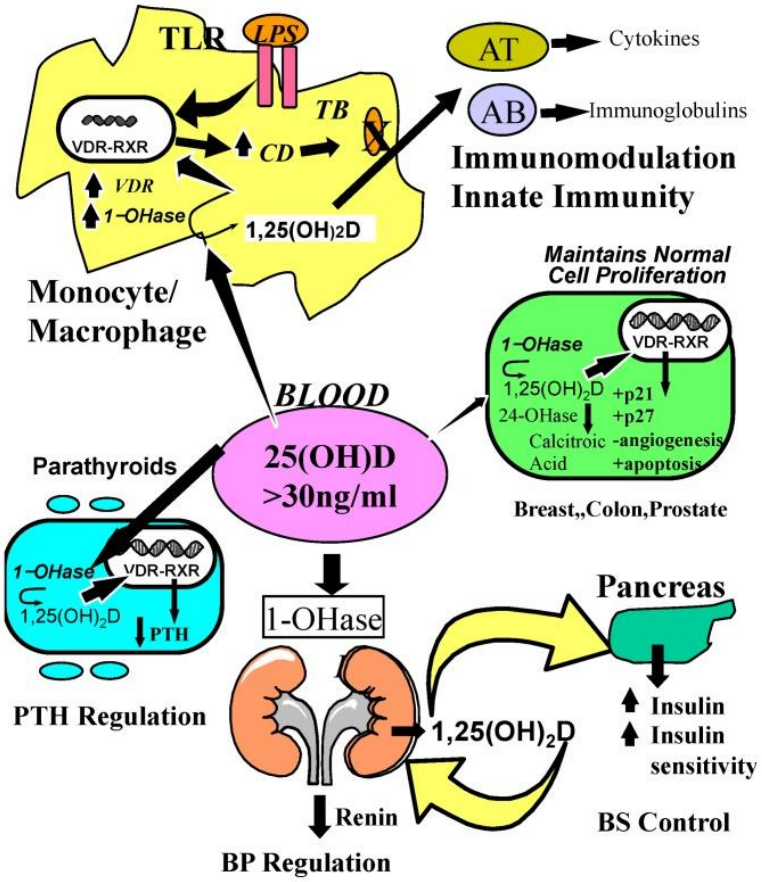
Figure (3): The mechanism by which the risk of cardiovascular disease increases due to vitamin D deficiency [18].



- **Vitamin-D role in Immune system:**

Vitamin D supplementation has shown immunomodulatory effects and induces autophagy, which can be protective against various diseases and infections (Figure 4). It has been found to increase antimicrobial responses in macrophages and stimulate autophagy through different signaling pathways that induce the expression of antimicrobial peptides such as LL-37 and β-defensin through activation of hormone-bound vitamin D receptor (VDR) that cause the transcription of genes involved in innate immunity [2,19]. Vitamin D supplementation has been found to reduce the risk of COVID-19 infection and the severity of the disease [9].

Figure (4): Role of vitamin D in the immune system [20].



- **Vitamin-D role in the reproductive system:**

It has been shown to modulate metabolic and hormonal indicators of women's fertility, such as higher pregnancy rates, improved ovarian reserve parameters, and curtailed fibroid growth [4,21]. Its deficiency can lead to reproductive disturbances and pathologies, including ovarian cysts. In women with polycystic ovarian syndrome (PCOS), vitamin D supplementation has shown benefits in terms of improved menstrual regularity, lowered testosterone and insulin levels, and improved AMH levels. Vitamin D deficiency has been implicated in the pathogenesis of gynecological disorders, including uterine fibroids and endometriosis. It is also involved in various physiological processes, including inflammation, oxidative stress, and mitochondrial respiration, which are crucial for reproductive health. In men, vitamin D levels have been positively correlated with sperm parameters, especially motility, and low vitamin D levels have been linked to decreased pregnancy rates in men [21,22]. Vitamin D supplementation has shown the potential to improve sperm parameters and reduce oxidative stress in infertile men with asthenozoospermia. However, more research is needed to fully understand the molecular mechanisms underlying the effects of vitamin D on male reproductive function.

- **Vitamin D's role in the mental system:**

Vitamin D plays a role in the central nervous system (CNS) and affects cognitive function and mental health [23-25]. Studies suggest that vitamin D supplementation may benefit healthy individuals' cognitive outcomes, potentially preventing cognitive decay. However, the evidence is mixed when it comes to the impact of vitamin D supplementation on mental health in adults with respiratory system diseases. Vitamin D deficiency during gestation has been associated with neurological disorders and an increased risk of developing mental illnesses later in life. Furthermore, vitamin D is involved in brain processes such as proliferation, apoptosis, and neurotransmission and has anti-inflammatory activity that may influence maternal health and fetal neurodevelopment. Vitamin D deficiency has been associated with depression and suicide [26]. Some studies suggest that vitamin D supplementation may alleviate symptoms of depression and anxiety, particularly in chronically stressed rodents and some clinical studies. In a survey of patients with autoimmune thyroiditis and hypothyroidism, cholecalciferol supplementation along with L-thyroxine was found to be more effective in reducing depression compared to L-thyroxine alone [23].

CONCLUSION:

Vitamin D is a versatile, multifaceted micronutrient with far-reaching implications for human health, making it crucial for maintaining overall health and preventing various diseases and conditions. Its roles extend beyond traditional functions in musculoskeletal health to encompass a broad spectrum of physiological processes across multiple organ systems. The intricate interplay of vitamin D in immune modulation, anti-inflammatory responses, reproductive health, cardiovascular risk, and mental well-being. Further research is warranted to elucidate its precise mechanisms and optimize its therapeutic applications across diverse medical domains.

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