Review

Vitamin D Resistance: Mechanisms, Clinical Implications, and Integrative Perspectives

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Review

Vitamin D Resistance: Mechanisms, Clinical Implications, and Integrative Perspectives

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Abstract

Vitamin D resistance describes a spectrum of conditions in which individuals fail to achieve expected biological responses to vitamin D despite supplementation and/or apparently adequate serum 25-hydroxyvitamin D [25(OH)D] concentrations and sun exposure. While rare hereditary forms such as Hereditary Vitamin D-Resistant Rickets (HVDRR) are well-characterized, emerging evidence suggests that acquired resistance may contribute to suboptimal responsiveness in a broader clinical population. Contributing factors include genetic variation in vitamin D metabolism and receptor pathways, chronic inflammation, metabolic dysregulation, micronutrient cofactor insufficiencies, and environmental exposures. This review synthesizes current understanding of vitamin D resistance mechanisms, diagnostic challenges, and implications for personalized supplementation strategies. We propose an operational definition of vitamin D resistance as a state of inadequate physiological response to vitamin D despite achieving conventionally sufficient 25(OH)D levels, best assessed using response-based markers such as PTH suppression, calcium handling, and clinical endpoints. We further outline a pragmatic, systems-based evaluation framework that incorporates endocrine, inflammatory, metabolic, medication-related, and micronutrient determinants to guide individualized dosing and monitoring.

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1. Introduction

Vitamin D is essential for calcium–phosphate homeostasis, immune regulation, and cell proliferation[1–4]. Standard clinical practice assesses vitamin D status primarily through serum 25(OH)D concentration with sufficiency thresholds often cited at ≥50 nmol/L (20 ng/mL) or higher. However, clinical observations indicate that some individuals do not manifest expected biochemical or physiological responses despite achieving conventional serum targets, a phenomenon increasingly framed as vitamin D resistance[5] suggesting a functional block in vitamin D utilization[6] and interindividual differences in vitamin D responsiveness[7].

Accordingly, we interpret "vitamin D resistance" as a systems-level phenomenon in which upstream determinants—metabolic stress, chronic inflammation or infection, micronutrient cofactor insufficiency, endocrine dysregulation, environmental exposures, and iatrogenic factors—shape clinical responsiveness to vitamin D. This perspective is consistent with the recognized interindividual variability in vitamin D response and supports response-based assessment beyond serum 25(OH)D alone[5–8], while providing a systems-oriented heuristic for clinical evaluation[9].

We first review hereditary forms, then summarize proposed mechanisms of acquired resistance, and finally outline response-based diagnostics and pragmatic management considerations.

In this review, 'systems-level' refers to multi-determinant physiology assessed using measurable response markers (e.g., PTH, calcium handling, clinical endpoints), rather than alternative diagnostic constructs.

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2. Classical and Emerging Definitions of Vitamin D Resistance

2.1. Hereditary Vitamin D-Resistant Rickets (HVDRR)

HVDRR (also known as vitamin D dependent rickets type II) is a rare autosomal recessive disorder caused by loss-of-function mutations in the vitamin D receptor (VDR) gene, resulting in target tissue unresponsiveness to 1,25-dihydroxyvitamin D[10,11]. Patients exhibit clinical rickets, hypocalcemia, secondary hyperparathyroidism, and elevated serum $1,25(OH)_2D$ levels due to impaired VDR signaling[10–13]. Adjunctive cinacalcet has been reported in selected HVDRR cases to help manage secondary hyperparathyroidism[14]. Mutations affecting the VDR ligand-binding or DNA-binding domains disrupt receptor–DNA interactions and impair transcriptional activation of vitamin D target genes[10,15].

2.2. Acquired or Functional Vitamin D Resistance

Beyond hereditary forms, acquired resistance refers to impaired biological responsiveness to vitamin D in the absence of classical VDR gene mutations. We distinguish low exposure or low bioavailability states (e.g., inadequate intake, malabsorption, or adipose sequestration) from functional vitamin D resistance, defined operationally as a failure to achieve expected biochemical or clinical responses—such as parathyroid hormone (PTH) suppression or improvements in calcium handling—despite attaining conventionally sufficient serum 25-hydroxyvitamin D [25(OH)D] concentrations[16–18].

3. Mechanisms Underlying Vitamin D Resistance

3.1. Genetic Variability in Vitamin D Pathways

Genome-wide association studies have identified multiple genetic loci that influence circulating 25(OH)D levels and vitamin D metabolism[19]. Variants in genes encoding VDR, vitamin D binding protein (DBP), and metabolizing enzymes such as CYP2R1 and CYP27B1 have been implicated in interindividual differences in vitamin D responsiveness[19–22]. Polymorphisms in VDR have also been associated with altered immune and bone outcomes and with differential responses to supplementation[20,23].

3.2. Metabolic and Inflammatory Influences

Accumulating evidence indicates that vitamin D responsiveness is strongly modulated by metabolic status and inflammatory burden. Obesity, insulin resistance, chronic low-grade inflammation, and persistent infections—hallmarks of modern metabolic disease—can impair vitamin D bioavailability, signaling, and downstream biological effects even when serum 25-hydroxyvitamin D [25(OH)D] concentrations appear adequate.

3.2.1. Obesity and Metabolic Syndrome

Obesity and insulin resistance are consistently associated with lower circulating 25(OH)D levels, an observation traditionally attributed to volumetric dilution and sequestration of vitamin D within expanded adipose tissue. However, emerging data suggest that this relationship is more complex and reflects altered vitamin D metabolism and signaling within metabolically dysregulated tissues.

Adipose tissue expresses key components of the vitamin D system, including CYP27B1, CYP24A1, and the vitamin D receptor (VDR). In obesity and metabolic syndrome, dysregulated adipokine secretion, ectopic lipid accumulation, and chronic low-grade inflammation appear to modify the expression and activity of these enzymes, potentially reducing the conversion of vitamin D to its active form and attenuating intracellular signaling. Observational studies demonstrate inverse associations between 25(OH)D levels and markers of insulin resistance, central adiposity, and

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metabolic syndrome severity, suggesting that vitamin D insufficiency both reflects and amplifies metabolic dysfunction[24,25].

Moreover, metabolic syndrome has been linked to impaired cutaneous vitamin D synthesis and increased cardiometabolic risk in vitamin D–deficient populations, supporting the concept that metabolic stress states increase vitamin D requirements beyond standard supplementation targets[26]. Collectively, these findings support the view that obesity-related vitamin D "deficiency" often represents a **functional resistance state**, in which higher intake or serum levels may be required to achieve equivalent biological effects.

3.2.2. Chronic Inflammation and Infections

Chronic inflammation and immune dysregulation are central contributors to impaired vitamin D responsiveness. Pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), have been shown (primarily in experimental models) to downregulate vitamin D receptor (VDR) expression, disrupt VDR–retinoid X receptor (RXR) heterodimerization, and suppress transcription of vitamin D–responsive genes[27,28]. These effects can substantially attenuate downstream biological activity even when circulating 25-hydroxyvitamin D [25(OH)D] levels are within conventionally adequate ranges[27].

In parallel, vitamin D signaling intersects with vitamin K–dependent pathways involved in calcium trafficking, osteocalcin activation, and vascular integrity. Vitamin D stimulates the expression of several vitamin K–dependent proteins, including osteocalcin and matrix Gla protein, which require vitamin K–mediated carboxylation for biological activity[29]. Experimental, observational, and limited interventional evidence suggests that concurrent insufficiency of vitamins D and K may exacerbate inflammatory, metabolic, and vascular dysfunction, particularly in insulin-resistant states such as type 2 diabetes mellitus, where chronic low-grade inflammation and altered bone–endocrine signaling are already present[29,30].

Acute and chronic infections further compound these effects. In conditions such as sepsis and persistent viral infections, altered vitamin D metabolism, increased catabolism, and suppression of VDR signaling have been documented, potentially contributing to immune dysfunction and adverse clinical outcomes[31,32]. Recurrent infections, gut barrier dysfunction, and endotoxemia may therefore sustain a pro-inflammatory milieu that perpetuates acquired vitamin D resistance[27,31,32].

Taken together, these observations support the concept that impaired vitamin D responsiveness in chronic disease reflects a network failure involving immune activation, inflammatory signaling, and cofactor insufficiency, rather than an isolated deficiency of vitamin D itself. This framework helps explain why escalating supplementation alone often yields limited clinical benefit unless upstream inflammatory and metabolic drivers are simultaneously addressed[27,29].

3.2.3. Exercise, Sleep, and Circadian Biology

Physical activity, sleep quality, and circadian regulation are increasingly recognized as key modulators of immune, endocrine, and metabolic tone, and may therefore influence vitamin D status and responsiveness. Regular exercise has been associated with higher circulating 25(OH)D levels independent of sun exposure or supplementation, potentially mediated through reductions in adiposity, improved insulin sensitivity, and altered vitamin D mobilization from peripheral tissues[33]. Acute exercise interventions have also been shown to transiently raise circulating vitamin D metabolites, suggesting that muscle activity and hemodynamic shifts may directly influence vitamin D bioavailability[34]. Reviews of exercise physiology further support bidirectional interactions between vitamin D signaling and muscular, immune, and cardiometabolic performance, reinforcing exercise as a systems-level modifier rather than a confounder[35].

Sleep duration, quality, and circadian alignment may similarly affect vitamin D biology. Meta-analyses and interventional studies indicate that vitamin D deficiency is associated with sleep disorders, impaired sleep efficiency, and altered circadian rhythms, while supplementation may improve selected sleep outcomes in deficient individuals[36,37]. However, randomized controlled

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trials have produced mixed results, with at least one well-designed RCT reporting no significant improvement in sleep parameters following vitamin D supplementation, underscoring the heterogeneity of response and the likelihood of context-dependent effects[38]. Emerging evidence further suggests that environmental disruptors—particularly endocrine-disrupting chemicals (EDCs)—may interact with sleep disturbance and vitamin D deficiency, compounding circadian misalignment and broader endocrine dysregulation in modern environments[39].

Collectively, these findings support the inclusion of exercise optimization, sleep restoration, and circadian hygiene as relevant—though often overlooked—contributors to vitamin D responsiveness, particularly in individuals with metabolic or inflammatory disease states.

3.2.4. Endocrine Axes as Amplifiers of Vitamin D Resistance

The activity and clinical responsiveness of vitamin D are closely intertwined with major endocrine axes, including thyroid, adrenal, and sex hormone systems. Dysregulation within these axes—common in metabolic, autoimmune, and chronic inflammatory conditions—may amplify functional vitamin D resistance by altering receptor expression, hormone–receptor crosstalk, and downstream transcriptional responses.

Thyroid Axis

Thyroid dysfunction, particularly hypothyroidism and autoimmune thyroid disease, has been consistently associated with lower circulating 25(OH)D levels and altered vitamin D signaling. Large population-based analyses, including NHANES data, demonstrate significant associations between hypothyroidism and vitamin D deficiency, independent of demographic confounders[40]. A recent critical review further highlights bidirectional interactions between vitamin D and thyroid autoimmunity, including shared immunoregulatory pathways, VDR expression within thyroid tissue, and potential effects of thyroid hormones on vitamin D metabolism and action[41]. Emerging mechanistic work suggests that vitamin D status may also influence tissue sensitivity to thyroid hormones, providing a plausible pathway through which thyroid dysfunction could blunt vitamin D responsiveness without overt deficiency[42,43].

Adrenal Axis and Stress Physiology

The adrenal axis represents another underappreciated modulator of vitamin D signaling. Systematic reviews and narrative syntheses indicate that vitamin D receptors and metabolizing enzymes are expressed in adrenal tissue, and that vitamin D status may influence adrenal steroidogenesis and stress responses[44,45]. Chronic stress and dysregulated cortisol signaling—hallmarks of modern metabolic disease—may therefore interfere with vitamin D–mediated immune and metabolic effects, contributing to a state of functional resistance even when serum 25(OH)D levels appear sufficient.

Sex Hormones

Sex hormones interact bidirectionally with vitamin D metabolism and signaling. Seminal experimental work demonstrated that vitamin D regulates aromatase expression and estrogen biosynthesis, establishing a direct molecular link between vitamin D and sex steroid regulation[46]. Clinical and translational studies further suggest that estrogen status may modulate VDR expression and vitamin D responsiveness, with implications for reproductive health, bone metabolism, and immune regulation[47,48]. In men, randomized controlled trials have reported that vitamin D supplementation can increase testosterone levels in deficient individuals, supporting functional crosstalk between vitamin D signaling and androgen physiology[49,50].

Collectively, these findings support the concept that endocrine dysregulation may act as a **resistance amplifier**, attenuating vitamin D signaling downstream of serum concentration. In such contexts, failure to address thyroid imbalance, chronic stress–adrenal dysregulation, or sex hormone disturbances may limit the clinical effectiveness of vitamin D supplementation alone.

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3.3. Micronutrient Cofactor Insufficiencies

Efficient vitamin D metabolism depends on multiple micronutrient cofactors, most notably magnesium, which is required for both hepatic 25-hydroxylation and renal 1α-hydroxylation of vitamin D, and vitamin K2, which plays complementary roles in calcium trafficking, bone mineralization, and prevention of ectopic calcification[29,30]. Deficiencies in these and other micronutrients can dampen the conversion, activation, and downstream biological effects of vitamin D metabolites, thereby contributing to functional vitamin D resistance[51,52].

Beyond mineral cofactors, emerging evidence suggests that B-vitamins—particularly folate and vitamin B12—participate in broader nutrient networks relevant to vitamin D action. Observational studies in pediatric and adolescent populations demonstrate positive correlations between serum 25(OH)D and folate or vitamin B12 status, suggesting shared dietary, metabolic, or inflammatory determinants[53,54]. Interventional data further indicate that combined B-vitamin and vitamin D supplementation can improve bone turnover markers more effectively than vitamin D alone, supporting a functional interaction within skeletal metabolism[55]. Mechanistic models additionally propose vitamin D–B-vitamin crosstalk in neurocognitive and neuroimmune pathways, implying that B-vitamin insufficiency may attenuate selected non-skeletal effects of vitamin D[56].

More broadly, vitamin D signaling operates within a redox- and transcription-dependent cellular environment that is sensitive to micronutrient sufficiency. Antioxidant and trace nutrients such as vitamin C and zinc contribute to receptor integrity, immune modulation, and nuclear transcriptional fidelity, while retinoid signaling intersects with vitamin D receptor (VDR) heterodimerization and gene regulation. Although individual deficiencies may appear subclinical, cumulative micronutrient insufficiency can impair vitamin D responsiveness at multiple levels—enzymatic activation, receptor signaling, and downstream effector pathways—supporting a systems-level interpretation of vitamin D resistance rather than an isolated nutrient deficit.

4. Diagnosing Vitamin D Resistance

Standard assessment using serum 25(OH)D alone may not capture functional responsiveness. Markers such as PTH, calcium balance, and clinical outcomes (e.g., bone density, immune markers) offer supplementary insights[57]. Persistent secondary hyperparathyroidism despite adequate 25(OH)D levels may indicate resistance rather than simple deficiency[5,16].

5. Clinical Implications of Resistance

Vitamin D resistance may contribute to suboptimal responses in conditions traditionally linked to vitamin D status, including autoimmune diseases, osteoporosis, and metabolic syndrome[16,24,26,27]. Recognition of resistance underscores the need for individualized evaluation and suggests that some individuals require tailored interventions beyond conventional dosing.

6. Vitamin D Dosing and Safety: Distinguishing Physiological Range from Toxicity Risk

Guideline bodies differ in recommended target ranges and upper intake thresholds for vitamin D, reflecting variation in evidentiary standards, population risk profiles, and clinical priorities; therefore, optimal serum targets should be individualized rather than universally prescribed.

A major source of confusion surrounding vitamin D resistance is the conflation of physiological adaptation with toxicity, often leading to overly conservative dosing. Population-based studies and clinical experience suggest that serum 25-hydroxyvitamin D [25(OH)D] concentrations of 50–100 ng/mL (125–250 nmol/L) are generally well tolerated and associated with favorable skeletal, immune, and metabolic endpoints when individualized risk assessment and biochemical monitoring are applied, under the supervision of a trained and experienced healthcare professional[58–61].

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Limited evidence from selected, closely monitored cohorts suggests that serum 25-hydroxyvitamin D concentrations in the range of 100–150 ng/mL (250–375 nmol/L) have not been consistently associated with clinically significant adverse effects when appropriate safeguards—such as controlled calcium intake and normal renal function—are in place[62–64]. These observations indicate that, in carefully selected patients, higher serum targets may be considered under medical supervision, particularly in the context of suspected vitamin D resistance.

By contrast, reported adverse effects—including hypercalcemia, hypercalciuria, nephrocalcinosis, and vascular calcification—**consistently emerge at substantially higher concentrations**, typically **above 150 ng/mL**, and more reliably **above 200 ng/mL (500 nmol/L)**, particularly in the context of unmonitored supplementation, excessive calcium intake, or underlying granulomatous or renal disease[65,66].

These findings underscore a critical clinical distinction:

Toxicity is dose- and context-dependent, not an inevitable consequence of higher serum vitamin D levels. In resistant individuals, failure to achieve clinical or biochemical endpoints at conventional "sufficient" ranges may reflect impaired vitamin D signaling rather than excess exposure[3,9]. Consequently, rigid adherence to low upper limits may paradoxically perpetuate deficiency-like states in patients with functional resistance.

From a systems physiology perspective, vitamin D should be evaluated not solely by serum concentration but by **physiological response**, including suppression of parathyroid hormone, normalization of calcium handling, immune modulation, and clinical outcomes. This supports a **personalized therapeutic window**, rather than a universal upper cutoff, particularly in conditions characterized by inflammation, immune dysregulation, or metabolic stress[16].

7. Therapeutic Strategies

7.1. Personalized Supplementation

High-dose vitamin D protocols, such as those reported by proponents of the Coimbra protocol for multiple sclerosis, illustrate that titrating supplementation to biochemical and clinical endpoints—most notably parathyroid hormone (PTH) suppression—may overcome functional vitamin D resistance in selected settings. These observations suggest that fixed-dose strategies may be inadequate in states of altered vitamin D metabolism or signaling. Such approaches require strict medical supervision, comprehensive laboratory monitoring (including calcium and renal parameters), and are not considered standard of care[16].

7.2. Systems-Level Determinants of Vitamin D Responsiveness

Beyond supplementation dose alone, vitamin D responsiveness is shaped by a constellation of systemic determinants, including medication exposure, dietary and metabolic state, micronutrient cofactor sufficiency, environmental and lifestyle factors, chronic infections, and endocrine regulation. Failure to address these upstream contributors may limit the biological effectiveness of vitamin D even when serum 25-hydroxyvitamin D [25(OH)D] concentrations appear adequate. The following subsections examine these determinants individually as modifiable contributors to functional vitamin D resistance.

7.3. Medications as an Underrecognized Contributor

Medication effects on vitamin D status represent a frequently overlooked cause of apparent resistance. Numerous commonly prescribed drugs—including glucocorticoids, anticonvulsants, antiretrovirals, antifungals, and certain lipid-lowering or weight-loss agents—can impair intestinal absorption, alter hepatic or renal metabolism, or accelerate vitamin D catabolism. A structured medication review should therefore be part of the evaluation in patients with suboptimal vitamin D responsiveness[67,68].

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7.4. Dietary Pattern, Carbohydrate Load, and Metabolic State

Diet composition appears to influence vitamin D metabolism and utilization beyond caloric intake alone. Higher carbohydrate intake and insulin resistance have been associated with lower circulating 25(OH)D and impaired downstream signaling, consistent with the broader metabolic–inflammatory model of vitamin D resistance[69]. In contrast, carbohydrate-restricted and ketogenic dietary patterns may favorably modulate vitamin D status through reductions in adiposity, improvements in insulin sensitivity, and altered lipid-mediated vitamin D distribution[70,71]. Consensus statements and interventional data from low-carbohydrate and ketogenic nutrition literature further suggest that weight loss and metabolic normalization are associated with rising 25(OH)D levels independent of supplementation dose[72,73]. When such dietary strategies are employed, attention to mineral balance and bone health remains important, particularly during prolonged carbohydrate restriction[74].

7.4.1. Fasting as a Metabolic Lever

In addition to carbohydrate restriction and ketogenic dietary patterns, fasting represents a related metabolic intervention that may influence vitamin D responsiveness through weight loss–independent mechanisms. Randomized and controlled studies of prolonged or structured fasting have reported changes in circulating vitamin D and related micronutrients, including vitamin B12, alongside improvements in metabolic markers, suggesting altered nutrient mobilization and utilization during fasting states[75]. Metabolomic analyses further indicate that fasting combined with physical activity induces coordinated shifts in lipid, amino acid, and energy metabolism, which may favorably modulate inflammatory tone and endocrine signaling relevant to vitamin D action[76]. More recent clinical observations support the concept that even brief or intermittent fasting interventions can rapidly modify metabolic and inflammatory profiles, reinforcing fasting as a potential adjunctive strategy in addressing functional vitamin D resistance[77].

7.4.2. Sunlight and Photobiomodulation Beyond Vitamin D

Emerging evidence suggests that the health effects of sunlight exposure extend beyond cutaneous vitamin D synthesis, involving photobiomodulation (PBM) mechanisms mediated by visible and near-infrared (NIR) light. Experimental and clinical studies indicate that PBM can modulate mitochondrial function, redox balance, nitric oxide signaling, and inflammatory pathways, thereby influencing systemic metabolic and immune regulation independent of serum 25(OH)D concentrations[78,79]. A randomized controlled trial of near-infrared light exposure demonstrated improvements in subjective well-being and physiological parameters, supporting the relevance of non–vitamin D photic signaling in human health[80]. Contemporary reviews argue that an exclusive focus on vitamin D may underestimate the broader biological effects of sunlight, particularly in modern indoor lifestyles characterized by light deprivation[81]. Within this framework, inadequate light exposure may represent an additional, underrecognized contributor to metabolic and inflammatory dysregulation that could indirectly amplify functional vitamin D resistance.

7.5. Environmental Exposures and Ultra-Processed Foods

Environmental toxicants and lifestyle exposures may also contribute to impaired vitamin D status and signaling. Air pollution, smoking, and exposure to endocrine-disrupting chemicals have been associated with lower vitamin D levels and increased inflammatory burden, potentially increasing vitamin D requirements[82,83]. In parallel, diets high in ultra-processed foods are associated with micronutrient dilution, systemic inflammation, and poorer vitamin D status, reflecting both reduced nutrient density and adverse metabolic signaling[84–87].

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7.6. Chronic Infections and Immune-Mediated Resistance

Persistent infections represent an additional integrative mechanism for acquired vitamin D resistance. Experimental data indicate that cytomegalovirus (CMV) infection can directly impair vitamin D signaling pathways in vitro, including effects on VDR expression and downstream gene activation[88]. CMV-related endothelial dysfunction has also been shown to interact with vitamin D pathways, providing a potential link between chronic infection, vascular inflammation, and impaired vitamin D responsiveness[89]. These findings support the concept that unresolved infections may blunt vitamin D efficacy even in the presence of adequate serum levels.

7.7. Integrative Implications

Taken together, these observations suggest that optimizing vitamin D responsiveness requires a **systems-level therapeutic strategy**. Addressing metabolic health, dietary pattern, medication burden, environmental exposures, and chronic infections may be as important as adjusting vitamin D dose itself. In this context, vitamin D resistance should be viewed not solely as a supplementation failure, but as a modifiable consequence of broader metabolic–inflammatory and environmental stressors.

In aggregate, optimizing metabolic health, reducing chronic inflammation, correcting micronutrient cofactor deficiencies, and mitigating upstream lifestyle and environmental stressors are integral to enhancing vitamin D responsiveness. Interventions targeting obesity, chronic stress, and other systemic drivers may therefore improve vitamin D utilization and clinical outcomes, even without further increases in supplementation dose[90,91].

8. Conclusions and Future Directions

Vitamin D resistance encompasses a continuum from rare hereditary receptor defects to more common, multifactorial functional resistance in adults. A holistic understanding of genetic, metabolic, and environmental contributors can refine diagnostic frameworks and optimize therapeutic approaches. Future research should aim to define biomarkers predictive of vitamin D responsiveness and resistance, clarify safe and effective individualized serum targets, and distinguish physiological adaptation from true toxicity. Such efforts may allow clinicians to move beyond population-based thresholds toward precision dosing strategies that optimize vitamin D signaling while maintaining safety across diverse clinical contexts.

Conceptualizing vitamin D resistance as a systems-level phenomenon may help reconcile heterogeneous trial outcomes and shift clinical focus from fixed serum targets toward restoration of the underlying metabolic, inflammatory, and endocrine context.

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