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Vitamin D Insufficiency as a Nutritional Stress Amplifier: An Evidence-Weighted Framework for Adaptive Reserve under Exercise and Energy-Deficit Stress

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Highlights

- Low 25(OH)D may modify stress-recovery trajectories under converging vulnerability conditions.
- Calcitriol-VDR signaling supports mineral-endocrine coupling.
- Energy deficit may reveal conditional effects on adaptive reserve.
- RED-S is proposed as a validation model for conditional effects.
- Dynamic stress–recovery phenotyping is prioritized over static markers.

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Review

Vitamin D Insufficiency as a Nutritional Stress Amplifier: An Evidence-Weighted Framework for Adaptive Reserve under Exercise and Energy-Deficit Stress

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Abstract

Vitamin D is a fat-soluble secosteroid whose biological activity depends on conversion of circulating 25-hydroxyvitamin D into calcitriol, the active ligand of the vitamin D receptor. Although vitamin D has often been discussed as a potential ergogenic nutrient, evidence for direct performance-enhancing effects in athletes remains inconsistent. This review proposes that vitamin D insufficiency, used here as a context-dependent descriptive label for low circulating 25(OH)D rather than as a universal diagnostic category, may function as a nutritional stress amplifier that narrows adaptive reserve when mechanical, energetic, endocrine, inflammatory, and neuroendocrine stressors converge. The strongest evidence derives from the vitamin D–calcium–phosphate–PTH–FGF23 axis, through which calcitriol-VDR signaling supports mineral homeostasis, skeletal remodeling, and resilience to repetitive skeletal loading. Emerging evidence suggests intersections with skeletal muscle repair, myokine and osteokine signaling, inflammatory regulation, and tissue adaptation, although athlete-specific validation is needed**.** Low energy availability and Relative Energy Deficiency in Sport provide a translational model in which low circulating 25(OH)D may become more relevant because multiple nutritional, endocrine, skeletal, and recovery stressors coexist**.** Brain-related pathways involving fatigue, sleep, HPA-axis-related recovery, BDNF, monoaminergic signaling, and interoceptive processing are retained only as hypothesis-generating domains, not as evidence that vitamin D status modifies cognition, mood, motivation, behavior, or central recovery mechanisms in athletes. Future studies should move beyond static 25-hydroxyvitamin D assessment and unstratified supplementation trials toward dynamic stress–recovery phenotyping. This framework positions low circulating 25(OH)D status as a testable conditional modifier of stress–recovery trajectories rather than an isolated determinant of athletic performance or a primary clinical target.

Keywords: Vitamin D insufficiency; Calcitriol-VDR signaling; Nutritional biochemistry; Adaptive reserve; Low energy availability; Relative Energy Deficiency in Sport; Dynamic stress–recovery phenotyping.

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1. Introduction

Vitamin D is a fat-soluble secosteroid whose biological activity depends on conversion of circulating 25-hydroxyvitamin D [25(OH)D] into 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$; calcitriol], the active ligand of the vitamin D receptor (VDR). Through VDR-dependent transcription, calcitriol regulates calcium-phosphate homeostasis, intestinal mineral absorption, parathyroid hormone feedback, renal mineral handling, bone remodeling, and skeletal mineralization [1–3]. This established endocrine core raises a broader question: when does calcitriol–VDR signaling become relevant to tissue adaptation and resilience under physiological stress? The question is especially pertinent to exercise and energy deficit. Vitamin D has often been framed as an ergogenic nutrient, yet supplementation studies report inconsistent effects on performance, strength, fatigue, and recovery. Outcomes vary with baseline 25(OH)D, calcium intake, sunlight exposure, sex, training background, sport discipline, and the presence of deficiency or insufficiency [4–6]. Vitamin D is therefore unlikely to act as a universal performance enhancer**.** Within the framework proposed here, its relevance is hypothesized to emerge when vitamin D-dependent systems are challenged by repeated loading, tissue repair, inflammatory and endocrine strain, sleep disruption, or limited energy availability.

We propose that vitamin D insufficiency can be understood as a nutritional stress amplifier: a modifiable biochemical state that may narrow adaptive reserve when several stressors converge. Adaptive reserve is used here as an operational, hypothesis-generating construct, not as a validated clinical measure. It describes the capacity to withstand repeated physiological challenge, limit functional disruption, restore homeostasis within an appropriate time course, and support beneficial adaptation. Exercise offers a useful test case because training combines skeletal loading, muscle microdamage, high energy turnover, inflammatory signaling, autonomic activation, and neuroendocrine stress **[7–9].** These stimuli drive adaptation when nutrient availability and recovery are adequate. When they coexist with low 25(OH)D, insufficient calcium intake, low energy availability, endocrine disruption, sleep loss, or impaired recovery, the margin for successful adaptation may shrink. The key question is not whether vitamin D improves performance in all athletes, but whether low 25(OH)D status adds to vulnerability under repeated stress. In this review, "vitamin D insufficiency" is used as a context-dependent descriptive label for low circulating total 25-hydroxyvitamin D [25(OH)D], rather than as a universally validated diagnostic category. Proposed cutoffs vary across guidelines, clinical and public-health perspectives, populations, analytical methods, and outcomes; accordingly, no single 25(OH)D concentration is assumed here to define impaired adaptive capacity [10,11]. For research stratification, candidate boundaries may nevertheless be prespecified to test sensitivity across commonly used ranges. Concentrations below 12 ng/mL (<30 nmol/L) represent a conservative low-status boundary associated with increased risk of deficiency-related skeletal effects; values below 20 ng/mL (<50 nmol/L) correspond to a widely used skeletal-health adequacy threshold; and values below 30 ng/mL (<75 nmol/L) may be examined as a historical or study-defined boundary, but should not be treated as a universally validated definition of insufficiency or as an athlete-specific target [10,11]. Continuous 25(OH)D analyses should therefore remain primary or co-primary, with threshold-based analyses used as prespecified stratification or sensitivity analyses. This terminology also does not imply that low circulating 25(OH)D is equivalent to a proportional reduction in circulating calcitriol or to uniformly impaired tissue VDR signaling. Studies testing the proposed model should report the assay method and standardization procedures, measurement units, prespecified thresholds or continuous-exposure analyses, the baseline distribution of 25(OH)D, and the rationale for any classification of participants as deficient, insufficient, or sufficient [10,11].

The muscle-bone interface provides the strongest mechanistic anchor for this framework. Muscle contraction loads the skeleton, while bone remodeling depends on mineral availability, osteoblast–osteoclast coupling, endocrine status, and recovery resources. Vitamin D intersects with this system

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through calcium–phosphate regulation, PTH–FGF23 feedback, calcitriol–VDR signaling, and the maintenance of a permissive mineral–endocrine environment for skeletal adaptation. In athletic and military populations exposed to repetitive loading, low vitamin D status has been associated with stress-fracture vulnerability, while combined calcium and vitamin D supplementation has reduced stress-fracture incidence in high-load settings [12–14]. These findings do not show that vitamin D alone prevents injury. They support a conditional model in which vitamin D sufficiency contributes to skeletal resilience alongside adequate calcium intake, energy availability, endocrine function, and recovery.

Beyond mineral metabolism, vitamin D biology may intersect with skeletal muscle repair, inflammatory regulation, and endocrine crosstalk between muscle and bone. Candidate mediators include myokines, osteokines, cytokines, and nutrient-sensitive stress signals, but their evidential strength varies widely. Some belong to established mineral–endocrine physiology; others rest mainly on experimental, preclinical, or limited human data. The brain-related component requires still greater caution. VDR expression and local vitamin D metabolism have been described in regions involved in motor control, reward processing, stress regulation, and neuroendocrine function [15,16], and vitamin D biology has been linked to neurotrophic, monoaminergic, inflammatory, sleep-related, and HPA-axis pathways. Here, these pathways are considered only in relation to fatigue, sleep, stress regulation, and recovery. They are not presented as evidence that vitamin D enhances cognition, mood, or motivation. Low energy availability and Relative Energy Deficiency in Sport offer the clearest translational setting in which to test the model. RED-S can involve impaired bone health, endocrine dysfunction, altered immunity, metabolic suppression, psychological symptoms, impaired recovery, and reduced performance capacity [17–19]. Vitamin D insufficiency is not proposed as a cause of RED-S or disordered eating. It may instead compound an already constrained state characterized by inadequate energy and nutrient intake, mineral imbalance, endocrine suppression, skeletal loading, and poor recovery. The proposed stress-amplifier framework is not intended to imply an athlete-specific vitamin D biology. Rather, it addresses the broader hypothesis that low 25(OH)D may become functionally relevant when nutritional and physiological stressors converge. Athletes and physically active individuals constitute the primary translational population considered in this review because repeated exercise, skeletal loading, high energetic demand, and constrained recovery provide a setting in which this conditional hypothesis can be examined. Accordingly, the framework is developed and experimentally operationalized in the context of exercise and sport, while the underlying mineral–endocrine principles are not assumed to be unique to athletes.

This review therefore examines low 25(OH)D status within the broader calcitriol-VDR system, not as a linear route from supplementation to performance, but as a nutritional exposure whose biological relevance depends on mineral-endocrine regulation, tissue context, energetic state, inflammatory load, and recovery capacity. The proposed muscle-bone–brain framework does not claim a new causal axis. It is intended to clarify when vitamin D status may be biologically meaningful, when it may simply mark broader nutritional vulnerability, and how its role can be tested through dynamic stress–recovery paradigms rather than isolated resting biomarkers. It is not intended to establish new clinical recommendations for athlete screening, injury prevention, RED-S management, or performance enhancement.

2. Literature search and evidence appraisal

This article was developed as a narrative and hypothesis-generating review designed to synthesize biochemical, physiological, and translational evidence on calcitriol-VDR signaling across muscle, bone, and brain-related stress-adaptation pathways. The review was not designed as a systematic review or meta-analysis. Literature searches were conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Searches covered literature from database inception to 24 June 2026. The final search was

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conducted on 24 June 2026. No formal review protocol was registered, and no systematic screening procedure, quantitative synthesis, or formal risk-of-bias assessment was undertaken.
Study selection was purposive and based on relevance to the predefined mechanistic domains, evidential proximity to athlete populations, study design and methodological quality, and contribution to areas of agreement, disagreement, or uncertainty. Because study identification and selection were purposive rather than systematic, the number of records screened was not prospectively logged and could not be reconstructed reliably; therefore, no screening count or flow diagram is reported. The final evidence base comprised 119 cited sources, including original studies, reviews, consensus statements, and clinical or methodological guidance documents.

Studies were included when they addressed vitamin D status or calcitriol-VDR biology in relation to mineral-endocrine regulation, skeletal loading, muscle function or repair, bone remodeling, inflammatory or endocrine stress, fatigue, sleep, LEA, RED-S, or recovery-related physiology. Studies were excluded when they were not relevant to these domains, when mechanistic claims could not be linked to exercise, energy-deficit stress, mineral-endocrine regulation, or recovery physiology, or when they consisted primarily of opinion without identifiable empirical or mechanistic support. English-language publications were prioritized. Studies reporting null, inconsistent, or negative effects of vitamin D supplementation were deliberately retained when relevant to the distinction between ergogenic, marker, modifier, and stress-amplifier interpretations. Searches combined vitamin D-related terms with domain-specific terms for mineral–endocrine regulation, musculoskeletal adaptation, exercise and recovery, LEA/RED-S, and exploratory neuroendocrine pathways. Representative main search combinations are provided in Supplementary Table S1; syntax was adapted to the requirements of each database. Reference lists of relevant primary studies and major reviews were also screened to identify additional articles. Priority was given to original research articles when specific mechanistic, biochemical, or athlete-related claims were made. Because analytical variability can materially affect classification of 25(OH)D status, studies were also appraised according to the measurement method and degree of assay standardization. LC-MS/MS generally offers greater analytical specificity and permits separate quantification of 25(OH)D_2 and 25(OH)D_3, whereas automated immunoassays may show method-dependent bias, unequal recovery of vitamin D metabolites, and matrix- or patient-related effects **[20,21].** LC-MS/MS methods are not free from analytical limitations and likewise require appropriate calibration and quality control. Accordingly, interpretation of absolute 25(OH)D concentrations should consider whether assays are traceable to reference measurement procedures and whether laboratories participate in accuracy-based external quality-assessment or standardization programs, including the Vitamin D External Quality Assessment Scheme (DEQAS) and the CDC Vitamin D Standardization-Certification Program (VDSCP) [20,21].

Evidence was interpreted according to both biological relevance and proximity to the target population. Methodological quality was considered qualitatively according to study design, sample size, control of major confounders, validity and standardization of exposure and outcome measurements, and the directness of the evidence to the population, mechanism, and outcome under consideration. Human studies in athletes and physically active individuals were considered the most directly relevant for translational interpretation. Human studies in non-athletic populations and animal or in vitro studies were included when they clarified mechanisms relevant to the proposed framework, but were not treated as direct evidence of athlete-specific outcomes. Established evidence refers to mechanisms supported by consistent human and experimental data; emerging evidence to pathways supported by mechanistic studies and limited human data; preclinical evidence to findings derived mainly from animal or cellular models; and hypothesis-generating evidence to biologically plausible mechanisms not yet directly demonstrated in athletes or human intervention studies. These categories were used to organize inferential strength rather than to assign formal certainty ratings.

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3. Vitamin D insufficiency as a nutritional stress amplifier: a testable hypothesis of conditional adaptive reserve

Four biological levels should therefore be kept analytically separate throughout this framework: circulating 25(OH)D as the principal measurable exposure; circulating or locally generated calcitriol as the active hormonal ligand; VDR expression as a measure of potential tissue responsiveness; and VDR transcriptional activity as the functional downstream response [1–3,22–25]. Low circulating 25(OH)D may reduce substrate availability for calcitriol synthesis under some conditions, but it does not by itself demonstrate reduced calcitriol availability, lower VDR abundance, or impaired VDR-mediated transcription in a given tissue [1–3].

The stress-amplifier framework is proposed here as a testable conceptual hypothesis rather than as an established biological model. It does not assume that low circulating 25(OH)D independently reduces adaptive capacity in all athletes, nor that low 25(OH)D necessarily indicates reduced circulating calcitriol, impaired tissue VDR activation, or a uniform downstream effect on muscle, bone, or brain-related recovery pathways. Instead, the hypothesis is that low 25(OH)D may become biologically informative under specific vulnerability conditions, particularly when it coexists with inadequate calcium intake, low energy availability, endocrine disruption, high skeletal loading, inflammation, poor sleep, or incomplete recovery. In this sense, low 25(OH)D may function as a marker of broader nutritional vulnerability, a conditional modifier of stress–recovery trajectories, a contributor to impaired mineral–endocrine coupling in selected contexts, or a modifiable exposure whose correction can be experimentally tested. These alternatives are not mutually exclusive, but they require different study designs and should not be inferred from resting 25(OH)D concentrations alone.

Box 1. Operational definition of adaptive reserve

Element	Definition within this framework
Concept	Adaptive reserve is an operational, non-diagnostic construct describing the capacity to withstand a defined physiological challenge, limit the magnitude and duration of disruption, and recover toward baseline within an appropriate time course.
Experimental inference	It is inferred from prespecified, domain-specific features of the stress–recovery trajectory, including peak perturbation, recovery rate, time to recovery, and completeness of return toward baseline.
What it is not	It is not a measurable biological pool, a clinical diagnosis, or a validated composite score.
Relationship to adjacent concepts	It overlaps with physiological resilience, recovery capacity, and stress tolerance but is used here more narrowly to denote the observable margin between a defined stressor and the magnitude, duration, and reversibility of the resulting perturbation; allostasis and allostatic load refer respectively to regulatory adjustment during challenge and the cumulative physiological cost of repeated or prolonged activation [26,27].

Accordingly, the stress-amplifier hypothesis would be supported only if low 25(OH)D status, or correction of low 25(OH)D, reproducibly modifies stress–recovery trajectories after accounting for mineral intake, energy availability, endocrine status, training load, sleep, injury history, and other relevant sources of vulnerability.

Here, "reproducibly modifies" refers to a directionally consistent interaction between 25(OH)D status or its correction and a prespecified stress–recovery outcome observed in at least two independent studies or cohorts using comparable analytical criteria. Replication across different populations or physiological challenges would strengthen support for the framework, whereas an isolated finding in a single study would be considered hypothesis-generating rather than confirmatory. The proposed nutritional stress matrix comprises five interacting conditions. Vitamin D availability reflects ultraviolet exposure, dietary intake, absorption, season, latitude, body composition, and related behavioral factors [3,5,6,28–30]. Mineral-endocrine coupling depends on calcium–phosphate balance, PTH–FGF23 regulation, calcitriol signaling, and skeletal loading [31–35]. Tissue responsiveness varies with VDR abundance, cellular context, local vitamin D metabolism, and analytical methodology [22–25]. Physiological stress reflects the cumulative mechanical, inflammatory, metabolic, and neuroendocrine demands imposed by exercise and recovery [7–9]. Energetic state determines whether these adaptive processes occur under adequate energy availability or within the endocrine and metabolic constraints associated with LEA and RED-S [17,18,36,37].

The predicted consequence of the matrix is not performance enhancement, but context-dependent preservation or narrowing of adaptive reserve. The model should therefore be tested through stress–recovery trajectories rather than resting measurements, with particular attention to interactions between 25(OH)D status, baseline physiological vulnerability, and time after challenge. As summarized in Fig. 1, the muscle–bone interface provides the strongest mechanistic anchor, RED-S offers a high-yield translational context, and brain-related recovery domains remain exploratory. The experimental framework is developed in Section 7.

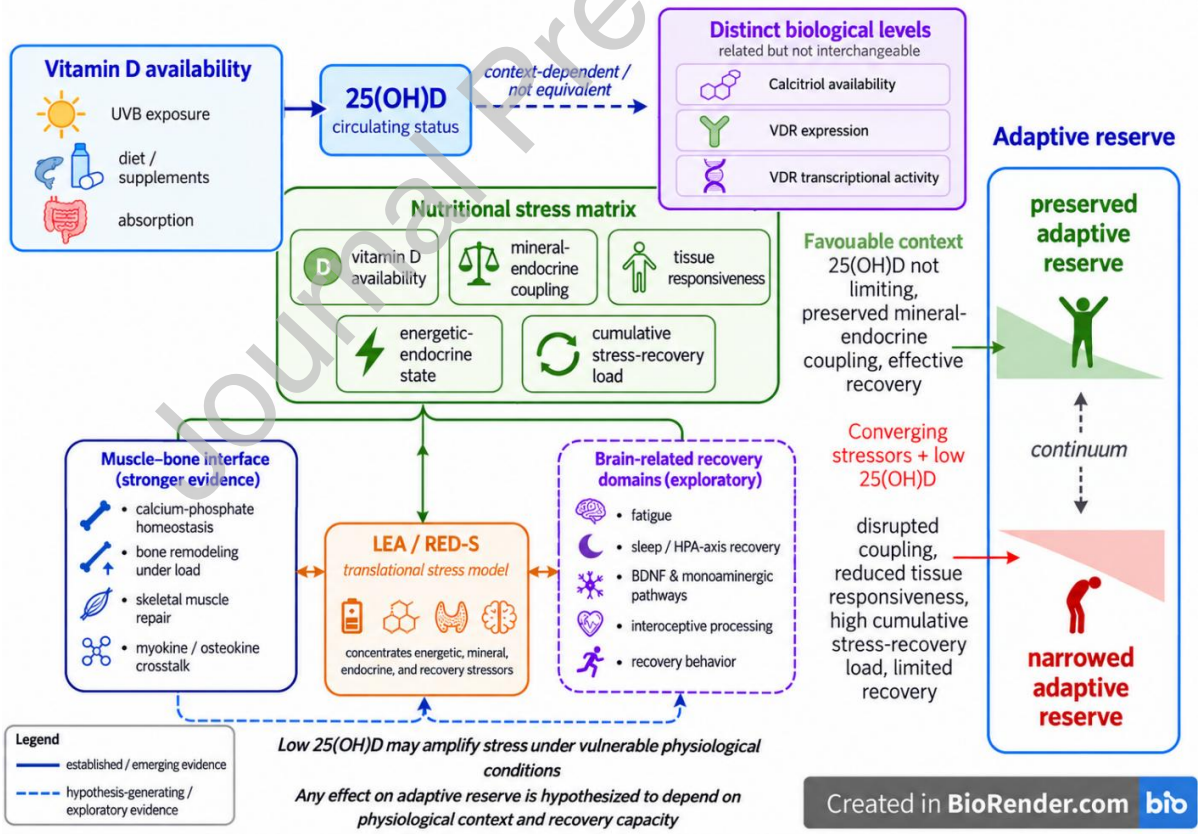


Fig. 1. Vitamin D insufficiency as a nutritional stress amplifier. Ultraviolet B exposure, dietary intake or supplementation, and intestinal absorption influence circulating 25-hydroxyvitamin D [25(OH)D], which provides

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substrate for calcitriol synthesis but is not a direct measure of circulating calcitriol concentrations or tissue VDR activation. Circulating 25(OH)D, calcitriol availability, VDR expression, and VDR transcriptional activity represent distinct biological levels. Calcitriol–VDR signaling is additionally regulated by mineral–endocrine feedback, renal and extrarenal metabolism, receptor abundance, ligand availability, co-regulatory proteins, and tissue-specific cellular context. The proposed nutritional stress matrix comprises five interacting components: vitamin D availability, mineral-endocrine coupling, tissue responsiveness, energetic-endocrine state, and cumulative stress-recovery load. Their relative contribution is context dependent and is not assumed to be equal. The muscle-bone interface provides the strongest mechanistic foundation through calcium-phosphate homeostasis, skeletal remodeling under load, muscle repair, and emerging myokine-osteokine crosstalk. Brain-related recovery domains, including fatigue, sleep and hypothalamic-pituitary-adrenal-axis regulation, neurotrophic and monoaminergic pathways, interoceptive processing, and recovery behavior, remain exploratory. Brain-related recovery domains are shown as exploratory extensions of the framework and are not intended to indicate evidential equivalence with the vitamin D–mineral–bone or musculoskeletal components. Low energy availability (LEA) and Relative Energy Deficiency in Sport (RED-S) are represented as a translational stress model in which energetic, mineral, endocrine, and recovery-related constraints converge. Adaptive reserve is depicted as a continuum: it is more likely to be preserved when nutritional and recovery conditions are favorable and may narrow when vitamin D insufficiency coexists with multiple physiological stressors. Solid elements indicate stronger mechanistic support; dashed elements indicate hypothesis-generating or exploratory relationships. The scheme does not imply a single causal axis or a direct ergogenic effect of vitamin D. The schematic is conceptual and not to scale. The figure was conceptually designed by the author and created using BioRender.com.

4. The muscle-bone interface under exercise stress: mineral homeostasis, endocrine coupling, and tissue repair

4.1 Calcitriol-VDR signaling, mineral-endocrine coupling, and skeletal adaptation under load

The strongest evidence supporting the nutritional stress-amplifier model derives from the interaction between calcitriol–VDR signaling, mineral availability, endocrine regulation, and skeletal loading. The muscle-bone interface provides the strongest biological anchor for the nutritional stress-amplifier model. Exercise imposes repeated mechanical loading on the skeleton, and muscle contraction is a major stimulus for bone modeling and remodeling [38,39]. Yet loading is adaptive only when mineral availability, endocrine support, energy availability, and recovery are sufficient [6,17,18,36,38]. Vitamin D becomes relevant at this interface because it helps maintain the mineral-endocrine environment in which muscle repair and skeletal remodeling occur. In this review, mineral coupling refers to the coordinated regulation of calcium and phosphate availability, PTH–FGF23 feedback, calcitriol signaling, and bone remodeling under load. Athletes exposed to impact and weight-bearing activity often develop favorable skeletal adaptations, including higher bone mineral density and improved bone geometry, particularly when training is supported by adequate energy and mineral intake [38,40]. The relationship is not uniform, however. Endurance athletes, those with menstrual dysfunction, athletes in leanness-focused sports, and those exposed to low energy availability may show impaired bone turnover, reduced bone mineral density, or increased stress-fracture risk despite substantial mechanical loading [6,17,18]. This apparent paradox captures the central argument of the present model: loading promotes adaptation only when the biological conditions for remodeling are preserved.

Vitamin D contributes mainly through calcium-phosphate homeostasis. Circulating 25(OH)D provides substrate for calcitriol synthesis, although its concentration does not linearly predict circulating calcitriol or tissue-specific VDR activation. Accordingly, associations between low 25(OH)D and skeletal outcomes should be interpreted primarily as evidence involving vitamin D status and mineral–endocrine

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context, unless calcitriol concentrations, VDR expression, or VDR-regulated transcriptional endpoints are directly measured. Calcitriol–VDR signaling, operating within PTH–FGF23 and calcium-phosphate feedback, regulates intestinal mineral absorption, renal handling, endocrine feedback, and bone remodeling [1,2,41,42]. When low 25(OH)D status limits vitamin D-dependent mineral support, particularly in combination with inadequate calcium intake, compensatory increases in PTH may preserve serum calcium at the expense of skeletal mineral balance. Experimental models further indicate that VDR signaling under calcium-deficient conditions may favor bone resorption and impair mineralization, whereas calcium sufficiency supports a more balanced remodeling response [31,33–35]. Vitamin D status therefore has little meaning when considered apart from calcium intake, phosphate balance, PTH, FGF23, and mechanical load.

This conditionality is especially relevant in athletic and military settings. Low vitamin D status has been associated with stress-fracture vulnerability in physically active populations, while combined calcium and vitamin D supplementation reduced stress-fracture incidence in female Navy recruits undergoing intense training [12,13]. Athlete data also suggest that persistent low 25(OH)D may be associated with higher stress-fracture rates [14]. These findings do not show that vitamin D alone prevents bone stress injury or that vitamin D assessment or correction should be considered a primary injury-prevention strategy. Rather, they support the interpretation of low 25(OH)D as one potentially modifiable exposure within a multifactorial process.

4.2 Skeletal-muscle VDR signaling and tissue repair

The muscular component is biologically plausible but less clinically settled. Vitamin D deficiency has been associated with impaired strength, altered neuromuscular function, soreness, delayed recovery, and muscle-injury vulnerability in some settings, although supplementation findings remain heterogeneous and appear most relevant when baseline 25(OH)D is low [43–47]. Human tissue evidence confirms that skeletal muscle can express VDR, but not that VDR signaling is uniformly abundant or functionally robust in mature myofibers. A study [25] reported calcitriol-responsive VDR expression in primary human myoblasts and increased muscle VDR mRNA after vitamin D_3 supplementation in older mobility-limited women. Another study [22] detected VDR mRNA in adult muscle biopsies but not CYP27B1 or CYP24A1, suggesting that prominent local synthesis and catabolism of calcitriol were not demonstrable in that cohort. By contrast, a calcifediol intervention in vitamin D-deficient frail older adults found VDR expression to be close to undetectable and produced no significant skeletal-muscle transcriptomic response [23]. More recent antibody-validation work detected VDR protein in biopsies from healthy young men, while also showing marked interindividual variability and unresolved putative isoforms [24].

Taken together, these studies support the presence of VDR in adult human skeletal muscle, but show that its abundance, detectability, and responsiveness depend on population, tissue state, cellular composition, and assay methodology. They do not establish that vitamin D repletion in individuals with low 25(OH)D directly improves muscle repair, recovery, strength, or athletic performance. Vitamin D is therefore better viewed as a permissive component of musculoskeletal physiology than as a direct enhancer of muscle adaptation. Myostatin illustrates how vitamin D-sensitive muscle biology might influence recovery. As a member of the transforming growth factor-β superfamily, myostatin restrains muscle growth, differentiation, and regeneration [48–50]. Experimental studies suggest that vitamin D deficiency or impaired VDR signaling may increase myostatin expression, whereas calcitriol can promote

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myogenic differentiation and reduce myostatin in selected cellular and animal models [51–54]. The mechanism is credible, but athlete-specific evidence showing that vitamin D correction modifies myostatin and improves recovery remains lacking.

These observations provide a mechanistic basis for considering vitamin D-sensitive muscle responses, while emphasizing that low 25(OH)D status, muscle VDR expression, calcitriol responsiveness, and downstream repair outcomes should not be treated as interchangeable measures. Downstream mediators of muscle–bone communication therefore remain predominantly emerging or exploratory in relation to vitamin D-dependent recovery in athletes.

4.3 Candidate interacting pathways in muscle–bone adaptation under nutritional and exercise stress

The mediators discussed in this section are best interpreted as candidate interacting pathways within muscle–bone adaptation, not as established vitamin D-dependent mechanisms in athletes. They may shape, reflect, or modify the physiological context in which low 25(OH)D status is interpreted, particularly under exercise stress, low energy availability, inflammation, or impaired recovery. However, for most of these mediators, a direct pathway linking low 25(OH)D, altered calcitriol–VDR signaling, mediator change, and improved or impaired athletic recovery has not been demonstrated. Irisin/FNDC5 provides a candidate link between muscle contraction, bone adaptation, and nutritional-endocrine context, but it should not be interpreted as an established vitamin D-dependent mediator of athletic recovery. Irisin is an exercise-responsive myokine implicated in osteoblast differentiation, bone remodeling, energy metabolism, and muscle-bone communication [55,56]. Experimental work suggests that vitamin D may regulate FNDC5/irisin signaling [57], while associations among vitamin D, irisin, and bone parameters have been reported in female athletes with functional hypothalamic amenorrhea [58]. This convergence is attractive in the context of low energy availability and skeletal vulnerability, but the pathway remains emerging. Its relevance should be tested through athlete studies that integrate 25(OH)D, energy availability, endocrine status, training load, irisin dynamics, bone-turnover markers, and recovery outcomes.

Other mediators extend the muscle-bone framework but currently add more mechanistic breadth than translational certainty. IL-6 is a clear example of context dependence: chronic elevation may accompany catabolism and inflammation, whereas exercise-induced IL-6 supports substrate mobilization, glucose uptake, satellite-cell regulation, and anti-inflammatory signaling [7,9,59]. Vitamin D may influence inflammatory tone, and combined exercise plus supplementation has reduced circulating IL-6 in some settings [60], but changes in VDR expression and IL-6 after exercise do not establish a direct vitamin D-IL-6 pathway [61]. The more useful question is whether low vitamin D status alters the resolution of exercise-induced inflammation, a hypothesis that requires repeated post-exercise measurements rather than resting cytokine values. Bone-derived signals add an endocrine dimension to the same network. Osteocalcin is regulated by calcitriol in osteoblasts and has been linked experimentally to glucose metabolism, muscle function, IL-6 release, and exercise capacity [62–64]. FGF23 is more firmly embedded in vitamin D and phosphate homeostasis, but its relevance to exercise lies mainly in mineral coupling rather than direct performance regulation [32,65,66]. Osteopontin, a vitamin D-regulated matricellular protein, contributes to bone remodeling, inflammation, cell adhesion, and early muscle repair in experimental models [67–69]. Together, these mediators reinforce the view of bone and muscle as endocrine and repair-responsive tissues, but they should be treated as context-sensitive readouts or candidate interacting pathways rather than as validated markers of vitamin D-dependent recovery in athletes. FGF21 occupies a different and more peripheral position. Rather than acting as a vitamin D-dependent mediator of muscle–bone adaptation, FGF21 is best interpreted here as a candidate readout of nutritional and metabolic strain. Protein restriction, fasting-related metabolic adaptation, and macronutrient redistribution can influence circulating FGF21 [70,71]. Exercise modality, sex, and

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sampling time may also affect FGF21 responses to exercise [72]. These features make FGF21 potentially useful for characterizing the broader nutritional-stress phenotype in which low 25(OH)D may occur, but they do not establish a calcitriol-VDR-FGF21 pathway in humans. FGF21 should therefore be treated as an exploratory contextual marker, not as a mediator of vitamin D action, muscle growth, bone adaptation, or performance.

5. Energy-deficit stress as the translational model: low energy availability, RED-S and the narrowing of adaptive reserve

Low energy availability (LEA) and Relative Energy Deficiency in Sport (RED-S) provide the clearest translational setting in which to examine the nutritional stress-amplifier model. Isolated low 25(OH)D status may have modest consequences under low-demand conditions. LEA, by contrast, constrains several adaptive systems at once. Muscle must repair exercise-induced damage with limited energetic substrate; bone must remodel under load with reduced endocrine and mineral support; immune and inflammatory responses must resolve during nutritional restriction; and central systems must regulate fatigue, sleep, stress, and recovery behavior in an altered metabolic state **[17–19,36,37].** Within the proposed framework, RED-S therefore provides the physiological convergence in which a conditional effect of vitamin D status may be most readily examined.

RED-S arises from problematic low energy availability and can affect metabolic, reproductive, musculoskeletal, immune, hematological, gastrointestinal, cardiovascular, psychological, and performance-related domains [17–19]. The resulting shift is not simply one of nutrient deficiency, but of biological prioritization: anabolic, reproductive, skeletal, and recovery processes are constrained as the organism conserves energy. Low 25(OH)D status is not proposed as a cause or defining feature of this syndrome. A central interpretive challenge is that low 25(OH)D may arise from the same nutritional and behavioral conditions that produce LEA-related vulnerability. Restrictive eating can reduce vitamin D and calcium intake, dietary fat, total energy intake, and food variety, while sport-specific behavioral and environmental factors may additionally limit sunlight exposure [30,73–75].

The stress-amplifier hypothesis therefore does not require low 25(OH)D to act as a primary driver of RED-S-related impairment. These conditions are particularly relevant in endurance, aesthetic, weight-category, and leanness-focused sports, where high training volume may coexist with weight-control practices, endocrine disturbance, and repetitive skeletal loading [30,73–75]. In this setting, low 25(OH)D should first be interpreted as a potential marker of broader nutritional vulnerability, whereas its role as an additional constraint on mineral-endocrine adaptation or recovery trajectories remains a testable possibility rather than an assumption based on baseline status alone. Bone provides the most direct example of this interaction. LEA reduces endocrine support for bone formation through changes in leptin, thyroid hormones, reproductive hormones, and IGF-1 signaling [17,36,37]. Menstrual dysfunction and hypoestrogenism add further risk in female athletes, while prolonged energy deficiency can also alter testosterone, thyroid function, and bone-related pathways in males. If vitamin D and calcium availability are inadequate at the same time, secondary hyperparathyroid drive and impaired mineral coupling may deepen the mismatch between skeletal loading and remodeling capacity. Bone stress injury then emerges not from loading alone, but from loading imposed on a system with insufficient resources for repair.

A similar logic applies to skeletal muscle. Energy deficit limits substrate availability, alters endocrine signaling, and can delay inflammatory resolution and tissue repair. Vitamin D insufficiency may add to this burden through calcium handling, mitochondrial function, oxidative-stress regulation, and myogenic pathways, although direct athlete evidence remains limited [44,52,76,77]. Experimental links with myostatin and FNDC5/irisin are biologically plausible, but their relevance is most likely to emerge in stressed phenotypes rather than in well-nourished, vitamin D-sufficient athletes [51,53,57]. RED-S is therefore valuable not because it creates a vitamin D-specific phenotype, but because it brings the

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principal components of the nutritional stress matrix into the same biological setting: energy deficit, mineral inadequacy, endocrine suppression, skeletal loading, impaired muscle repair, fatigue, sleep disturbance, and reduced recovery capacity. It provides the contrast needed to ask whether vitamin D status remains merely a background nutritional marker or becomes a meaningful modifier when adaptive reserve is already constrained.

The clinical boundary is therefore deliberately limited. Vitamin D assessment and correction should not be interpreted as primary interventions for RED-S, disordered eating, recurrent bone stress injury, or impaired recovery. Recovery from LEA- or RED-S-related vulnerability requires restoration of energy availability, adequate macronutrient and micronutrient intake, calcium sufficiency, endocrine recovery, appropriate training-load modification, sleep restoration, psychological support where indicated, and multidisciplinary care [17–19,78]. Within this broader context, clinical features such as recurrent bone stress injury, menstrual or other reproductive-endocrine disturbances, a history of restrictive or disordered eating, and marked or prolonged energy restriction may provide context for considering 25(OH)D status; however, these features should not be treated as independent indications for testing, and any decision to measure 25(OH)D should remain individualized and form part of shared clinical decision-making [17–19,78]. Management of low 25(OH)D, when indicated, may help restore a more favorable mineral-endocrine environment, but it cannot compensate for continued under-fueling, inadequate calcium intake, excessive training stress, poor sleep, or unresolved psychological and medical factors.

6. Brain-related recovery pathways as an exploratory extension of the stress-amplifier hypothesis

The brain-related component is retained as an exploratory extension of the stress-amplifier hypothesis, not as a third evidential pillar equivalent to the vitamin D–mineral–bone or musculoskeletal components. It is included because fatigue, sleep, stress-axis activity, pain, perceived effort, and recovery behavior can influence the transition from physiological stress to restoration [79–84]. However, in the evidence reviewed here, athlete-specific evidence directly linking low 25(OH)D status to these domains remains limited, and no causal pathway has been established from low circulating 25(OH)D to altered brain calcitriol availability, neural VDR activation, cognition, mood, motivation, compulsive exercise, interoception, or recovery-related decision-making. The purpose of this section is therefore to define plausible recovery-related questions for future studies, not to claim that vitamin D insufficiency produces central or behavioral effects in athletes.

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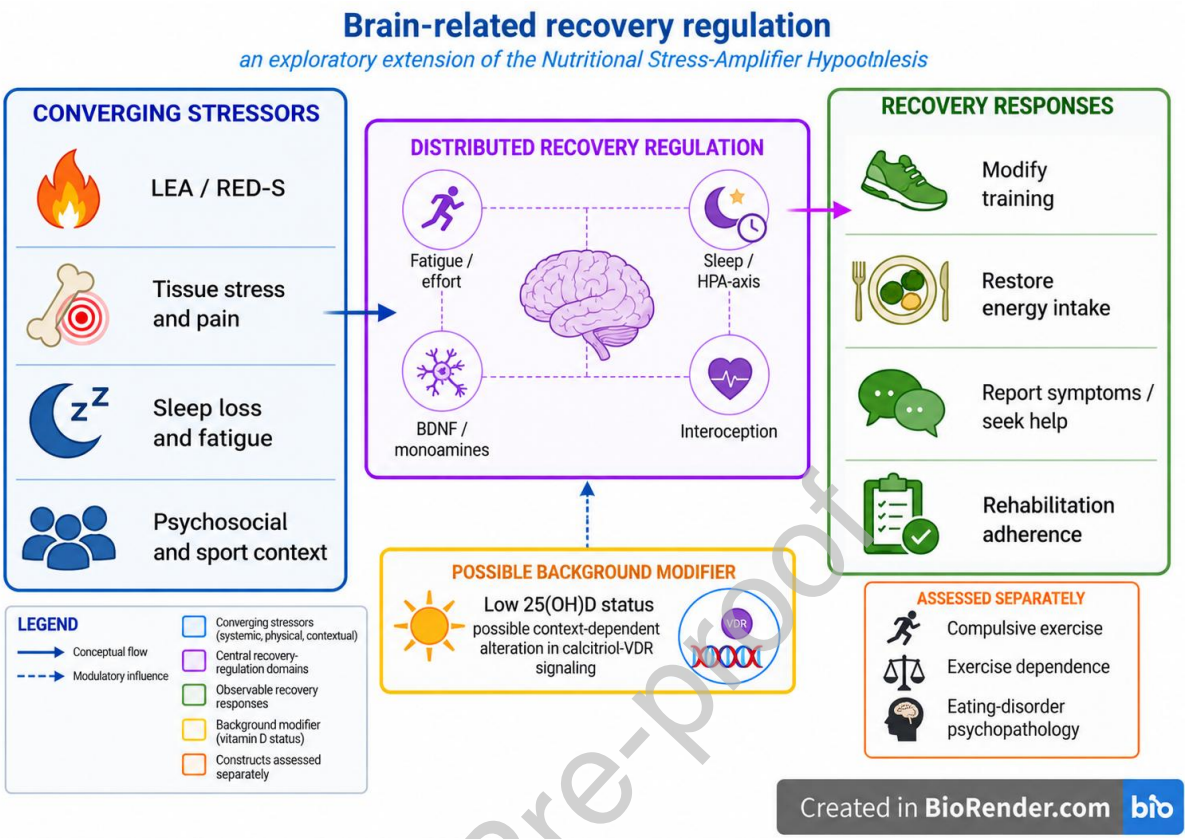


Fig. 2. Brain-related recovery regulation within the nutritional stress-amplifier model. This figure represents an exploratory conceptual extension rather than an established vitamin D-dependent brain pathway. Energetic, peripheral, sleep-related, and psychosocial stressors converge on distributed systems involved in recovery regulation. These inputs include low energy availability (LEA) and Relative Energy Deficiency in Sport (RED-S), tissue stress and pain, sleep loss and accumulated fatigue, and the wider sport and psychosocial context. Central fatigue and effort regulation, sleep and hypothalamic–pituitary–adrenal (HPA)-axis recovery, neurotrophic and monoaminergic pathways, and interoceptive processing are shown as parallel and interacting domains rather than as a linear causal sequence. Together, these domains may shape observable recovery responses, including modification of training, restoration of energy intake, symptom reporting and help-seeking, and adherence to rehabilitation. Low circulating 25-hydroxyvitamin D [25(OH)D] is positioned only as the measurable nutritional exposure and possible background modifier. Altered calcitriol–vitamin D receptor (VDR) signaling represents a potential downstream mechanism, not an assumed or directly measured consequence of low 25(OH)D. Compulsive exercise, exercise dependence, and eating-disorder psychopathology are shown separately because they are distinct constructs requiring construct-specific assessment **[85,86].** Solid arrows indicate the principal conceptual flow from converging stressors to recovery regulation and observable responses; dashed arrows indicate conditional or exploratory relationships. The scheme does not imply that vitamin D insufficiency causes psychiatric symptoms, disordered eating, compulsive exercise, or recovery-related behavior. The schematic is conceptual and not to scale. The figure was conceptually designed by the author and created using BioRender.com.

6.1 Central fatigue and cumulative stress-recovery burden

Central fatigue integrates physiological cost, perceived effort, motor drive, and motivational state during prolonged or repeated exercise, in which serotonergic and dopaminergic signaling have been implicated [79,80]. Under low energy availability, these processes operate within a broader context of reduced substrate availability, endocrine conservation signals, and stress-axis activation. Low 25(OH)D status may identify a nutritional context in which recovery-related neural pathways warrant

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investigation, but it should not be interpreted as evidence of reduced brain calcitriol availability, impaired neural VDR activation, or altered central fatigue regulation. VDR and 1α-hydroxylase have been identified in brain regions involved in motor, reward, and stress-related functions [15,16], but these anatomical observations do not establish athlete-specific functional effects. Vitamin D-related neuroinflammatory, oxidative, mitochondrial, and monoaminergic mechanisms remain biologically plausible [76,87,88]. Within this framework, fatigue is treated as a functional indicator of unresolved stress–recovery strain, not as a direct measure of allostatic load [26,27].

The relevant hypothesis is therefore not that vitamin D directly prevents fatigue or regulates allostasis, but that correction of insufficiency may modify recovery trajectories in selected vulnerable phenotypes. This possibility has not been directly demonstrated. In this sense, central fatigue provides a functional bridge between peripheral tissue stress and neuroendocrine recovery regulation.

6.2 Sleep and HPA-axis regulation as recovery-related outcomes

Within the present framework, sleep is considered a functional outcome of stress-recovery regulation rather than a direct target of vitamin D action. Sleep integrates the effects of training load, fatigue, pain, inflammatory activity, energy availability, endocrine state, competition schedules, travel, psychological stress, and recovery opportunity. Persistent sleep disturbance may therefore signal that accumulated physiological stress is not being adequately resolved, but it cannot be attributed to vitamin D insufficiency in isolation.

Human evidence linking vitamin D with sleep remains heterogeneous. Cross-sectional data in physically active adults and selected intervention studies in non-athletic populations have reported associations between vitamin D exposure and sleep-related outcomes [81,82], whereas other randomized evidence has shown no significant benefit [83]. Actigraphy-based observational data have also associated lower vitamin D concentrations with greater sleep variability, but causality and relevance to athletes remain uncertain [84]. These findings support further investigation but do not establish vitamin D as a sleep-promoting intervention. Interpretation is further complicated by sunlight exposure, season, latitude, outdoor activity, training schedule, travel, and sleep timing, which may influence both vitamin D status and sleep. Circadian entrainment should therefore be treated as a potential confounding or modifying context rather than as a demonstrated vitamin D-regulated pathway.

The HPA axis represents a related but distinct recovery domain. Repeated exercise, competition pressure, injury, sleep restriction, weight-control practices, and low energy availability can alter stress-axis activity and recovery capacity [7–9,17–19]. Vitamin D-related modulation of inflammatory or neuroendocrine tone may be biologically plausible, but direct evidence that correction of vitamin D insufficiency normalizes HPA-axis function or cortisol rhythms in athletes remains insufficient. Sleep and HPA-axis activity should therefore be considered parallel, interacting indicators of recovery stress rather than components of an established vitamin D-dependent coupling mechanism.

6.3 Neurotrophic, monoaminergic, and interoceptive pathways: exploratory relevance to recovery

Neurotrophic, monoaminergic, and interoceptive pathways are included only as exploratory domains that may help frame future studies of fatigue, perceived effort, bodily-signal processing, and recovery behavior. They are not presented as established mediators of vitamin D action in athletes. Adaptive or maladaptive persistence is used descriptively to refer to flexible versus rigid continuation of training under signs of insufficient recovery; it is not proposed as a diagnosis, a validated psychometric construct, or a vitamin D-sensitive behavioral phenotype. Compulsive exercise, exercise dependence, and eating-disorder psychopathology remain distinct constructs requiring construct-specific assessment [85,86]. BDNF is exercise-responsive and contributes to neural plasticity and stress adaptation [89–92]. Vitamin D-related associations with BDNF derive mainly from preclinical and non-athlete studies [93–95], and

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their relevance to athletes exposed to exercise stress, poor sleep, or energy deficit remains untested. Serotonergic signaling contributes to central fatigue, sleep pressure, pain, affective regulation, and perceived effort [79,96–100]. Experimental evidence indicates that calcitriol can influence molecular components of serotonin metabolism [87], but whether low 25(OH)D modifies serotonergic signaling in athletes with LEA or RED-S remains unknown. Dopamine links reward processing, effort valuation, motor drive, and behavioral persistence. Altered dopaminergic function has been described in anorexia nervosa and restrictive eating phenotypes [101–103], while experimental studies suggest that vitamin D can influence aspects of dopaminergic biology [16,104–108]. These findings establish biological plausibility, but not a pathway from low 25(OH)D to exercise behavior. Interoception is retained only as a hypothesis-generating recovery domain involving the detection and interpretation of internal bodily signals [109]. However, no direct evidence currently links low 25(OH)D status to interoceptive processing or establishes interoception as a vitamin D-sensitive recovery mechanism in athletes.

Future athlete studies would therefore require construct-specific measures and careful control of energy availability, eating-disorder psychopathology, pain, sleep, training load, and reproductive-endocrine status. Recovery-oriented behavior is likewise descriptive and includes observable actions such as training modification, restoration of energy intake, symptom reporting, help-seeking, and rehabilitation adherence. These outcomes should be assessed separately from compulsive exercise, exercise dependence, and eating-disorder psychopathology. No evidence currently shows that low 25(OH)D status or its correction modifies these behaviors; they are included only as exploratory outcomes for future studies.

7. Testing the stress-amplifier model: dynamic phenotyping and experimental priorities

7.1 Why static and unstratified vitamin D designs are insufficient

Most athlete studies have approached vitamin D as a potential ergogenic supplement, asking whether supplementation improves strength, power, endurance, fatigue, or recovery. This design assumes a broadly uniform effect. The stress-amplifier model predicts the opposite: any effect should depend on baseline vitamin D status and become most visible when nutritional, endocrine, mechanical, or recovery-related constraints already limit adaptation. The supplementation literature illustrates this problem. Systematic reviews and meta-analyses agree that supplementation raises circulating 25(OH)D, but differ in their conclusions about performance. Some report possible benefits for endurance, anaerobic power, or strength, whereas others find no significant overall effect or benefits limited mainly to selected strength outcomes [110–112]. Taken together, this literature illustrates the heterogeneity of performance-oriented supplementation findings and does not provide direct evidence for the proposed stress–recovery interaction or adaptive-reserve framework. These conclusions need not be mutually exclusive. Trials vary in baseline 25(OH)D, supplement form and dose, sport, training status, season, outcome selection, and the proportion of participants who are actually deficient **[110–112].** A small benefit in a vulnerable subgroup can easily disappear when deficient, insufficient, and sufficient athletes are pooled. Baseline 25(OH)D is therefore necessary but not sufficient for stratification. Calcitriol-VDR signaling operates within a calcium-phosphate-PTH-FGF23 network, and the biological meaning of low 25(OH)D depends on calcium intake, phosphate balance, skeletal loading, bone-turnover state, and endocrine function. An athlete with low 25(OH)D but adequate nutrition, manageable loading, and no injury history is not equivalent to one with the same concentration, inadequate calcium intake, menstrual or endocrine disruption, and recurrent bone stress injury. Designs that classify them together are unlikely to identify a conditional effect.

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Energy availability creates a similar source of heterogeneity. Low energy availability can alter endocrine function, bone turnover, immune regulation, fatigue, and recovery independently of vitamin D **[17–19,36,37].** Sleep, dietary protein and fat, iron status, recent injury, training load, and psychological strain add further variation. These factors should not be treated merely as background characteristics. They define the physiological setting in which vitamin D status is being tested. RED-S-related vulnerability is addressed more specifically in Section 7.3, but the general methodological point applies to all athlete studies: vitamin D should be analyzed within a characterized nutritional and endocrine phenotype. Outcome selection is equally important. Performance is a distal endpoint shaped by training history, technical skill, genetics, motivation, substrate availability, sleep, and injury [4–6,110–112]. A trial may therefore find no change in performance even when a biologically relevant recovery process has changed. Conversely, an improvement in performance cannot readily be attributed to vitamin D without evidence that the proposed biochemical or tissue-level pathway was affected. Reliance on resting measurements creates a final limitation. Adaptation unfolds over time. Bone-turnover markers vary after exercise according to loading mode, feeding state, sex, and sampling schedule, while fatigue and recovery markers depend on training load, muscle damage, inflammation, sleep, and the phase of recovery [113,114]. A normal resting value may conceal an exaggerated response to stress or a delayed return to baseline.

The central design question should therefore shift from whether vitamin D supplementation improves performance in athletes as a group to whether vitamin D status modifies the response to a defined challenge in a prespecified vulnerability phenotype. This requires baseline stratification, characterization of mineral and energy availability, appropriate control of environmental and training exposures, and repeated tissue-specific outcomes. Static, unstratified trials can establish that supplementation changes 25(OH)D; they are poorly equipped to determine whether insufficiency constrains adaptive reserve.

7.2 Dynamic stress–recovery phenotyping as the central test of the stress-amplifier hypothesis

Dynamic stress–recovery phenotyping is the central experimental test of the stress-amplifier hypothesis. If low 25(OH)D functions as a conditional modifier of adaptive reserve, its relevance should be most apparent not in resting biomarker values or mean supplementation effects, but in the trajectory from physiological challenge to recovery. Resting 25(OH)D, cytokines, cortisol, muscle enzymes, or bone-turnover markers provide useful background information, but they do not show how well an athlete absorbs and resolves stress. Dynamic phenotyping addresses this limitation by measuring biochemical, endocrine, functional, and recovery-related responses before, during, and after a standardized challenge. Adaptive reserve is not measured directly. In experimental terms, it is inferred from prespecified features of the response trajectory: resistance to perturbation, peak deviation from baseline, recovery rate, time to recovery, and completeness of recovery. These features should initially be analyzed separately rather than merged into an unvalidated composite score. Two athletes may have similar resting creatine kinase, P1NP, cortisol, or fatigue scores yet differ markedly in the amplitude or duration of their response to eccentric exercise, repetitive loading, intensified training, sleep restriction, or nutritional rehabilitation. Existing exercise-challenge studies show the value of this approach. In endurance-trained runners, vitamin D supplementation followed by eccentric exercise was associated with lower post-exercise troponin, myoglobin, creatine kinase, TNF-α, and selected inflammatory responses [115]. By contrast, vitamin D_2 supplementation in NASCAR pit crew athletes increased circulating $25(OH)D_2$, reduced $25(OH)D_3$, did not improve muscle function, and was associated with greater post-exercise muscle-damage responses [116]. The studies differ in population, vitamin D form, protocol, and sampling schedule, so they cannot be read as a simple positive-versus-negative comparison. Together, they show why challenge studies must specify baseline status, supplement form, training background, exercise modality, and recovery kinetics.

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Bone adaptation requires the same temporal approach. Acute exercise changes bone-turnover markers, but the magnitude and direction of those changes depend on loading mode, participant characteristics, nutritional state, sex, feeding, and sampling time [113]. Short-term low energy availability can also alter bone formation and resorption in physically active individuals [117]. The relevant vitamin D-related signal may therefore be an altered bone-turnover trajectory after loading, rather than an isolated resting concentration of P1NP, CTX, osteocalcin, or FGF23. Fatigue, sleep, and stress-axis outcomes are similarly dynamic. Fatigue reflects overlapping muscular, metabolic, inflammatory, endocrine, immune, psychological, and central influences; no single biomarker captures it [114]. Sleep and HPA-axis activity provide complementary information about recovery and should be assessed alongside perceived fatigue, training load, energy availability, and inflammatory responses. The question is whether vitamin D status is associated with the magnitude or persistence of stress-related disruption, not whether it correlates with a single resting fatigue or cortisol value. Challenge models should be selected according to the biological domain being tested. Eccentric exercise is suited to muscle-damage and repair trajectories, impact or resistance loading to skeletal responses, and intensified training blocks to cumulative fatigue and recovery, and nutritional rehabilitation or return-to-training protocols to more complex multisystem adaptation. It is not intended as a universal panel: each study should select markers that directly address its prespecified pathway and challenge.

Behavioral outcomes require the same discipline. Compulsive exercise, exercise dependence, eating-disorder psychopathology, training modification, symptom reporting, and rehabilitation adherence are distinct constructs and should be assessed separately. Validated scales should be paired with observable behaviors where appropriate, but these measures should not be combined into an unvalidated maladaptive-persistence score. Table 1 organizes candidate measures according to the proposed experimental sequence: baseline exposure, vulnerability modifiers, standardized challenge, dynamic proximal outcomes, exploratory mechanistic readouts, and distal clinical or performance outcomes. This distinction is important because variables such as bone mineral density, dietary intake, injury history, and reproductive-endocrine status characterize the underlying phenotype but are not themselves acute recovery biomarkers.

Table 1. Multilevel phenotyping framework for testing vitamin D insufficiency as a nutritional stress amplifier.

Measurement layer	Domain	Candidate measures	Role in the experimental model
1. Baseline exposure and nutritional context	Vitamin D status and determinants	Total 25(OH)D, assay method and standardization, vitamin D intake or supplementation, ultraviolet exposure, season, latitude, indoor/outdoor training, skin pigmentation, body composition	Defines the principal nutritional exposure and its environmental and analytical determinants
2. Baseline vulnerability phenotype	Energy availability and dietary support	Energy-availability estimates, dietary energy intake, calcium, protein and dietary-fat intake, meal pattern, indicators of restrictive eating or problematic LEA	Characterizes the energetic and nutritional context in which low 25(OH)D may become functionally relevant

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Measurement layer	Domain	Candidate measures	Role in the experimental model
2. Baseline vulnerability phenotype	Endocrine and reproductive status	Leptin, T3, IGF-1, estradiol, progesterone, testosterone, menstrual or reproductive function, clinically relevant RED-S indicators	Identifies endocrine constraints that may modify musculoskeletal adaptation and recovery
2. Baseline vulnerability phenotype	Training, recovery and injury context	Sport type, training volume and intensity, recent load progression, sleep pattern, prior bone stress injury, recurrent musculoskeletal injury, return-to-training status	Defines mechanical and recovery-related vulnerability before the challenge
3. Structural and longitudinal phenotype	Skeletal status	Bone mineral density, bone geometry where available, stress-injury history, imaging findings, longitudinal injury incidence	Provides structural and clinical context; these measures are not acute post-challenge biomarkers
4. Dynamic response phenotype	Vitamin D–mineral–endocrine system	Calcium, phosphate, PTH, FGF23, calcitriol where mechanistically justified	Assesses mineral–endocrine responses and the regulatory context in which calcitriol–VDR signaling operates
4. Dynamic response phenotype	Bone remodeling	P1NP, CTX, osteocalcin and other prespecified bone-turnover markers	Quantifies the magnitude, direction and recovery kinetics of skeletal responses to loading or energy deficit
4. Dynamic response phenotype	Muscle damage and functional recovery	Creatine kinase, myoglobin, LDH, skeletal-muscle troponin where appropriate, maximal or isometric strength, countermovement jump, soreness, neuromuscular performance	Captures the amplitude and resolution of muscle perturbation and recovery
4. Dynamic response phenotype	Inflammatory and stress regulation	IL-6, TNF-α, CRP, cortisol profile, heart-rate variability where appropriate	Evaluates inflammatory and neuroendocrine response magnitude, persistence and return toward baseline
4. Dynamic response phenotype	Perceived and behavioral recovery	Fatigue, perceived recovery, sleep duration and quality, daytime sleepiness, symptom reporting, training modification, rehabilitation adherence, return-to-training time	Provides functional outcomes of stress resolution without assuming a vitamin D-specific behavioral mechanism
5. Exploratory mechanistic phenotype	Muscle–bone crosstalk	Myostatin, irisin/FNDC5, osteopontin and selected osteokines or myokines	Tests candidate mechanisms that remain insufficiently validated in athletes

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Measurement layer	Domain	Candidate measures	Role in the experimental model
5. Exploratory mechanistic phenotype	Brain-related recovery	BDNF and other prespecified neurotrophic or neuroendocrine measures	Supports hypothesis-generating analyses and should not be interpreted as a direct measure of central vitamin D action
6. Clinical and performance outcomes	Distal outcomes	Bone stress injury incidence, time-loss injury, return-to-sport, training tolerance, strength, power or endurance performance	Determines whether altered recovery trajectories translate into clinically or functionally meaningful outcomes

Table 1. Multilevel phenotyping framework for testing whether low 25-hydroxyvitamin D status modifies adaptive reserve under exercise and energy-deficit stress. The table distinguishes baseline nutritional and physiological context, dynamic stress–recovery responses, structural and longitudinal measures, exploratory mechanistic readouts, and distal clinical or performance outcomes. Baseline variables define the energetic, endocrine, mineral, training, and recovery context in which 25(OH)D status is interpreted, whereas dynamic measures capture the magnitude, duration, and completeness of responses to standardized exercise loading, intensified training, or nutritional-rehabilitation challenges. Structural and clinical measures provide longer-term information on skeletal vulnerability, injury, and functional consequences. Exploratory mediators are included to guide hypothesis-driven studies but are not equally validated or clinically actionable in athletes.

Note: Measures should be selected according to the prespecified biological hypothesis, participant phenotype, and experimental challenge; the table is not intended as a universal biomarker panel. Baseline and structural variables characterize the context in which vitamin D status is interpreted, whereas dynamic outcomes should be measured repeatedly from pre-challenge baseline through peak perturbation and early and late recovery. Exploratory mediators such as myostatin, irisin/FNDC5, osteopontin, and BDNF are not equally validated and should not be interpreted at the same inferential level as 25(OH)D, PTH, calcium, P1NP, CTX, or functional recovery outcomes.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; CTX, C-terminal telopeptide of type I collagen; FGF23, fibroblast growth factor 23; FNDC5, fibronectin type III domain-containing protein 5; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; LDH, lactate dehydrogenase; LEA, low energy availability; P1NP, procollagen type I N-terminal propeptide; PTH, parathyroid hormone; RED-S, Relative Energy Deficiency in Sport; T3, triiodothyronine; TNF-α, tumor necrosis factor-α.

The table should therefore be read as an experimental logic rather than as a biomarker checklist. Its purpose is to separate what defines the baseline phenotype, what constitutes the physiological challenge, what changes dynamically after that challenge, and what represents a longer-term clinical or functional consequence. The stress-amplifier framework generates four testable predictions. First, the independent effect of low 25(OH)D status should be small or absent in nutritionally replete, well-recovered athletes exposed to manageable training stress. Second, associations between 25(OH)D and recovery outcomes should be stronger when low energy availability, inadequate calcium intake, endocrine disruption, high skeletal loading, or impaired recovery are present. Third, the effects of vitamin D repletion should be greater at lower baseline 25(OH)D concentrations and attenuated in participants with higher baseline status. Fourth, vitamin D-related effects should emerge more clearly in the magnitude, duration, or completeness of post-challenge recovery than in distal performance outcomes. These predictions should

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be tested through prespecified interaction analyses and repeated stress–recovery measurements rather than through unstratified comparisons of supplementation groups.

Because the framework spans outcomes with different biological scales and measurement properties, no single minimum interaction effect or generic sample-size threshold is proposed. Instead, each study should prespecify a primary outcome and define the smallest biologically or clinically meaningful interaction effect for that outcome. Sample-size calculations should then be based on the relevant interaction term, incorporating expected variance, repeated-measures structure, attrition, and the planned level of statistical power. In observational designs, this would generally involve powering the study to detect interactions between 25(OH)D status and prespecified vulnerability factors or time; in intervention studies, the primary test should focus on treatment-by-vulnerability and treatment-by-time interactions rather than on the main effect of supplementation alone.

7.3 RED-S as an experimental validation model

RED-S offers a high-yield human model for testing the stress-amplifier hypothesis because it concentrates the nutritional, endocrine, musculoskeletal, and recovery-related constraints under which conditional vitamin D effects are predicted to emerge. It should be used here as a validation context, not treated as a mechanism caused by vitamin D insufficiency.

The multisystem structure of RED-S also supports the use of integrated phenotyping. The 2023 International Olympic Committee REDs Clinical Assessment Tool-Version 2 (IOC REDs CAT2) combines primary and secondary indicators spanning clinical history, endocrine and reproductive function, bone health, metabolic and hematological measures, psychological features, and sport participation risk [118]. However, the IOC REDs CAT2 is primarily a clinical assessment and severity/risk-stratification tool rather than a validated stand-alone instrument for research phenotyping. Its categorical traffic-light classifications integrate heterogeneous indicators, some of which depend on clinical history, self-reported symptoms, or practitioner judgment; therefore, research studies should not treat CAT2 categories as interchangeable with quantitatively defined physiological strata, and individual components should be prespecified and analyzed separately where appropriate [118]. Reviews of proposed RED-S biomarkers likewise show substantial heterogeneity and no universally validated diagnostic biomarker panel [119]. For vitamin D research, the implication is straightforward: 25(OH)D should be examined within a broader physiological profile rather than as a standalone exposure. Validation studies should recruit athletes across clearly characterized vulnerability strata, including energy-replete controls and athletes with indicators of problematic LEA or RED-S. Baseline characterization should include 25(OH)D, calcium and protein intake, dietary fat, PTH and phosphate-related measures, sex and reproductive-endocrine status, sport type, season, training load, sleep, fatigue, injury history, and RED-S risk. Participants should be analyzed according to prespecified and explicitly justified 25(OH)D strata, and preferably also through continuous-exposure models; assay method, standardization, and baseline concentration distributions should be reported. Within this design, four interpretations of low 25(OH)D should be separated analytically. First, low 25(OH)D may be a marker of broader nutritional vulnerability. Second, it may act as a conditional modifier if associations between baseline vulnerability and recovery trajectories differ according to 25(OH)D status. Third, it may contribute mechanistically in selected contexts, particularly through mineral–endocrine coupling, if changes in calcium intake, PTH, phosphate-related measures, bone-turnover markers, or calcitriol-related endpoints support such a pathway. Fourth, it may represent a modifiable exposure if correction of low 25(OH)D within an otherwise comparable nutritional-rehabilitation program changes stress–recovery kinetics. These interpretations require different analytical tests and should not be collapsed into a single causal claim.

The model can then be tested using standardized challenges or longitudinal rehabilitation. Exercise or loading protocols could examine whether baseline vitamin D status modifies the amplitude and recovery of bone-turnover markers, muscle-damage indices, inflammatory responses, neuromuscular function,

fatigue, sleep, and cortisol profiles. Nutritional-rehabilitation studies could assess whether management of low 25(OH)D, when clinically indicated, is associated with different recovery trajectories during restoration of energy availability and correction of broader nutritional deficits. The primary outcome is the trajectory after stress or rehabilitation, not a single resting value. Intervention studies should compare correction of low 25(OH)D within otherwise comparable nutritional-recovery programs, rather than contrast vitamin D supplementation with persistent under-fueling or inadequate treatment of LEA. This design would prevent persistent energy deficiency from obscuring or falsely amplifying any vitamin D-related effect. It would also allow investigators to test interaction effects among baseline 25(OH)D, calcium availability, endocrine status, loading, and recovery rather than relying only on the main effect of supplementation. The central prediction is that vitamin D status will have little detectable influence in nutritionally replete, well-recovered athletes exposed to manageable stress, but greater relevance in athletes whose adaptive reserve is constrained by LEA, mineral inadequacy, endocrine disruption, high skeletal loading, poor sleep, or previous bone stress injury. Evidence for the model would therefore consist of a reproducible interaction between vitamin D status or correction and the magnitude, duration, or completeness of stress-recovery responses. An increase in serum 25(OH)D alone would not validate the hypothesis.

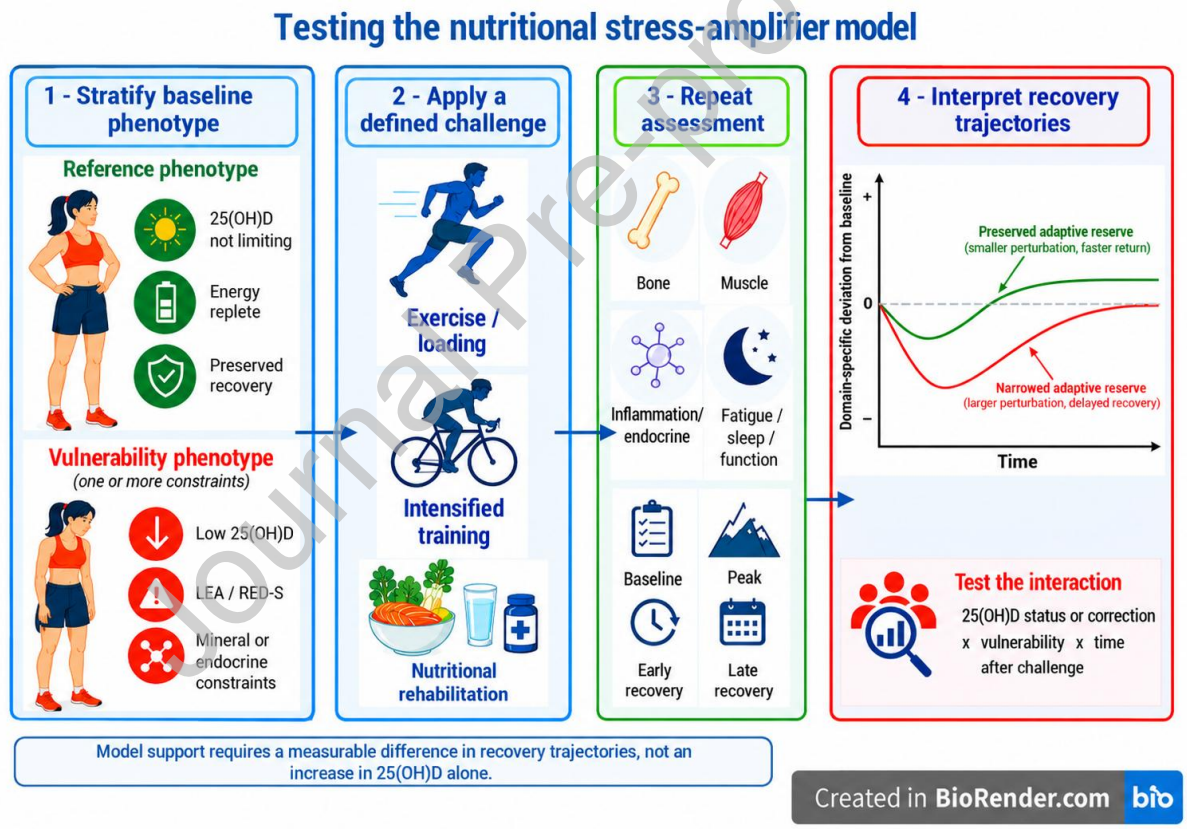


Fig. 3. Testing the nutritional stress-amplifier model through dynamic stress–recovery phenotyping. The proposed experimental sequence begins with prespecified characterization of the baseline phenotype. A reference phenotype combines 25(OH)D status not considered limiting in the prespecified study context, sufficient energy availability, and preserved recovery, whereas a vulnerable phenotype may include low circulating 25-hydroxyvitamin D [25(OH)D], low energy availability or Relative Energy Deficiency in Sport (RED-S), and mineral or endocrine constraints. The athlete illustrations are schematic and do not imply that vulnerability is specific to either sex. Participants are then exposed to a defined challenge, such as exercise or skeletal loading, an intensified

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training period, or nutritional rehabilitation. Repeated assessments should capture complementary domains of adaptation, including mineral-bone responses, muscle repair, inflammatory and endocrine regulation, fatigue, sleep, and functional recovery, with sampling from baseline through peak perturbation and early and late recovery. The illustrative curves represent two possible response patterns: 1) preserved adaptive reserve, characterized by a proportionate perturbation and faster, more complete return toward baseline, and 2) narrowed adaptive reserve, characterized by a larger or more persistent perturbation and delayed or incomplete recovery. The curves are conceptual and do not represent quantitative thresholds. Each trajectory represents an illustrative domain-specific response rather than a composite score; in empirical studies, mineral-bone, muscle, inflammatory-endocrine, fatigue, sleep, and functional outcomes should be analyzed separately using prespecified measures. In the schematic, resistance to perturbation corresponds to the initial displacement from baseline, peak deviation to the maximal excursion, recovery rate to the return slope, time to recovery to the duration before return toward baseline, and completeness of recovery to the extent of final return toward baseline. The primary analysis should be a prespecified interaction among 25(OH)D status or correction, baseline physiological vulnerability, and time after challenge; the main effect of supplementation alone is not the primary test of the framework. The model would be supported by a reproducible difference in recovery trajectories, not by an increase in circulating 25(OH)D alone. The schematic is conceptual and not to scale. The figure was conceptually designed by the author and created using BioRender.com.

8. Evidence hierarchy and limits of inference

The proposed framework integrates components that differ substantially in evidential maturity and proximity to athlete-specific outcomes. This hierarchy also applies to causal interpretation. Low 25(OH)D can be interpreted as a nutritional marker, a conditional modifier, a mechanistic contributor, or a modifiable exposure, but the level of evidence required differs for each interpretation. Table 2 therefore distinguishes established mineral physiology, conditionally supported musculoskeletal effects, emerging endocrine crosstalk, hypothesis-generating brain-related pathways, and translational strategies for testing the nutritional stress-amplifier model.

Table 2. Evidence hierarchy and inferential boundaries of the proposed nutritional stress-amplifier model

Domain	Evidence level	Interpretation within the model	Main inferential boundary
Vitamin D–calcium–phosphate–PTH–FGF23 network and skeletal loading	Established	Provides the strongest mechanistic anchor linking vitamin D insufficiency, mineral coupling, bone remodeling, and vulnerability to repetitive mechanical stress	Established mineral physiology does not demonstrate ergogenic effects; bone stress injury remains multifactorial
Skeletal-muscle VDR signaling, myostatin, and irisin/FNDC5	Emerging	Supports context-dependent vitamin D responsiveness and candidate pathways of muscle repair and muscle–bone communication	VDR abundance and transcriptomic responses vary by population and methodology; athlete-specific causal effects remain unproven
IL-6, osteocalcin, osteopontin, and endocrine tissue repair	Emerging	Illustrates context-dependent communication among exercise, inflammation, bone	Acute exercise responses differ from chronic inflammation; these mediators are not validated

Domain	Evidence level	Interpretation within the model	Main inferential boundary
		endocrine function, and tissue repair	markers of vitamin D-dependent recovery
FGF21 and nutritional stress signaling	Hypothesis-generating	Positions FGF21 as a convergent research readout of nutritional and metabolic strain	Not a validated LEA/RED-S biomarker; sex-related responses need replication, and no direct calcitriol-VDR-FGF21 axis is established
BDNF, serotonin, and calcitriol-dopamine signaling	Preclinical	Exploratory links to fatigue and recovery regulation	Findings do not demonstrate that vitamin D repletion improves mood, motivation, exercise drive, or performance in athletes
Sleep, HPA-axis regulation, interoception, and maladaptive persistence	Hypothesis-generating	Exploratory recovery-regulation domains	Interoception is multidimensional; no evidence that vitamin D alters interoceptive measures or behavioral persistence in athletes
LEA and RED-S	Emerging	Distinguishes marker, modifier, and modifiable-exposure interpretations of low 25(OH)D in LEA/RED-S	RED-S is driven by problematic LEA, not vitamin D insufficiency; vitamin D correction cannot replace nutritional rehabilitation
Dynamic stress–recovery phenotyping	Hypothesis-generating	Operationalizes adaptive reserve through response magnitude and recovery kinetics after defined challenges	Adaptive reserve remains an operational construct; no validated composite score or threshold exists

Table 2. Evidence levels reflect both general mechanistic maturity and proximity to vitamin D-specific, athlete-related outcomes. Established evidence is supported by consistent biochemical, experimental, and human data. Emerging evidence has mechanistic support but limited athlete-specific confirmation. Preclinical evidence is supported predominantly by experimental or mechanistic studies without direct confirmation in the target athlete population. Hypothesis-generating evidence identifies biologically plausible pathways that have not been directly validated in athletes with low 25(OH)D status. LEA and RED-S are presented as translational test conditions, whereas dynamic stress–recovery phenotyping is proposed as an experimental validation strategy. The table does not imply that all domains contribute equally or constitute a single causal pathway. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BDNF, brain-derived neurotrophic factor; FGF21, fibroblast growth factor 21; FGF23, fibroblast growth factor 23; FNDC5, fibronectin type III domain-containing protein 5; HPA, hypothalamic–pituitary–adrenal; IL-6, interleukin-6; LEA, low energy availability; PTH, parathyroid hormone; RED-S, Relative Energy Deficiency in Sport; VDR, vitamin D receptor.

8.1 Interpreting evidential gradients and limits of inference

The principal limit of inference is the marked asymmetry of the evidence summarized in Table 2. Vitamin D-dependent regulation of calcium–phosphate homeostasis, PTH–FGF23 feedback, and skeletal mineralization is supported by established biochemical and physiological evidence [1–3,31–35,41,42]. By contrast, skeletal-muscle VDR biology and candidate muscle–bone mediators are supported by heterogeneous human, experimental, and preclinical evidence, with limited athlete-specific causal

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validation [22–25,51–72]. Brain-related recovery pathways remain still more indirect, being supported mainly by biological plausibility, non-athlete human studies, or preclinical evidence rather than by intervention studies in athletes with low 25(OH)D [15,16,76,81–84,87–109].

Accordingly, the stress-amplifier interpretation should be regarded as a hypothesis derived from these different evidential layers rather than as an established causal model. LEA and RED-S provide a clinically and physiologically relevant context in which nutritional, endocrine, skeletal, and recovery-related constraints converge [17–19,36,37,73–75], but current evidence does not establish that low 25(OH)D independently causes these disturbances or that its correction reverses them.

The proposed framework is therefore supported only to the extent that future studies demonstrate that 25(OH)D status or its correction modifies prespecified stress–recovery trajectories after relevant nutritional, endocrine, environmental, and training-related factors are characterized [113–117]. Failure to demonstrate such interactions would favor interpretation of low 25(OH)D primarily as a marker of broader nutritional vulnerability rather than as a conditional modifier of recovery.

9. Conclusions: from vitamin D status to conditional adaptive reserve

Vitamin D is unlikely to function as a universal ergogenic nutrient. The strongest evidence supports the role of calcitriol–VDR signaling in calcium–phosphate homeostasis, mineral–endocrine regulation, and skeletal remodeling [1–3,31–35,41,42], whereas athlete-specific evidence for muscle–bone signaling is less established and brain-related recovery pathways remain largely hypothesis-generating [22–25,51–72,76,81–85,87–109]. Low circulating 25(OH)D should therefore be interpreted neither as a direct measure of calcitriol–VDR activity nor as an independent determinant of athletic performance, but as a nutritional exposure whose relevance may depend on physiological context.

The stress-amplifier hypothesis is therefore testable through dynamic stress–recovery phenotyping rather than static 25(OH)D measurements alone. Support for the model would require reproducible evidence that 25(OH)D status or its correction modifies the magnitude, duration, or completeness of recovery after a defined challenge, particularly under conditions of nutritional or physiological vulnerability [113–117]. LEA and RED-S provide useful translational contexts for testing this conditional relationship [17–19,36,37,73–75], but current evidence does not establish low 25(OH)D as a cause of these conditions or vitamin D correction as their primary treatment.

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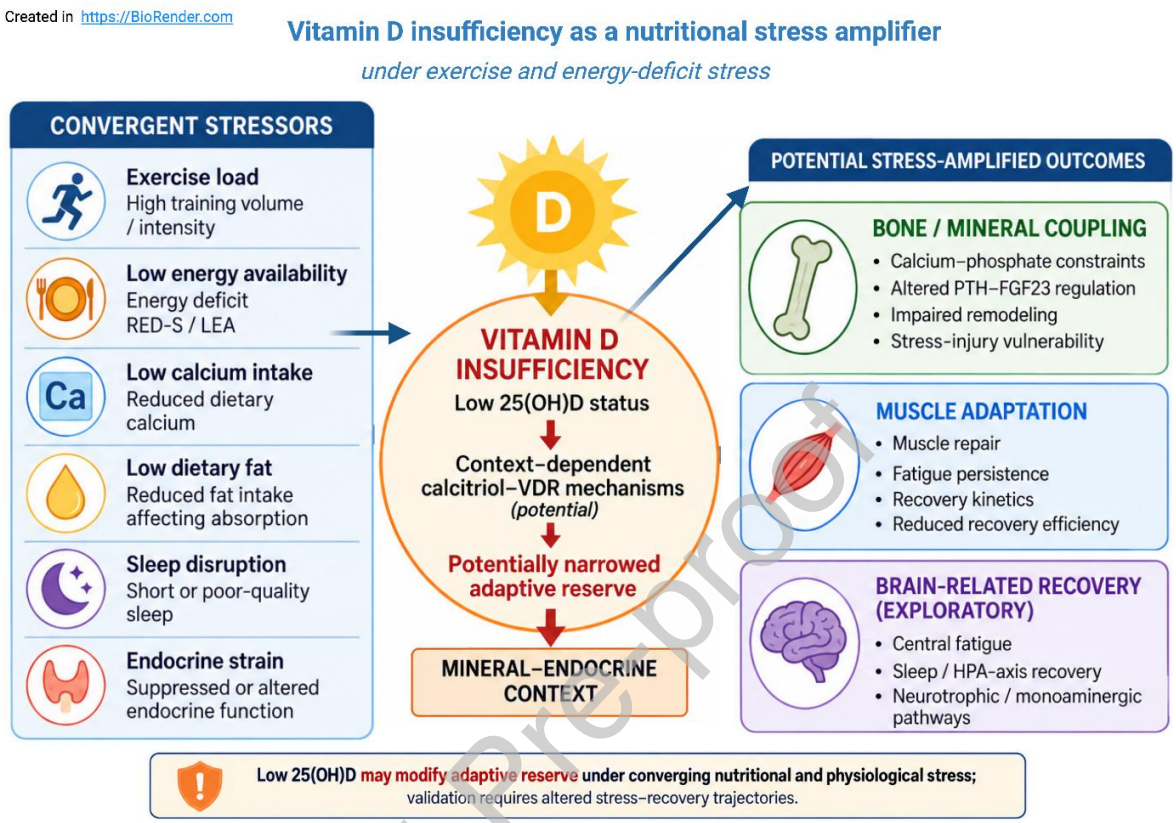
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Conflict of Interest

The author declares that he does have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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