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Vitamin D Deficiency and Resistance in Long-Term Illnesses

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Abstract: The identification of the role of vitamin D in the human body has evolved drastically over the years. Now considered an essential vitamin, D was previously labelled as a hormone. The synthesis is initiated within the keratinocytes due to the sunlight exposure and is transformed into an active form through a series of reactions in the liver and kidney, where the enzymes required for this conversion are present. As a result of restricted production or availability, vitamin D deficiency is a concerning issue in children and adults. Along with this, certain genetic, molecular and metabolic disturbances result in the development of vitamin D resistance. The role of pathogens and environmental toxins that result in this condition is also asserted. The review also explores the mechanism of vitamin D resistance in chronic diseases, such as the reduced enzyme activity due to a variety of factors, leading to chronic kidney disease. Impaired hydroxylation in the liver contributes to chronic lung disease, and how obesity, endocrine, and inflammatory disorders impact this mechanism is also acknowledged. The clinical consequences of vitamin D dysfunction are wide, such as effects on bone, teeth and even muscles. It also plays a role in the pathogenesis of Multiple Sclerosis and may lead to associated symptoms. The review also discusses the diagnostic methods, which mainly focus on clinical and biochemical studies. The management and therapeutic strategies that underlie the importance of vitamin D supplementation and the use of enzyme analogues and symptomatic management.

Keywords: *"Vitamin D Resistance" "Vitamin D Deficiency" "VDR polymorphism" "Rickets" "Sarcopenia" "Osteomalacia".*

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I. INTRODUCTION

Vitamin D is technically classified as a conditionally essential vitamin. Still, it is one of the most important vitamins required for bone, muscle, and reproductive health in both men and women. While a fraction of it is obtained from diet, it is mainly produced in the skin by exposure to sunlight [1]. 7-Dehydrocholesterol, a direct precursor of cholesterol, is converted to pre-vitamin D3 by a reaction that takes place in the keratinocytes of the human skin [2].

In the late nineteenth century, the bones of rachitic children, mostly in cities of northern latitudes, had a low content of calcium and phosphate. However, prevention or cure of the deficiency of these elements was not obtained through the dietary supplementation of calcium and phosphate, which led to the theory that deficiency of some other factor was involved in the skeletal problems in these children. Since it mostly affected inhabitants of northern latitudes, its connection to sunlight exposure was confirmed. The early twentieth century marked a surge in experiments and clinical studies that confirmed the effects of sunlight and cod liver oil, as well as a calcium-depositing vitamin, in curing skeletal problems in children with calcium and phosphate deficiency [3]. This calcium-depositing vitamin is now known as vitamin D.

Even today, vitamin D deficiency remains a common issue in both children and adults. Vitamin D deficiency can lead to growth retardation and skeletal deformities in utero and in childhood. Osteomalacia, an increased risk of fracture, muscle weakness, and exacerbation of osteopenia and osteoporosis, are the adult manifestations of vitamin D deficiency [4].

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Vitamin D receptor (VDR) is widely distributed in many human tissues, including the intestine, kidney, bone, parathyroids, thyroid, skin, adrenal, liver, breast, pancreas, muscle, prostate, and many other organs.[1,5] and it is one of 1600 transcription factors encoded by our genome. It is directly modulated through its activities by 1,25(OH)2D3, which makes it comparable to estrogen receptors and glucocorticoid receptors [2]. Heterogeneous mutations in the VDR cause vitamin D resistance [5]. Hypophosphatemia is one of the important clinical manifestations of vitamin D resistance, which, in the long term, leads to insufficient formation of hydroxyapatite along with a compensatory increase in osteoid, which results in skeletal complications [6]. Vitamin D is critical for the human body, having far-reaching effects on health, and is essential for the entire lifespan from prenatal to end-of-life stages [7].

II. PHYSIOLOGY OF VITAMIN D

Synthesis of vitamin D primarily occurs in the skin after exposure to sunlight [8]. The UVB photons penetrate the epidermis and dermis, where they get absorbed by the 7-dehydrocholesterol in the plasma membranes of skin cells. This reaction causes the opening of the B ring at carbons 9 and 10 by the excitation of double bonds in 7-dehydroxycholesterol, transforming the rigid steroid structure into previtamin D3, a more flexible molecule [9].

The previtamin D3 produced in the skin is metabolised further to its active form. The first step in the activation takes place in the liver [9]. 25-Hydroxy vitamin D (25OHD), the major circulating form of vitamin D, is formed by the hydroxylation of previtamin D3 produced in the skin by the hepatic enzyme 25-hydroxylase [9,10]. The 25-hydroxylase activity is found in both liver mitochondria and endoplasmic reticulum. This hydroxylated form provides a clinically useful marker for the vitamin D status [9].

The enzyme 25 OHD 1 α hydrolylase converts 25 OHD to 1,25(OH)2D, the most potent metabolite of vitamin D, which has a huge role in the regulation of calcium metabolism. 24,25(OH)2D, the second most important metabolite of 25 OHDis also produced by the kidney [9].

The vitamin D receptors play important roles in many physiological and pathological mechanisms. They have a central role in musculoskeletal diseases such as osteoporosis as they regulate bone development and calcium homeostasis [11].

The first identified gene that functions as an essential host factor and genetically influences the modulation of the gut microbiome is the human VDR. It contributes significantly to genetic, immunological, environmental, and microbial aspects of human health and disease [12]. There is growing evidence in recent years showing the expression of VDR in the podocytes that suggests its potent renal protective activity against diabetic neuropathy [13].

The role of VDR in the pathogenesis of various diseases and its protective effects against these diseases are numerous, and many of its functions are still under study [12,13].

A deficiency of vitamin D results in reduced calcium absorption, ultimately leading to the release of calcium from bones to maintain circulating calcium levels. Sustained deficiency results in continuous bone turnover and resorption, which weakens the bone architecture and leads to secondary hyperparathyroidism, increasing the risk of fractures, ultimately resulting in osteomalacia and osteoporosis [14].

Maintenance of skeletal muscle is greatly dependent on vitamin D [14]. Muscle function and physical function are impaired before bones in case of vitamin D insufficiency [15]. VDR is present in muscles where it plays a major role in muscle damage and regeneration with the help of CYP27B1, the enzyme that hydroxylates vitamin D to its active form [16].

Therefore, the importance of vitamin D, its receptors, and genes that take part in metabolism and pathogenesis is greatly influenced by the vitamin D status in the body, and also the effect of the enzymes and proteins that take part in the steps of vitamin D synthesis and metabolism [10, 12, 14, 16].

III. MECHANISMS OF VITAMIN D RESISTANCE

Vitamin D resistance can be a result of molecular, genetic, or metabolic disturbances that impair vitamin D signalling pathways [17-19]. Polymorphisms in the genes expressing proteins involved in the vitamin D system, such as cytochrome P450 enzymes (CYP2R1, CYP27A1, CYP27B1 - hydroxylases) that helps in the formation of active vitamin D, vitamin D-binding Protein (VDBP) that is synthesised primarily by the liver is crucial for the transport of all vitamin D metabolites, the cell-surface receptor megalin-cubulin, vitamin D receptor (VDR), and retinoid-related orphan receptors (RORα and RORɣ) that are vitamin D hydroxy derivatives, are found to increase the susceptibility to vitamin D resistance [17,20,21].

Based on previous studies, polymorphism in VDR is the major contributing factor in vitamin D resistance [17,18]. VDR is a steroid receptor that is expressed in most cell types. In the nucleus, VDR forms a heterodimer with retinoid-X receptor (RXR), which then binds to vitamin D response elements (VDERs) and activates various transcription genes [22]. VDR has a DNA-binding domain (DBD) and ligand-binding domain (LBD), in which genetic mutations in DBD can cause total vitamin D resistance even when binding to VDR is normal [18]. The rs7116978 CC genotype and the rs731236 GG genotype were found to be predictors of low vitamin D responsiveness [17]. Other mutations, such as nonsense mutations, insertions/substitutions, insertions/duplications, deletions and splice site mutations in VDR are also found to cause 1,25(OH)2D resistance [18].

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VDR can also be partially blocked by pathogens, glucocorticoids (chronic stress), and environmental toxins. A study demonstrated that chronically elevated levels of glucocorticoids can potentiate VDR-mediated transcription of CYP24A1, an enzyme responsible for the degradation of 1,25(OH)2D3, by recruiting the glucocorticoid receptor to the CYP24A1 promoter region. Various physiological and pathophysiological factors can also influence VDR response. Various pathogens are found to inhibit VDR mRNA and protein expression, causing blockade of VDR [17,23].

Single-nucleotide polymorphisms (SNPs) of the VDBP gene in rs7041 and rs4588 are correlated with circulating 25(OH)D, and the alleles are Gc1F, Gc1S and Gc2. These polymorphisms can lead to altered binding affinity, which can reduce the bioavailability of vitamin D in target organs [22-25]. Since vitamin D is fat-soluble, it is sequestered in the fat tissue in obese people, making it less available in target organs [26]. Polymorphisms within genes of the vitamin D system and factors that could exacerbate blockade of the vitamin D receptor need further evaluation [17].

IV. VITAMIN D RESISTANCE IN CHRONIC DISEASES

The occurrence of vitamin D resistance in various chronic diseases, including chronic kidney disease, chronic liver disease, autoimmune diseases, and many others, has been found to result from the loss of functional tissue and alterations in metabolism [27-29].

- *Chronic Kidney Disease (CKD): Reduced 1-alpha Hydroxylase Activity*

Vitamin D levels are regulated by parathyroid hormone and FGF23. When there is a decrease in serum calcium, PTH activates 1-alpha-hydroxylase, while FGF23 inhibits 1-alpha-hydroxylase and activates 24-hydroxylase, which decreases vitamin D [30]. The activity of 1-alpha-hydroxylase is decreased in CKD due to the loss of functional renal tissue, elevated phosphate and FGF23 levels, and reduced tubular responsiveness to PTH, collectively leading to suppression of the enzyme's synthesis and function [23,27,31]. In renal proximal tubular cells, $1,25(OH)_2D_3$-DBP or -lipoproteins enter the cells through receptor (megalin)-mediated endocytosis, which then binds to VDR and is translocated to the nucleus. In the nucleus, it heterodimerises with retinoid X receptor (RXR) to facilitate gene transcription involved in calcium and phosphate homeostasis, PTH suppression, and immune modulation. In CKD, megalin expression is reduced due to uremia, which reduces the intake of vitamin D complexes by cells and can lead to vitamin D resistance, even when vitamin D levels are normal [32].

- *Chronic Liver Disease: Impaired Hydroxylation*

Vitamin D3, produced in the epidermis, binds to vitamin D-binding protein (DBP) for transport to the liver, where hydroxylation enzymes hepatic 25-hydroxylase or sterol-27-hydroxylase are present, which convert vitamin D3 to 25(OH)D [30,33,34]. The majority of 25(OH)D is bound to DBP, which is synthesised by the liver and is transported to the kidney for conversion to its active metabolites [20,28]. Vitamin D resistance can develop in CLD due to reduced functional hepatocytes [4]. In CLD, serum DBP is decreased, which contributes to reduced vitamin D transport, bioavailability, and tissue responsiveness [28, 35]. In addition, VDR expression is downregulated in CLD, which diminishes hepatocellular response even when the active form of vitamin D is available [36].

- *Endocrine Disorders: Diabetes Mellitus, Obesity, And Their Link to Resistance*

In beta cells of the pancreas, expression of the VDR gene and other beta-cell markers is downregulated as a result of chronic hyperglycemia or beta-cell loss/differentiation, which reduces cellular responsiveness to vitamin D even when serum vitamin D levels are normal. It can lead to decreased insulin synthesis, secretion, or sensitivity [37,38]. Vitamin D is a fat-soluble vitamin. In adipose tissue, VDR and enzymes in vitamin D metabolism are expressed. Vitamin D has major roles in adipogenesis, lipogenesis, lipolysis, and the secretion of inflammatory hormones [26]. Cutaneously synthesised vitamin D3 is sequestered in body fat, in obese individuals, and makes it less available for various metabolic processes [26,39]. The bioavailability of vitamin D is further affected by impaired 25-hydroxylation and 1-alpha hydroxylation in obesity [39]. VDR expression in adipocytes is altered by various pro-inflammatory cytokines, the expression of which is regulated by vitamin D [40]. Altered VDR expression and its activity can lead to vitamin D resistance at the tissue level [40,41].

- *Rheumatologic And Inflammatory Diseases: RA, IBD, Systemic Inflammation*

Recent studies suggest that disruption of the vitamin D signalling pathway contributes to the pathogenesis of RA, since $1,25(OH)_2D$ enhances Treg activity and suppresses proliferation and activity of TH1 and TH17, which are known to cause chronic inflammation in RA [29]. There is evidence that states VDR expression is lower in RA and is associated with the inflammatory process, and can affect prognosis and pathogenesis of RA [42]. VDR, present in the small intestine and colon, has several functions, including intestinal barrier function, proliferation and differentiation, innate immunity, regulation of the cell junctions, and antimicrobial peptide release. In patients with IBD, VDR expression is downregulated, which exacerbates the severity of the disease [43,44]. However, in a recent study, it was concluded that no significant correlation is present between VDR expression and circulating 25(OH)D in IBD [43-45]. Recent studies support downstream regulation in VDR and DBP genes in systemic inflammation that can progress the disease [46].

- *Other Chronic Illnesses: HIV, Tuberculosis*

In HIV, the key enzymes involved in vitamin D metabolism are upregulated by lipopolysaccharide (LPS) and HIV gp120, leading to its dysregulation, and the expression of VDR mRNA is also decreased, which reduces the cell's ability to respond to $1,25(OH)_2D$ [47]. Recent findings suggest that downregulation of the VDR gene expression and VDR polymorphisms, namely the FokI polymorphism, are the contributing factors of vitamin D resistance in MDR-TB patients [48].

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V. CLINICAL CONSEQUENCES OF VITAMIN D RESISTANCE

Vitamin D has a significant impact on the transcription of various genes and has evolved into an active hormone. The pleiotrophism of vitamin D is attributed to the presence of its receptors in various tissues, which highlights the non-calcemic actions of vitamin D [49].

As vitamin D plays a key role in calcium and phosphorus metabolism, its resistance would lead to decreased absorption of calcium (which contributes to secondary hyperparathyroidism) and phosphorus from the intestine, along with increased alkaline phosphatase [50]. The resistance to vitamin D is manifested as an autosomal recessive disease known as Hereditary Vitamin D Resistant Rickets (HVDRR) or Hereditary Vitamin D Receptor Defects (HVDRD) [51]. The clinical manifestations of the disease include bone pain, weakness of muscles, dystonia, and hypocalcemia-related convulsions. Abnormal rib cage movement leads to respiratory infections. Children have delayed walking due to pain in the lower extremities, with an increased incidence of fractures and pseudofractures seen in affected children. Dental caries and hypoplasia of teeth are more common among them [18]. Hypocalcemia will eventually lead to hyperparathyroidism, which can activate the osteoclast, resulting in bone remodeling and the increased presence of phosphorus in urine, along with the bone changes such as thinning and increased porosity, which can manifest as rickets, osteomalacia, and osteoporosis [52]. The physical finding of this is the bowed legs in children with rickets, due to abnormal growth plate development, which is clinically manifested as a ricketic rosary of ribs and enlargement of wrists [50]. Patients with Vitamin D-dependent rickets due to a loss-of-function mutation on chromosome 12q13.11, responsible for encoding of VDR, result in resistance to vitamin D, and about half of them have alopecia due to normal follicle cycling failure, which results from sparse hair on the scalp to alopecia of the entire body [18,53]. The vitamin D receptor is found in skeletal muscle owing to the importance of vitamin D for the normal development of muscles. With increasing age, the quantity of the receptors has been observed to decrease, even though the quantity of 25-hydroxy vitamin D was normal. This resulted in a decrease in muscle strength and mass (sarcopenia) [54]. Genetic polymorphism of Fok1 was found to be responsible for sarcopenia. Grip strength of the old women was also related to genetic polymorphisms of Vitamin D Receptors [55].

Autoimmune diseases showed a high response to increased doses of vitamin D, suggesting that vitamin D resistance plays a significant role in the pathogenesis of autoimmune diseases. 1, 25-dihydroxy vitamin D has multiple functions in the immune system. Activated 1,25-dihydroxy vitamin D caused gene expression by VDR, resulting in the production of proteins with antimicrobial effects, along with the proteins of autoimmune processes. Ninjurin 1, an example of a protein made by the activation of 1,25-dihydroxy vitamin D, made the APCs cross the blood-brain barrier, thereby establishing a key role in the pathogenesis of Multiple Sclerosis [17]. VDR polymorphism is also related to the development of several autoimmune diseases, like SLE, T1DM, Rheumatoid arthritis, and autoimmune thyroid diseases [56]. There is also an increased susceptibility to infectious diseases in vitamin D resistance [50]. Vitamin D also has a major role in carcinogenesis, as SNPs of vitamin D were related to breast, prostate, colorectal, and skin tumors [17]. 1,25-dihydroxy vitamin D has an impact on pancreatic functioning, along with immunoprotection, sensitization of receptors, and reduced resistance to insulin. *Fok*I polymorphism in the VDR gene placed the Chinese people at higher risk [57]. Elevated serum concentration of 1,25-dihydroxy vitamin D transforms the mesenchymal cells of the vessel walls into osteoblast-like cells, thereby producing a bone-matrix-like material, which then undergoes calcification, thereby affecting cardiovascular health [50].

To conclude, vitamin D is essential for the normal development of bones; therefore, the supplementation of vitamin D may help in the treatment of disease, but the form of vitamin D to be administered should be decided based on the defect in the metabolism of vitamin D as it is always better to provide the metabolite of vitamin D that is affected in the disease [58].

VI. DIAGNOSIS OF VITAMIN D RESISTANCE

Both clinical and biochemical studies first identified vitamin D-resistant rickets. Initially, rickets was associated with poverty and malnutrition, which later proved to be a disease that could be cured with cod liver oil. The effects of this therapy were first explained by Edward Mellanby in 1919. Further investigations discovered the role of ultraviolet rays in the disease cure [59]. PTH is required for Vitamin D resistance diagnosis. The PTH value should be normal with a normal serum concentration of 25-hydroxy vitamin D, which is > 40 ng/dl; then vitamin D resistance is suspected. There should not be a nutritional deficiency of calcium and phosphorus, and hyperparathyroidism along with this. Even though the serum concentration of 25-hydroxy vitamin D is normal, an increase in the concentration of 1,25-dihydroxy vitamin D is observed. The production of 1,25-dihydroxy Vitamin D is associated with the enzymatic activity of CTY2R1, CYP27A1, and CYP27B1, and degradation with the enzymatic activity of CYP24A1 with, thereby determination of enzymatic activity helps in the measurement of the concentration of 1,25-dihydroxy vitamin D. PTH has a major impact on the enzymatic activity leading to an increase in 1,25 dihydroxy vitamin D, which is needed for the proper VDR signaling, therefore a decrease in 25, hydroxy vitamin D / 1,25 hydroxy vitamin D ratio will be observed, with hyperparathyroidism, the latter being important biomarker for vitamin D resistance[17]. A decrease in serum calcium and phosphorus is observed with an increase in serum 1,25-dihydroxy vitamin D, ranging from 50-1000 pg/mL, while 30-100 pg/mL is the normal serum concentration in children. Lack of induction of CYP24A1 leads to elevated or normal concentration of 25-hydroxy vitamin D as it requires VDR action [53] Almost 45 mutations have been found, including nonsense, missense, insertions/ substitutions, deletions, and splice site mutations, which result in vitamin D

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resistance[18] For example a missense G to A mutation in exon 4, which caused the replacement of valine with methionine in the 26th position in VDR's DNA binding domain was found in the DNA sequencing of two Iranian siblings [59]. Various biochemical and genetic studies are being conducted to improve the diagnostic procedures through a better understanding of physiology [53].

VII. MANAGEMENT AND THERAPEUTIC IMPLICATIONS

- *High-Dose Vitamin D Supplementation: Evidence and Limitations*

Vitamin D deficiency is indicated when the serum 25(OH)D levels are below 25-30nmol/L (10-12ng/mL), and it must be treated. The threshold for sufficiency of vitamin D in serum level is considered to be ≥50 nmol/L (20 ng/mL), and some recommend ≥75 nmol/L (30 ng/mL) as the mark [60].

Vitamin D is available in vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). For treating deficiency, Vitamin D_3 is considered more potent and effective than vitamin D_2 in raising and maintaining serum 25(OH)D levels [52]. In severe deficiency serum 25(OH)D < 12 ng/mL / < 30 nmol/L, initial therapy of 6000IU (150 µg) daily *or* 25 000–50 000 IU (625–1250 µg) weekly of vitamin D_2 or D_3 for 8 weeks. After reaching a level of >30 ng/mL, maintenance therapy of 1000-2000IU (25–50 µg) daily. In moderate deficiency (12–20 ng/mL / 30–50 nmol/L), 800–1,000 IU (20–25 µg) is administered daily for 3 months. The levels are then rechecked, and maintenance doses are given after the levels are found to be normal. In insufficiency (20–30 ng/mL / 50–75 nmol/L), 600-800 IU (15–20 µg) daily is given to restore sufficiency [52,60].

Vitamin D supplementation has shown beneficial effects, but it also has some serious limitations. As we know, Vitamin D is fat-soluble; if taken without food or fat, it can decrease the absorption and effectiveness. Overdose or prolonged high-dose intake can build up in the body and cause toxicity. When serum 25(OH)D levels exceed 88 ng/mL, this can result in hypercalcemia, which can cause symptoms such as vomiting, loss of appetite, excessive urination, thirst, and muscle weakness. Long-term excess can even damage the kidneys and cause bone pain [52]. The safe upper limit for long-term use is clearly not known, and mistakes in manufacturing and labelling errors can lead to accidental overdosing. Lack of knowledge in correct optimal serum 25(OH)D levels and inadequate patient education can lead to misuse and, lately, hypervitaminosis [61].

- *Active Vitamin D Analogues (Calcitriol, Alfacalcidol)*

Calcitriol, the active form of a vitamin D analogue, is used in managing hypocalcemia, which is associated with chronic kidney disease, hypoparathyroidism, and secondary hyperparathyroidism. It enhances calcium and phosphate absorption in the gut, promotes bone resorption, and regulates parathyroid hormone levels. In case of toxicity, prompt withdrawal, hydration, and supportive therapy with corticosteroids or bisphosphonates is required [62].

Alfacalcidol (1α-hydroxycholecalciferol) is a vitamin D_3 analogue, which is converted to the active form calcitriol in the liver. It is used in patients with impaired renal activation of vitamin D. When alfacalcidol is combined with calcitonin, it can be used in osteoporosis treatment. Markers for bone formation have increased, and inflammation and bone resorption have decreased. So use of calcitonin can improve the effects of vitamin D analogues [63].

- *Adjunctive Treatments: Anti-Inflammatory Therapy and Weight Management*

Vitamin D supplementation is useful in managing inflammation and immune-related disorders. Calcitriol, active vitamin D, binds to VDRs in immune cells and Pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), which are increased in autoimmune diseases, are reduced by calcitriol, and anti-inflammatory cytokines (IL-10, IL-4) are increased. There is also an improvement in insulin sensitivity, heart health, and brain health, along with anti-inflammatory properties [64].

Vitamin D helps in weight management by improving insulin sensitivity, regulating adipocyte function, and enhancing brown fat thermogenesis. Management of obesity is achieved through lifestyle modifications along with vitamin D3 supplementation (2000–5000 IU/day) [65].

- *Individualised Approaches In the Chronic Disease Population*

The population with chronic diseases, and the treatment for the vitamin D therapy, must be individualised, and starts with baseline serum 25(OH)D measurements, then reaching high target ranges(30-50ng/mL) for high-risk patients. Dosing should be considered based on clinical factors (obesity, malabsorption disorders, CKD, hepatic disease, other medications) that affect and alter vitamin D bioavailability. The treatment plan includes regular monitoring of serum 25(OH)concentration, calcium levels, response to dose, and ensuring both efficacy and safety [66].

VIII. FUTURE DIRECTIONS

- *Need For Better Biomarkers of Vitamin D Resistance*

Serum 25(OH)D is not an efficient biomarker to find resistance in tissues. Resistance can result from VDR or metabolic gene polymorphism, ageing, pathogen-mediated VDR blockade, chronic stress and toxins. Elevated PTH is the most practical biomarker, but other, more accurate markers are needed. Potential indicators like $1,25(OH)_2D/25(OH)D$ ratio, VDR expression, genetic profiling of VDR, related enzymes, and 20(OH)D can be studied. Future research should focus on authenticating these biomarkers to plan individualised vitamin D therapy [17].

- *Potential For VDR-Targeted Therapies*

VDR agonists can change the immune responses and so have potential in restoring immune tolerance. Treatment efficacy is influenced by VDR signalling, which is affected by genetic variation, environmental factors, enzyme polymorphism, and developing therapies that could enhance VDR activity and minimise side effects could help in

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personalised treatments. Individuals with acquired vitamin D resistance and low responders must be identified by the physicians for tailoring the dosing strategy, which could help in achieving optimal outcomes and minimise side effects [67].

IX. CONCLUSION

Vitamin D and its receptor play a role in muscle repair, immune modulation, and protection against metabolic and renal diseases. Vitamin D resistance can occur due to the mutations and polymorphisms in genes encoding the vitamin D receptor (VDR), vitamin D binding protein (VDBP), and hydroxylase enzymes (CYP2R1, CYP27A1, CYP27B1), among which the VDR mutations play the most important role. Altered enzyme activity, reduced receptor expression, and metabolic dysfunction in chronic kidney disease, chronic liver disease, diabetes, obesity, autoimmune disorders, and infections like HIV and tuberculosis contribute to resistance.

Vitamin D resistance disrupts calcium and phosphorus homeostasis, thereby affecting multiple organ systems. Other than its effect on the skeletal system, there are systemic manifestations due to the pleiotropic actions of VDR, such as sarcopenia, autoimmune diseases (such as SLE, T1DM, and rheumatoid arthritis), certain cancers, and metabolic disorders like type 2 diabetes. Low circulating calcium and phosphate, high levels of PTH, and high circulating 1,25-dihydroxy vitamin D levels are determinants of vitamin D resistance. A personalised approach that considers the underlying cause and metabolic capacity of each patient is essential for the effective management of resistance and deficiency of vitamin D. With proper dosing, Vitamin D_3 is preferred due to its potency and sustained action. Calcium balance, bone health, and broader metabolic and immune functions are improved from vitamin D therapy.

The role of other biomarkers in reflecting tissue resistance is being established, and further studies are needed for future research focusing on these biomarkers. VDR agonists or targeted therapies could improve the outcome of personalised treatments.

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- D.Y. conceptualised the study, designed the structure, coordinated the literature review process, and edited the full manuscript.
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