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Consensus statement on vitamin D role in metabolic health☆

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ABSTRACT

The 8th International Conference Controversies in Vitamin D, held in September 2024, convened leading experts to address the multifaceted role of vitamin D in human health. Key discussions focused on its influence on metabolic health, including effects on sarcopenia, muscle function, and energy metabolism, as well as its role in obesity, cardiovascular health, and diabetes. Preclinical evidence was presented, suggesting a pivotal role of vitamin D in regulating muscle function and repair, potentially preventing sarcopenia. A relationship between low vitamin D (25[OH]D) concentrations and increased risk of cardiovascular diseases and diabetes was supported by several preclinical and clinical studies. Vitamin D supplementation was recently demonstrated to help improve glycemia and reduce the progression to diabetes and increase the likelihood of regression to normal

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glucose regulation in adults with prediabetes. Despite mixed outcomes from large, population-based randomized clinical trials, the conference underscored the critical need for personalized research, through disease-specific clinical trials, to fully elucidate the therapeutic potential of vitamin D supplementation, particularly in chronic conditions such as cardiovascular diseases and diabetes. In conclusion, while vitamin D demonstrates considerable promise in modifying a wide array of metabolic health concerns, rigorous scientific inquiry is essential to deepen our understanding of its mechanisms as well as potential protective effects and establish evidence-based guidelines for supplementation. This growing body of work has the potential to significantly enhance clinical outcomes and improve public health strategies, calling for continued exploration and collaboration in the field of vitamin D research.

1. Introduction

The 8th International Conference on Controversies in Vitamin D, titled "Vitamin D: a Pleiotropic Hormone", was held in Rome (Italy) from September 1st to 4th, 2024, as part of a series that began with the first meeting in 2017 in Pisa [1–11]. This conference brought together international experts to critically review and address the most contentious issues surrounding vitamin D, providing new perspectives and fostering multidisciplinary progress in the field. Participants were selected based on their recognized expertise, as demonstrated by their peer-reviewed publication record.

To develop the Consensus Statements presented in this review, the Co-Chairs (AG and JPB) assigned specific discussion topics to participants according to their area of expertise. Each subgroup conducted structured discussions on their assigned topic, considering evidence from in vivo studies, observational research, randomized controlled trials, and systematic reviews/meta-analyses. While the available literature was not selected or reviewed through a formal systematic review process, the evidence considered was identified through expert-driven, focused appraisal of the most relevant and impactful studies in the field. Draft statements were initially proposed by the subgroup chairs, followed by plenary discussions in which all participants critically evaluated, debated, and refined the statements. This iterative and collaborative process ensured that the review reflects a comprehensive synthesis of expert knowledge, highlighting key points in vitamin D research while maintaining transparency regarding the methodology used to gather and evaluate evidence.

The proceedings of this meeting represent a significant contribution to the ongoing evolution of vitamin D research, inspiring further innovation and multidisciplinary collaboration in this critical area of study.

2. Vitamin D and muscle

Consensus statements:

- Physical activity and increases in protein intake are the most efficacious approaches to lower the risk for sarcopenia.
- Vitamin D has roles in modulating T-cells plasticity and promoting regulatory T-cells development. Preclinical studies suggest that vitamin D may influence mitochondrial function, and some in vitro and animal studies indicate potential synergy with exercise in supporting muscle regeneration, although direct evidence in humans remains limited.
- Preclinical evidence demonstrates the pivotal role of vitamin D in regulating muscle function and repair through multiple biological pathways; clinical studies have yielded inconsistent results regarding the efficacy of vitamin D supplementation on muscle mass, strength, and physical performance.
- Recent large trials found no significant reduction in fall risk following vitamin D supplementation in older adults, either daily or monthly; however, the fall assessments in these trials were not rigorous, suggesting the need for more detailed assessments. Some trials suggest a U-shaped relationship between 25-hydroxyvitamin D [25(OH)D] concentrations and fall risk. Optimal 25(OH)D concentrations for minimizing fall risk may range between 20 and 40 ng/mL, with risks increasing at both lower and higher concentrations.

The term 'sarcopenia' (Greek 'sarx' or flesh + 'penia' or loss) was proposed in 1989 to describe the age-related decrease of muscle mass. The European Society of Clinical Nutrition and Metabolism (ESPEN) defines sarcopenia as a syndrome characterized by the progressive and generalized loss of skeletal muscle mass, strength, and function (performance) with a consequent risk of adverse outcomes [12]. More recently, the Global Leadership Initiative in Sarcopenia (GLIS) proposed a global conceptual definition of sarcopenia, which includes muscle mass, muscle strength, and muscle-specific strength (muscle strength/muscle size) as components of the definition [13–15].

Sarcopenia is a multifactorial condition that can be classified as primary (i.e., age-related loss of muscle mass, strength, and function), or secondary sarcopenia (i.e., resulting from inactivity, disease, or inadequate nutrition) [16]. It results from a combination of physiological changes, including the decline in total body protein — especially after age 65 — and hormonal alterations, chronic inactivity, and inadequate nutritional intake. These are further exacerbated by aging-related anorexia, elevated inflammatory cytokines, and changes in gut-derived hormones like cholecystokinin. These interconnected factors highlight the complex interplay between age-related physiological changes and external influences in the progression of sarcopenia [17].

Emerging evidence links sarcopenia to 'inflammaging', a state of chronic low-grade inflammation that impairs muscle repair and contributes to metabolic decline [18].

Physical exercise is known to be beneficial for the aging population. It helps reduce weight gain, sarcopenia, loss of metabolic control, and low-grade inflammation [19]. While acute exercise can cause myofiber damage and trigger inflammatory events, leading to the differential activation of tissue macrophages (M1 and M2 macrophage polarization) [20]; regular physical activity promotes adaptive repair mechanisms by activating proliferation and fusion of muscle stem cells, progressively contributing to tonic and trophic effects that sustain muscle mass and strength [21]. The main actors in this process are regulatory T cells (Tregs), particularly RORγ+ gut-derived Tregs. These cells play a critical role in muscle regeneration and immune homeostasis [20,22]. Gut-derived RORγ+ Treg emissaries play a key role in the homeostasis of extra-gut tissues and promote distal tissue regeneration. The microbiota regulates muscle repair via RORγ+ Treg cells, which accumulate in the damaged muscle, where they shield differentiating muscle stem cells from IL-17 A. Vitamin D contributes to this reparative process by enhancing gut microbiota diversity, promoting T-cell plasticity, and inducing the development of RORγt/FoxP3+ Tregs [22–25].

Beyond Tregs regulation, vitamin D is crucial for maintaining muscle function and energy metabolism [26], suggesting a synergistic role for vitamin D and physical exercise in supporting muscle maintenance and healthy aging. Conversely, vitamin D deficiency may result in decreased muscle strength, reduced muscle mass, and disrupted energy metabolism, which can impact weight control and physical activity capacity [27].

Several biological pathways explain the effect of vitamin D on

muscle. Vitamin D receptor (VDR) is essential for maintaining adequate muscle mass and strength as it activates intracellular signaling pathways relative to calcium metabolism and myoblast proliferation and differentiation [27]. Vitamin D enhances mitochondrial biogenesis through increased expression of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), upregulates mitochondrial DNA copy number, modulates fusion and fission processes, increases adenosine triphosphate (ATP) production capacity, and improves oxidative function through enhanced activity of electron transport chain complexes [28,29]. Conversely, vitamin D deficiency leads to mitochondrial dysfunction, decreased ATP production, increased reactive oxygen species (ROS) production, and oxidative damage. Genes encoding sarcoendoplasmic reticulum calcium transport ATPase (Serca) channels and calbindin (a calcium-handling protein) may be down-regulated in vitamin D-deficient populations, leading to decreased muscle strength. Vitamin D deficiency may increase myostatin concentrations, upregulate E3-ubiquitin ligase MuRF1 (enzyme targeting proteins for proteolysis), and dysregulate myogenic regulatory factors independently from the aging process, such as the Notch signaling pathway, which is responsible for muscle progenitor cell renewal and differentiation [27–29].

The pivotal roles that vitamin D plays in muscles and the immune system highlight the additional therapeutic potential of vitamin D supplementation for aging and sarcopenic patients, especially considering the disproportional prevalence of vitamin D deficiency in the elderly [29]. Nonetheless, the beneficial effects of vitamin D supplementation on muscle mass, muscle strength, and physical performance are still debated [30].

A large meta-analysis including over 5600 individuals (mean age: 61.1 years) revealed a small but significant positive effect of vitamin D supplementation on global muscle strength measured by grip strength, quadriceps muscle strength and leg extension strength, but no effect was found on muscle mass; the supplementation was most effective for increasing muscle strength in people who had 25(OH)D concentrations <30 nmol/L (<12 ng/mL) and who were 65 years of age or older [31]. Another study showed a cumulative effect of vitamin D with other determinants of muscle health: an interactive effect was found between serum 25(OH)D and physical activity on functional tests and muscle strength [32]. A meta-analysis of eight studies involving more than 750 patients found that vitamin D (100-1600 IU/day) plus protein (10-44 g/day) supplementation improved muscle strength in patients with sarcopenia but had no effect on muscle mass or performance assessed by walking speed [33]. This finding is of particular interest, as a study in older community-dwelling men found that slower walking speed was associated with a higher mortality risk [34]. The PROVIDE study was a multicenter, controlled, double-blind, parallel-group trial that randomized 380 sarcopenic, primarily independent-living older adults into an active group receiving a vitamin D and leucine-enriched whey protein nutritional supplement to be consumed twice daily and the control group receiving an isocaloric control product to be consumed twice daily [35]. The intervention was effective in improving postprandial muscle protein synthesis, appendicular skeletal muscle mass, and lower-extremity function (measured using the chair stand test) [35]. Another study on older adults (4139 patients, 65 % women, 67.9 ± 6.7 years) evaluated the relationship between serum 25(OH)D concentrations and physical activity with timed up-and-go test (TUG) performance, handgrip strength, calf circumference, and body muscle mass. Serum 25(OH)D concentrations and physical activity were linearly related to TUG time and handgrip strength but not to calf circumference or body muscle mass in older adults after adjusting for sex, age, body mass index (BMI), education level, smoking status, and serum calcium levels; this suggests that the impact of vitamin D on muscle strength and physical performance in older adults is closely linked to their level of physical activity [36]. Key evidence from observational studies, randomized clinical trials and systematic reviews and meta-analyses are summarized in Table 1.

In conclusion, preclinical evidence demonstrates the pivotal role of vitamin D in regulating the immune system, reducing inflammation, and supporting muscle function and repair through multiple biological pathways, including mitochondrial function, calcium handling, and myoblast differentiation. However, clinical studies have yielded inconsistent results regarding the efficacy of vitamin D supplementation on muscle mass, strength, and physical performance. These inconsistencies can largely be attributed to variations in study design, including differences in supplementation regimens (dose and frequency), characteristics of the study population, baseline serum 25(OH)D concentrations, and participants' physical activity levels. Future research focusing on personalized approaches —such as tailoring supplementation based on baseline serum 25(OH)D concentrations, age, comorbidities, nutritional status, and physical activity— may help clarify the therapeutic potential of vitamin D for older adults, particularly those with sarcopenia and low serum 25(OH)D concentrations. Falls are a common and often devastating problem among older adults, causing significant morbidity, mortality, and use of healthcare services, with most of these falls being associated with one or more identifiable risk factors [37]. Among these, sarcopenia has been directly linked to an increased probability of falls, fractures, and mortality in multiple studies [38–40].

The mechanism(s) underlying the relationship between serum 25(OH)D concentrations and fall/fracture risk are not fully understood. In a comprehensive meta-analysis of clinical trials, Bislev et al. found no link between muscle performance and fall risk [41]. Pfeiffer et al. reported that supplementing insufficient older women with 1000 IU/day vitamin D supplementation significantly lowered body sway, a measure of balance, by 9 %; the treatment also reduced the risk of falling and the total number of falls [42]. Recent findings suggest that high serum 25(OH)D concentrations can increase circulating fibroblast growth factor-23 (FGF-23) [43,44], a hormone released by osteocytes in response to elevated 25(OH)D concentrations. FGF-23 reduces the production of active vitamin D [1,25(OH)$_2$D] by downregulating 1α-hydroxylase (CYP27B1) and upregulating 24-hydroxylase (CYP24A1) [45]. Elevated

Table 1
Key evidence on vitamin D supplementation and muscle/sarcopenia outcomes.

Study (or First Author), Year (Reference)	Population / sample size	Intervention / comparator	Follow-up	Outcome(s)	Main findings	Study type
Beaudart, 2014 [31]	Adults ≥65 years, *n* = 5615	Vitamin D (different dose) vs placebo	6–24 months	Muscle mass, strength, performance	↑ strength (small effect) in deficient; no effect on mass	Meta-analysis of 30 randomized controlled trials
PROVIDE Study, 2015 [35]	Sarcopenic older adults, *n* = 380	800 IU vitamin D + protein vs placebo	13 weeks	Muscle protein synthesis, strength	↑ synthesis, ↑ strength	Randomized controlled clinical trial
Yang, 2020 [36]	Older adults, *n* = 4139	Serum 25(OH)D concentrations + PA vs control	Cross-sectional follow-up	Grip strength, TUG	Interaction serum 25(OH)D concentrations–PA; ↑ performance with higher serum 25(OH)D concentrations + PA	Observational study

N = Number of individuals; PA = Physical activity; TUG = Timed up and go test.

FGF-23 levels have been linked to frailty [46], a key risk factor for falls. Consequently, the associated reduction in $1,25(OH)_2D$ and increase in frailty may contribute to impaired bone mineralization and a higher risk of fractures [46].

The latest vitamin D mega-trials investigated the relationship between serum 25(OH)D concentrations, vitamin D supplementation, falls, and fractures; however, fall assessment in the mega-trials was not rigorous, understandably given the size of the studies and the limited interaction between study staff and participants [47]. Fall assessment was based on annual mail-out questionnaires in VITAL and D-Health and more frequent mail-out questionnaires (every 1 or 4 months) in ViDA (Vitamin D Assessment). Thus, mega-trials are not particularly useful in defining the optimal serum 25(OH)D concentrations range to minimize falls because of these sub-optimal fall assessments and because they studied vitamin D-replete older populations. In addition, recent Cochrane reviews have expanded the perspective beyond vitamin D intervention alone. One review focusing on older people in care facilities concluded that multifactorial interventions—especially when implemented with staff engagement and tailored to residents' needs—probably reduce the rate of falls and the risk of falling, whereas vitamin D supplementation alone probably reduces the rate of falls but makes little or no difference to the overall risk of falling [48]. A second Cochrane review of population-based interventions found the evidence for community-wide strategies, including policies for vitamin D supplementation, exercise, and environmental modifications, to be of very low certainty, with inconsistent results across studies [49].

In this context, there is evidence from studies with detailed fall assessments that more falls occur in individuals with both low and high 25(OH)D concentrations [50]. In a one-year dose-finding vitamin D intervention trial in postmenopausal women, Smith et al. reported a U-shaped association between the intra-trial mean 25(OH)D concentration and the risk of falling [51]. The nadir of fall risk in this study was in the 25(OH)D concentration range of 35 to 41 ng/mL (87-102 nmol/L). Similarly, in the Boston STOP IT trial in men and women aged 65 years and older, there was a U-shaped association between the intra-trial mean 25(OH)D concentration and the risk of falling, with a nadir region of 20 to 40 ng/mL [52]. Fall risk was recently assessed in a secondary analysis of an earlier 4-year vitamin D plus calcium trial in 2303 postmenopausal women [53]. In this trial, the mean baseline 25(OH)D concentration was 32.6 ng/mL. There was no association of 25(OH)D with all falls at 25(OH)D concentrations below 60 ng/mL; however, participants with intra-trial 25(OH)D concentrations $\geq$60 ng/mL had a significantly greater risk of experiencing two or more falls than participants with 25(OH)D concentrations in the range of 30 to 40 ng/mL [53]. In the STURDY (Study to Understand Fall Reduction and Vitamin D in You) study, a trial testing the effect of 1000 IU versus 200 IU of vitamin D daily on fall risk in 647 older adults with a history of falling, participants with an achieved 25(OH)D concentration of 40 ng/mL had a trend toward more first falls than those with a level < 30 ng/mL [54]. Finally, in a three-armed supplement trial in older adults, monthly treatment with vitamin D resulted in achieved intra-trial 25(OH)D concentrations of 30.8, 39.2, and 44 ng/mL in groups 1, 2, and 3, respectively. The percentages of fallers over the 1-year intervention period were 47.9 %, 66.9 %, and 66.1 %, respectively, with groups 2 and 3 both having more fallers than group 1 [55].

There is increasing evidence of a nonlinear association between serum 25(OH)D and fall risk. The precise range of the nadir region for falls is not yet clear, but the lower 25(OH)D boundary appears to be around 20 ng/mL. The upper boundary may be around 40 ng/mL or as high as 60 ng/mL, in line with recent expert discussions [56]. Refining this estimate will require additional data and the use of standardized 25(OH)D values in alignment with the Vitamin D Standardization Program (VDSP) guidance [1].

3. Vitamin D and cardiovascular health

Consensus statements:

- There is a curvilinear relationship between low 25(OH)D concentrations and an increased risk of cardiovascular diseases. Patients with heart failure have low concentrations of 25(OH)D, and 25(OH)D lower than 10 ng/mL is associated with left ventricular dilatation. Hypovitaminosis D is associated with left ventricular adverse remodeling after myocardial infarction, which may be mediated by effects on inflammation, endothelial dysfunction, calcium homeostasis, and the renin-angiotensin-aldosterone system.
- Though randomized controlled trials show inconsistent results, some studies suggest that vitamin D supplementation might be useful in the reduction of left ventricular adverse remodeling and atrial fibrillation occurrence correlated with aging, heart failure, and hypertension. Vitamin D supplementation trials (e.g., VITAL and other trials that report CVD outcomes) are limited due to inconsistencies in dosage regimens and heterogeneous populations, including varied baseline 25(OH)D concentrations.
- Serum 25(OH)D deficiency is common among cardiac surgery candidates. Optimal serum 25(OH)D concentrations are associated with reduced operative risk, lower incidence of adverse events, and potentially shorter hospital stays. Future research should focus on trials testing individualized vitamin D supplementation regimens and investigating the multi-endocrine interplay in critically ill patients, particularly in cardiac surgery candidates.
- The current evidence derived mainly from trials investigating vitamin D supplementation effects on cardiovascular disease suggests that increasing 25(OH)D concentrations in vitamin D-replete populations does not significantly reduce the risk of ischemic heart disease.

Left ventricular adverse remodeling (LVAR) represents a maladaptive response to myocardial damage, as observed in cases of myocardial infarction (MI) and cardiomyopathies or hemodynamic alterations, such as those seen in arterial hypertension or cardiac valve dysfunction. Despite advances in primary percutaneous coronary intervention procedures and pharmacological therapy, approximately 30 % of patients with acute MI develop heart failure because of LVAR [57,58]. Therefore, investigating and understanding the molecular pathways underlying LVAR offers the potential to improve patient outcomes and to pave the way for more personalized and effective interventions in managing MI and its complications [58]. In this context, circulating 25(OH)D concentrations have been inversely associated with cardiovascular outcomes, with lower concentrations strongly linked to unfavorable events [59–63]. For instance, in a study conducted by Ameri et al. (2013), individuals with severe vitamin D deficiency (less than 10 ng/mL) displayed increased left ventricular end-diastolic and systolic diameters and volumes, indicating the potential correlation between left ventricular dysfunction and the severity of vitamin D deficiency [64]. In addition, hypovitaminosis D is common among patients with MI, and insufficient serum 25(OH)D concentrations are associated with LVAR in patients with MI [65].

Multiple mechanisms have been proposed to explain the pathophysiological role of hypovitaminosis D in promoting heart failure following MI through processes including inflammation, endothelial dysfunction, hypertrophy, and hypertension (Fig. 1 and Fig. 2). More precisely, it has been demonstrated that vitamin D reduces the production of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), IL-1β, and IL-6, through the inhibition of nuclear factor kappa enhancer of light chain (NF-κB) activity in activated B cells. Conversely, in the absence of 25(OH)D, a pro-inflammatory state is promoted, with an increase in TNF-α transcription leading to a reduction in nitric oxide (NO) concentration through the downregulation of endothelial NO synthase (eNOS) [66–68]. Vitamin D regulates intracellular calcium

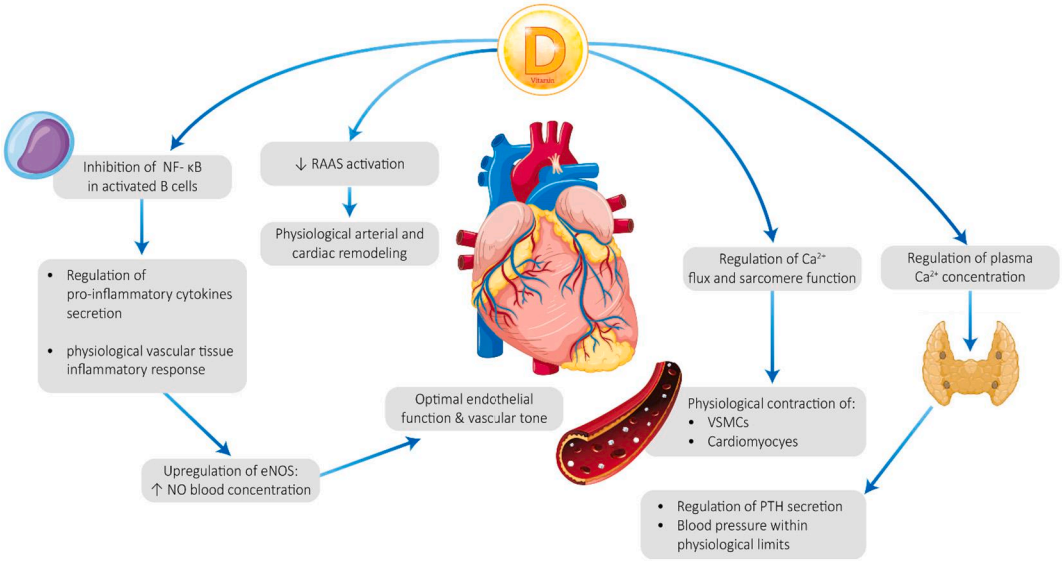


Fig. 1. Pathophysiology of cardiovascular effects of vitamin D. Vitamin D deficiency influences cardiovascular health through multiple biological pathways, including inflammation, endothelial dysfunction, altered calcium homeostasis, and activation of the renin–angiotensin–aldosterone system (RAAS). Experimental evidence shows that vitamin D reduces the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 via inhibition of NF-κB [65–67]. In vitro studies have confirmed effects on endothelial nitric oxide synthase (eNOS) signaling and vascular smooth muscle cell contraction [65,66], while in vivo studies associate hypovitaminosis D with increased PTH, hypertension, and RAAS overactivation leading to maladaptive ventricular remodeling [67–71]. **Evidence base:** Adapted from in vitro mechanistic studies [65–67] and in vivo/clinical evidence linking vitamin D deficiency with cardiovascular dysfunction [63–71].

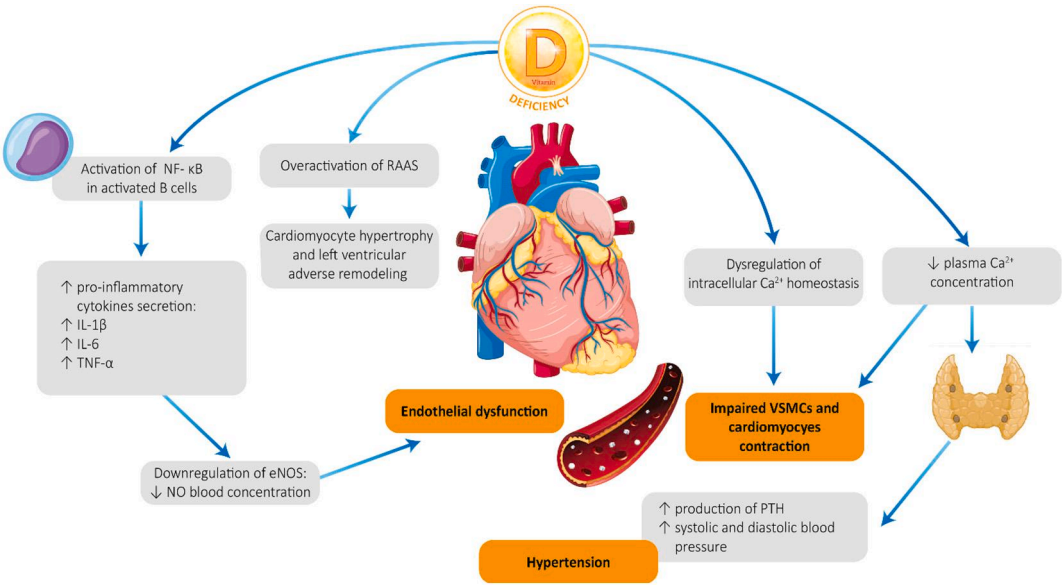


Fig. 2. Clinical consequences of hypovitaminosis D on the heart. Low serum 25(OH)D concentrations are associated with adverse clinical outcomes, including left ventricular dilatation, impaired remodeling after myocardial infarction, increased blood pressure, and heightened risk of heart failure [56–64,91–95]. These effects are mediated by the pathways illustrated in Fig. 1, which translate into higher morbidity and mortality in patients with cardiovascular disease. The figure summarizes clinical and epidemiological findings linking hypovitaminosis D to poor cardiovascular outcomes. **Evidence base:** Derived from observational and interventional in vivo studies in patients with myocardial infarction, heart failure, and cardiac surgery [56–64,91–95].

homeostasis, which is crucial for NO production; hence, insufficient serum 25(OH)D concentrations have been associated with diminished NO synthesis via multiple distinct mechanisms, ultimately leading to inflammation and endothelial dysfunction [67]. Calcium overload in vascular smooth muscle cells (VSMCs) and cardiomyocytes because of hypovitaminosis D results in their altered contraction [66,67]. Furthermore, low concentrations of 25(OH)D result in a reduction in plasma calcium concentration, which in turn stimulates the parathyroid glands to produce parathyroid hormone (PTH), which is associated with higher systolic and diastolic blood pressure [68,69]. Finally, hypovitaminosis D has been linked to an overactivation of the renin-angiotensin-aldosterone system (RAAS), which, via angiotensin II, maintains cardiac hypertrophy [70–72]. Specifically, RAAS induces extracellular matrix turnover through the activation of metalloproteinases, thereby promoting ventricular dilation. Hypovitaminosis D-mediated activation of RAAS contributes to an enhanced pro-inflammatory response, which exacerbates hypertrophy [70–72].

Overall, endothelial dysfunction, impaired VSMCs contraction, high PTH concentrations, and activation of RAAS are associated with the development of arterial hypertension. Given that a 20 mmHg increase in

systolic blood pressure is associated with a 28 % increase in the risk of HF, vitamin D deficiency may serve as a common contributing factor linking arterial hypertension and heart failure [73]. The complex role of vitamin D in cardiovascular health has led to extensive research into the potential of vitamin D supplementation. Trials in vitamin D-replete adults at low risk for cardiovascular disease (CVD) such as the ViDA and VITAL studies, have not shown benefit of vitamin D supplementation in CVD prevention [11,74,75]. A meta-analysis of 21 randomized controlled trials also did not show benefit of vitamin D on CVD outcomes [76]. However, these trials included only a small number of participants with 25(OH)D concentrations <30 nmol/L, making their conclusions less certain [77]. Post-hoc analysis of the ViDA trial suggested slight improvements in central blood pressure (pressure in the aorta near the heart), though not in peripheral blood pressure (measured in arteries farther from the heart, such as the brachial artery). However, the significance of these findings is limited due to the small scale of the substudy [78]. Similarly, the Finnish Vitamin D Trial (FIND) did not show a significant reduction in major cardiovascular events, one of its primary endpoints, possibly due to sufficient vitamin D status in most participants at baseline [79]. Nonetheless, exploratory analyses indicated that high-dose vitamin D supplementation might help reduce atrial fibrillation risk by 27 %-32 % in older adults, even among those with relatively high baseline 25(OH)D concentrations [80].

In the D-Health trial, a numerically lower incidence of major cardiovascular events—particularly MI and coronary revascularization—was reported in the vitamin D group compared to the placebo group, although the absolute risk difference was small, and the confidence interval just overlapped with a null effect (HR 0.91; 95 % CI 0.81-1.01). Notably, the benefits appeared more pronounced for MI specifically (HR 0.81; 95 % Cl 0.67-0.98) and in individuals already taking cardiovascular medications at baseline [81]. The VINDICATE trial administered 4000 IU/day of cholecalciferol for 1 year in patients with chronic heart failure and hypovitaminosis D, reporting improvements in left ventricular function and remodeling among deficient patients [82]. An overview of key randomized controlled trials and meta-analyses on cardiovascular outcomes is reported in Table 2. Where available, we specify in the table the form of supplementation administered. Circulating concentrations between forms were not compared, as direct head-to-head data are lacking.

The literature does not clearly support the effect of vitamin D supplementation in reducing blood pressure in patients with hypertension. For instance, a meta-analysis by Witham et al. (2009) including 11 randomized controlled trials described a small and statistically significant decrease in blood pressure [83]. On the other hand, a systematic review of 46 trials conducted in 2015 concluded that vitamin D supplementation was ineffective in reducing systolic and diastolic blood pressure in patients with low serum 25(OH)D concentrations and arterial hypertension [84]. These results were supported by other meta-analyses that have reported no effects of vitamin D on blood pressure [85,86]. However, it is worth mentioning that vitamin D supplementation has been described as an effective adjuvant when administered in combination with traditional antihypertensive drugs [87].

Mendelian randomization studies have reported a causal association between genetically determined low serum 25(OH)D concentrations and increased risk of HF [88]. Specifically, per 1 standard deviation (SD) increase in standardized log-transformed 25(OH)D level, the relative risk of HF decreased by 16.5 % (OR: 0.835, 95 % CI: 0.743–0.938, $P = 0.002$). However, the role of vitamin D supplementation on arterial blood pressure and CVD is still inconclusive [89]. There is currently no consensus on the dosage regimen and frequency of intake, and the optimal dosage range is generally calibrated based on the therapeutic objective, which may vary across the studies conducted so far [11,83]. It is also important to mention that in some trials, some of the participants included already had optimal baseline serum 25(OH)D concentrations [76,90] which resulted in no discernible effect from the supplementation. In other instances, some of the enrolled patients had been diagnosed with CAD or MI, which precluded the possibility of observing any beneficial effects resulting from the supplementation, given that the patient's overall condition was already critical, and they had suffered severe cardiac damage [11]. Therefore, although vitamin D supplementation has been described as ineffective in the general population, it cannot be ruled out as a potential preventive and therapeutic strategy in some subgroups defined according to their 25(OH)D serum concentrations and gene variants [11,91].

One approach to clarify the potential role of vitamin D in CVD would be to design and conduct a trial where participants receive vitamin D based on their baseline level and aiming for a target level. Once the optimal blood values have been achieved, this level would be maintained throughout the study. The influence of vitamin D supplementation in cardiac surgery candidates represents an additional area of interest and research. Indeed, several studies have shown that cardiac surgery candidates are often characterized by vitamin D deficiency [92]. Zitterman and colleagues have reported a higher rate of adverse cardiac and cerebrovascular events, showing an increased in-hospital mortality, post-operative myocardial infarction, low cardiac output, stroke as well as 6 and 12-month mortality [93]. This negative outcome, however, was observed only in patients with serum 25(OH)D concentration lower than 30 nmol/L or higher than 100 nmol/L [93].

Barker and collaborators tested the supplementation of cholecalciferol (50.000 IU) the evening prior to the scheduled surgery and at 1 and 2 postoperative day [94]. This supplementation was sufficient to prevent hypovitaminosis induced by the cardiac surgery procedure, but the effects on this supplementation remained to be determined.

The association between circulating concentrations of 25(OH)D and clinical results of cardiac surgery (reduction of inotropes and vasopressors use, with serum 25(OH)D concentrations <20 ng/mL associated with poorer postoperative prognosis and complications) was also demonstrated through a systematic review and meta-analysis of 16

Table 2
Key randomized controlled trials and meta-analyses on vitamin D supplementation and cardiovascular outcomes.

Study (or First Author), Year (Reference)	Population / sample size	Intervention / comparator	Follow-up	Outcome(s)	Main findings	Study type
VITAL Study, 2019 [75]	Adult individuals, $n = 25,871$	Vitamin D3 (cholecalciferol) 2000 IU/d vs placebo	5 years	CV events (MI, stroke)	No reduction in overall CVD risk	Randomized controlled clinical trial
ViDA Study, 2017 [74]	Adult individuals who were treated for ≥1 year with vitamin D, $n = 5110$	Vitamin D3 (cholecalciferol) 100,000 IU/mo vs placebo	3.3 years	MI, stroke, CVD mortality	No significant benefit	Randomized controlled clinical trial
Barbarawi, 2019 [76]	Adult individuals, $n = 83,291$	Vitamin D (different dose and formulations) vs placebo	1-12 years	CVD outcomes	No overall benefit; uncertainty in deficient subgroups	Meta-analysis of 21 randomized controlled clinical trials
VINDICATE Study, 2016 [82]	HF patients, $n = 229$	Vitamin D3 (cholecalciferol) 4000 IU/d vs placebo	1 years	LV remodeling, function	Improved cardiac function in deficient	Randomized controlled clinical trial

CV = Cardiovascular; CVD = Cardiovascular disease; LV = Left ventricular; MI = Myocardial infarction; n = Number of individuals; VINDICATE = VitamIN D treatIng patients with Chronic heArT failurE.

studies [95].

Other studies have shown the negative effects exerted by hypovitaminosis D in cardiac surgery patients (like anemia, infection, prolonged hospital stay, postoperative fibrillation, sepsis, heart apoptosis, acute renal failure). However, an interesting recent finding and hypothesis was described by Boran Tumer who showed that preoperative serum concentrations of 25(OH)D < 25 nmol/L are associated with delirium after cardiac surgery procedures [96].

The above-mentioned aspects certainly deserve additional investigations and represent a clear direction of research in the understanding of vitamin D pleiotropic effects in patients affected by cardiovascular diseases requiring surgical interventions.

4. Vitamin D, glycemic control, and diabetes

Consensus statements:

- There are clear inverse correlations between vitamin D status and insulin resistance, the risk of diabetes, and chronic diabetic complications.
- Vitamin D supplementation improves glycemia, reduces the progression to diabetes, and increases the likelihood of regression to normal glucose regulation in adults with prediabetes, but the optimal dosage remains unclear. No safety concerns were reported, even though higher doses than the National Academy of Medicine (NAM) for skeletal health recommendations and the Recommended Dietary Allowance (RDA) by the Institute of Medicine were used.
- More specific trials should be designed to investigate the role of vitamin D pathway metabolites (including 1,25(OH)2D, 24-25(OH)2D, DBP) and the related changes in glycemic control parameters after vitamin D supplementation to better understand the mechanism of the benefit and to optimize the supplementation strategies.

Observational studies have shown an inverse association between serum 25(OH)D concentrations and the likelihood of developing insulin resistance and type 2 diabetes (T2DM) [97]. A meta-analysis showed an inverse association between vitamin D status and insulin resistance (r = -0.217; 95 % CI 0.161 to -0.272) as assessed with the Homeostatic Model Assessment for insulin resistance [98]. Low serum 25(OH)D concentrations (<5 nmol/L) have been associated with nearly a twofold increase in the risk of fasting hyperglycemia or diabetes mellitus [99]. As summarized in many meta-analyses, longitudinal cohort studies suggest approximately a 40 % lower risk of developing diabetes mellitus in individuals with the highest serum 25(OH)D concentrations compared to those with the lowest concentrations [100]. However, the observational design of these studies limits the ability to establish causality, due to residual confounding. For risk of T2DM, there appears to be a linear association between higher 25(OH)D concentrations and reduced risk, with no clear threshold for benefit [100]. A cross-sectional study used multivariable analyses to investigate the relationship between serum 25(OH)D concentrations, glycemic variability (GV) assessed with mean amplitude of glycemic excursions (MAGE), coefficient of variation (CV), standard deviation of glucose (SD), and time in range (TIR), and hemoglobin A1c (HbA1c) in 325 patients with T2DM. The study showed that lower 25(OH)D concentrations were associated with higher CV, MAGE, SD, and HbA1c, and lower TIR ($P < 0.05$). Serum 25(OH)D was inversely associated with CV ($\beta = -0.211$) and HbA1c ($\beta = -0.061$), confirming its role in reducing glycemic variability and improving glycemic control [101]. A large prospective study from the UK Biobank, with over 379,000 participants followed for an average of 14 years, demonstrated a strong inverse association between serum 25(OH)D concentrations and the risk of developing T2DM across different glycemic statuses. Individuals with normoglycemia and prediabetes who had 25(OH)D concentrations ≥75 nmol/L had a significantly lower risk of T2DM compared to those with concentrations <25 nmol/L (HRs: 0.62 and 0.64, respectively). It was shown that this risk reduction occurred with a concentration-dependent effect (e.g., each 10 nmol/L [4 ng/mL] increment in 25(OH)D concentrations corresponded to a 7 % and 6 % reduced risk among normoglycemic and prediabetic individuals, respectively) [102–104]. The protective effect of vitamin D in prediabetes was influenced by VDR gene polymorphisms, particularly in carriers of the T allele of rs1544410 [102,103]. Notably, even if these findings are in part confirmatory of previous works demonstrating an important impact of hypovitaminosis D on the risk of developing T2DM (Fig. 3) in high-risk populations with prediabetes, this was the first study with enough power both in terms of size of the cohort and length of follow-up able to demonstrate a clear protective effect of sufficient vitamin D status against incident T2DM also in subjects with normoglycemia at the study start [103–105].

The SUNNY (Effect of Vitamin D Supplementation on Glycemic Control in Patients With Type 2 Diabetes) trial reported no significant effect of intermittent vitamin D supplementation (50,000 IU/month) on HbA1c, fasting insulin, and glucose levels after six months, even though mean baseline serum 25(OH)D concentrations significantly increased in the vitamin D group; subgroup analyses in patients with a serum 25(OH)D concentration lower than 50 nmol/L or an HbA1c level higher than 7 % also showed no improvement [105]. However, a recent meta-analysis, which included 46 randomized controlled trials with 2164 intervention subjects and 2149 placebo controls, found significant improvements. The pooled analyses showed a weighted mean difference of -0.20 % (95 % Cl -0.29, -0.11; $P < 0.001$) for HbA1c, -5.02 mg/dL (95 % Cl ·6.75, -3.28; P < 0.001), for fasting plasma glucose (FPG), and -0.42 (95 % Cl -0.76, -0.07; $P = 0.019$) for the HOMA-IR. The most significant efficacy was observed with doses >2000 IU/day, shorter intervention periods, and in subjects with deficient 25(OH)D status [106].

The role of vitamin D supplementation in reducing the risk of T2DM among individuals with high-risk prediabetes has been investigated in three trials specifically designed for diabetes prevention among adults with prediabetes: the Tromsø study in Norway with 511 participants, the vitamin D and type 2 diabetes (D2d) study in the U.S. with 2423 participants, and the Diabetes Prevention with active Vitamin D study (DPVD) study in Japan with 1256 participants [107–109]. Vitamin D reduced the risk of developing diabetes mellitus compared to the placebo in a nearly identical degree in all three trials. The hazard ratio for vitamin D versus placebo was 0.90 (95 %CI 0.69 to 1.18) in the Tromsø study, 0.88 (95 %CI 0.75 to 1.04) in the D2d study, and 0.87 (95 %CI 0.67 to 1.17) in the DPVD study. The reported relative risk reductions were smaller than each trial was powered to detect (25 to 30 %) [107–109]. A meta-analysis of individual participant data from these three trials showed that vitamin D reduced the risk of progression from prediabetes to T2DM by 15 % (HR 0.85; 95 % Cl 0.75 to 0.96) and increased the likelihood of regression to normal glucose regulation by 30 % (HR 1.30; 95 % CI 1.16 to 1.46), without any safety concerns [110]. Two other meta-analyses that combined aggregate data from these three trials and smaller, short-term trials that reported the effect of vitamin D on T2DM risk also found similar reductions in the risk of new-onset T2DM with vitamin D in adults with prediabetes [111,112], with an increase in the likelihood of regression to normal glucose regulation [112]. Key evidence from randomized controlled trials and meta-analyses on glycemic control and diabetes is summarized in Table 3.

The optimal serum 25(OH)D concentration and the appropriate dose of vitamin D supplementation for reducing T2DM risk are not yet clear, but the administered doses in trials appear to be higher than the dose recommended by the National Academy of Medicine (NAM) for skeletal health [110,113]. In summary, in adults with prediabetes, vitamin D administration is effective in reducing insulin resistance and consequently the risk of developing T2DM, while increasing the likelihood of regression to normal glucose regulation; further research is needed to optimize supplementation strategies to improve glycemic control.

The applicability of vitamin D to reduce T2DM risk in the general population at average risk for diabetes mellitus is still limited [114–116], although very recent findings were able the demonstrate a

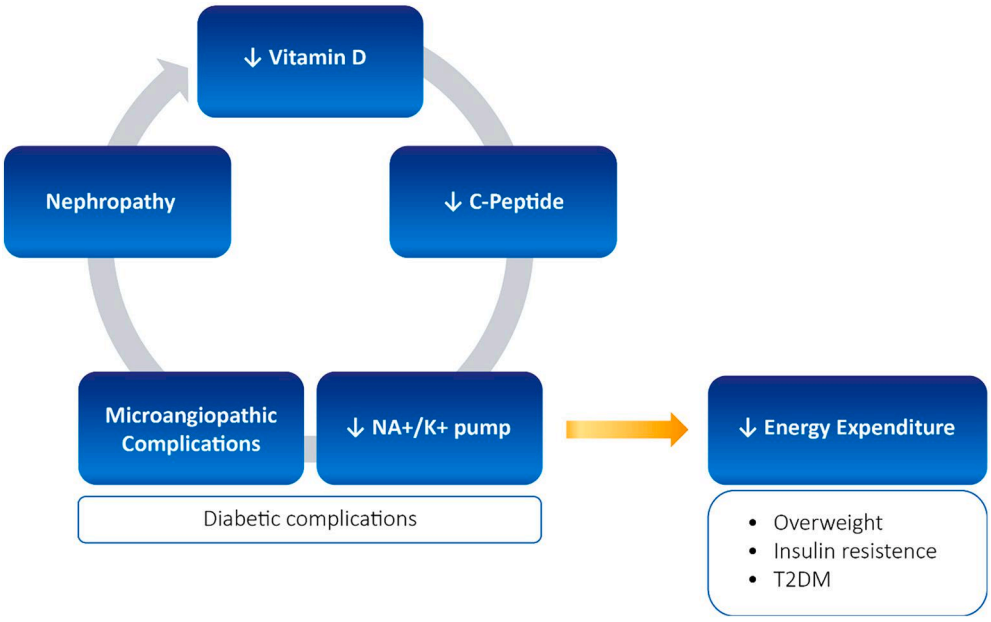


Fig. 3. Effects of hypovitaminosis D in diabetes: a negative loop. Vitamin D deficiency contributes to impaired insulin sensitivity, increased risk of type 2 diabetes mellitus, and worsened glycemic control. Observational studies consistently show inverse associations between 25(OH)D concentrations and insulin resistance, fasting hyperglycemia, and diabetes incidence [96–103]. Interventional studies indicate that vitamin D supplementation reduces progression to diabetes and promotes regression to normoglycemia in adults with prediabetes [104–109]. Pathways underlying this loop include modulation of insulin secretion and sensitivity, reduction of inflammation, and interaction with genetic factors such as VDR polymorphisms [101,102]. Mechanistic insights are largely from preclinical and in vitro work, while clinical trials provide in vivo confirmation in humans. **Evidence base:** Based on in vitro and animal studies exploring insulin signaling and inflammation [97,100], as well as in vivo human observational cohorts and intervention trials [99,102–109].

Table 3
Key randomized controlled trials and meta-analyses on vitamin D supplementation and glycemic control/diabetes.

Study (or First Author), Year (Reference)	Population / sample size	Intervention / comparator	Follow-up	Outcome(s)	Main findings	Study type
SUNNY Study, 2015 [105]	T2DM adults, n = 275	Vitamin D 50,000 IU once a month vs placebo	6 months	HbA1c, FPG, insulin	No significant effect overall	Randomized controlled clinical trial
Farahmand, 2023 [106]	T2DM adults, n = 4313	Vitamin D vs placebo	Various	HbA1c, FPG, HOMA-IR	Significant improvements, esp. in deficient	Meta-analysis of 46 randomized controlled trials
Tromsø Study, 2016 [107]	Prediabetes adults, n = 511	Vitamin D vs placebo	2 years	Incident T2DM	Non-significant reduction	Randomized controlled clinical trial
D2d Study, 2019 [108]	Prediabetes adults, n = 2423	Vitamin D vs placebo	2.5 years	Incident T2DM	HR 0.88 (NS)	Randomized controlled clinical trial
DPVD Study, 2022 [109]	Prediabetes adults, n = 1256	Alfacalcidiol vs placebo	3 years	Incident T2DM	HR 0.87 (NS)	Randomized controlled clinical trial
Pittas, 2023 [110]	Prediabetes adults, n ≈ 4200	Vitamin D vs placebo	2–3 years	T2DM incidence	↓ risk of progression (HR 0.85); ↑ regression to normoglycemia	Meta-analysis

Note: DPVD used alfacalcidol (an active vitamin D analog). Active analogs differ pharmacodynamically from native vitamin D (cholecalciferol/ergocalciferol) and therefore are reported separately. FPG = Fasting plasma glucose; HbA1c = Hemoglobin A1c; HR: Hazard ratio; NS = Not significant; T2DM = Type 2 diabetes mellitus.

protective effect of adequate 25(OH)D concentrations on the risk of incident T2DM also in subjects with normoglycemia [103–105].

In summary, in adults with prediabetes, vitamin D administration reduces the risk of developing diabetes mellitus and increases the likelihood of regression to normal glucose regulation. Based on available evidence, the 2024 Endocrine Society clinical practice guideline on vitamin D for the prevention of disease [117] suggests empiric vitamin D to lower the risk of diabetes mellitus in adults with prediabetes, in addition to lifestyle modification.

Further research is needed to optimize supplementation strategies and to determine its cost effectiveness as a diabetes prevention intervention.

5. Vitamin D, obesity, and metabolic syndrome

Consensus statements:

- Obesity is inversely correlated with vitamin D status, with higher adiposity linked to lower vitamin D, and weight loss increases 25(OH)D concentrations.
- Obesity may cause low vitamin D due to dilution in larger body mass, storage of vitamin D in adipose tissue, and decreased activity of CYP2R1. This results in a reduced increase in 25(OH)D concentrations following supplementation.
- Vitamin D deficiency is linked to obesity, potentially through different mechanisms. However, the role of vitamin D supplementation in obesity and related disorders is still unclear.
- Metabolic syndrome includes risk factors for T2DM and CVD, including obesity, hypertension, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL), and it is linked to low 25(OH)D concentrations. Vitamin D deficiency may exacerbate metabolic disorders, particularly through inflammation.

- Vitamin D supplementation lowers the risk of diabetes mellitus in adults with prediabetes, but evidence for improvement in other metabolic syndrome components like hypertension and dyslipidemia is less clear.
- Pathophysiological links between vitamin D and obesity and metabolic syndrome are complex, requiring further research.

Several observational studies, including meta-analyses, have consistently shown inverse associations between different measures of adiposity (BMI, fat mass, percentage of fat mass, waist-hip ratio) and 25(OH)D concentrations [118–123]. While several studies support the hypothesis that obesity may be linked to low 25(OH)D concentrations, any theoretical reverse effect is probably very small [118–123].

Many explanations have been put forward to explain the low 25(OH)D concentrations observed in people with obesity.

Heaney's group first hypothesized a dilutional effect underlying the low circulating values of 25(OH)D in obese subjects [124]. Vitamin D deficiency is associated with obesity (Fig. 4) and related comorbidities. Vitamin D is a fat-soluble steroid, and a volumetric dilution of the hormone into increased body mass is claimed as the most plausible explanation for this relationship. Indeed, adipose tissue is the main storage site for vitamin D and its metabolites. Furthermore, it has been suggested that adipose tissue may act as a system that prevents the uncontrolled synthesis of 25(OH)D in the liver [125]. Indeed, there is no difference in circulating 25(OH)D concentrations between subjects with normal or increased body weight after adjustment for body size. Clinical and experimental studies suggest that obesity is associated with decreased expression of specific genes that regulate the metabolism of vitamin D by coding synthesis of the enzyme 25-hydroxylase (CYP2R1) and 1-hydroxylase [126]. Finally, an upregulation of CYP24A1 activity has been suggested in experimental models [127].

On the other hand, a causal role for low serum 25(OH)D in body mass accumulation has been suggested [128]. Seasonal reduction in vitamin D may act as a physiological signal to allow fat storage or thermogenesis at low temperatures [129]. Several potential mechanisms could be proposed to support such a hypothesis, though experimental evidence is often controversial [129–133]:

1. Increased PTH levels secondary to hypovitaminosis D would raise intracellular calcium in adipocytes, thus stimulating lipogenesis and weight gain.
2. Vitamin D might regulate fat accumulation by directly affecting the activities of enzymes involved in lipolysis.
3. Vitamin D could influence energy homeostasis by regulating leptin expression.
4. Vitamin D appears to modulate fecal fat excretion.
5. Vitamin D might regulate mitochondrial uncoupling protein (UCP) expression.
6. Vitamin D might stimulate the secretion of the intestinal incretins.

Based on these premises, it has been suggested that vitamin D supplementation may have a role in obesity and associated metabolic disorders. However, at present, the results of observational studies and randomized controlled trials exploring the effects of dietary calcium and vitamin D status on body fat mass and body weight are still inconclusive [133]. In this regard, it should be noted that several confounding factors, including selection biases and differences in dose regimens and follow-up, may explain the discrepancies among various studies. A summary of key randomized controlled trials and meta-analyses on obesity and metabolic syndrome is provided in Table 4.

The Endocrine Society clinical practice guideline on vitamin D for the prevention of disease [117] suggests against routine screening of 25(OH)D concentrations in adults with obesity due to the lack of preferential benefit of vitamin D supplementation among obese people in

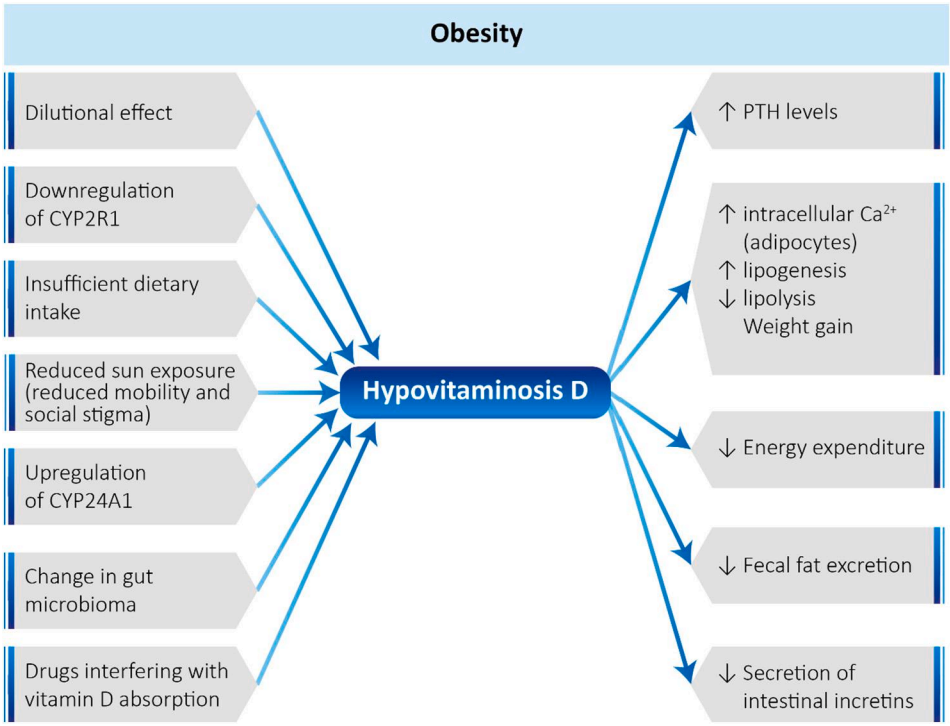


Fig. 4. Potential mechanisms underlying hypovitaminosis D in obesity. Vitamin D deficiency is frequently observed in obesity, partly due to volumetric dilution, sequestration in adipose tissue, and reduced CYP2R1 activity [123–126]. Experimental studies suggest additional mechanisms, including effects on parathyroid hormone–mediated lipogenesis, regulation of lipolytic enzymes, modulation of leptin, incretin secretion, and mitochondrial uncoupling proteins [127–132]. Most of these pathways are supported by in vitro and animal models, whereas clinical data mainly support the dilution and sequestration hypotheses. **Evidence base:** Derived from in vitro and animal studies on adipocyte metabolism and energy regulation [127–132] and from in vivo human observational studies linking adiposity with low vitamin D status [117–122,123–126].

Table 4
Key randomized controlled trials and meta-analysis on vitamin D supplementation/status and obesity/metabolic syndrome.

First Author, Year (Reference)	Population / sample size	Intervention / comparator	Follow-up	Outcome(s)	Main findings	Study type
Heaney, 2009 [124]	Adults with obesity, n ≈ 200	Vitamin D vs placebo	12 months	25(OH)D response	Blunted ↑ in 25(OH)D with supplementation	Randomized controlled clinical trial
Golzarand, 2018 [133]	Adults with obesity, *n* = 17,245	Vitamin D vs control	Various follow-up	Percentage fat mass	Serum 25(OH)D concentrations are inversely correlated with percentage fat mass but cholecalciferol supplementation has no effect on percentage fat mass	Meta-analysis of 35 studies (randomized clinical trials and observational studies)
Hajhashemy, 2021 [136]	General adult population, *n* = 309,206	Vitamin D status	NA	Metabolic syndrome	Inverse dose–response association between serum 25(OH)D concentrations and metabolic syndrome risk in adults	Meta-analysis of 43 studies (38 cross-sectional, one nested case–control, and four cohort's studies)

clinical trials, despite their lower serum 25(OH)D concentration compared to those with normal weight. Randomized controlled trials specifically focused on people with obesity are advised to determine if vitamin D lowers the risk of disease, and to establish the dosage and target levels that are required for disease prevention.

Metabolic syndrome describes the co-occurrence of metabolic risk factors for T2DM and CVD [134]. Individuals with abdominal obesity are at risk for low 25(OH)D concentrations, as are individuals with T2DM and CVD [120]. Obesity affects vitamin D requirements; higher doses of vitamin D may be required to replete low 25(OH)D concentrations and to maintain an adequate vitamin D status [135]. In cross-sectional observational studies, higher 25(OH)D concentrations are associated with lower odds of metabolic syndrome, but longitudinal observational studies do not consistently show a relationship [136]. Low vitamin D status could aggravate metabolic disorders, particularly through mechanistic pathways involving inflammation [137,138]. Whether vitamin D supplementation improves the components of metabolic syndrome is uncertain, and the highest quality clinical trial evidence is from trials involving the individual syndromic components. The strongest evidence for vitamin D supplementation is in people with prediabetes; as mentioned above, a systematic review and meta-analysis of individual participant data from three randomized controlled diabetes prevention trials among adults with prediabetes showed that vitamin D reduced the risk of developing diabetes mellitus [110]. Whether vitamin D supplementation has the potential to improve hypertension and dyslipidemia remains uncertain. In appraising the evidence, one must note that vitamin D supplementation might confer some metabolic benefits in individuals with overt vitamin D deficiency, but many trials have been conducted in individuals who are largely vitamin D replete. Future research efforts will likely be most fruitful if they focus on individual metabolic syndrome components rather than using the syndrome as primary endpoint. Additional research is needed to establish the relationship between vitamin D and those metabolic syndrome components and the implications for clinical care.

6. Conclusions

The 8th International Conference Controversies in Vitamin D emphasized the crucial role of vitamin D in various metabolic health conditions, including sarcopenia, CVD, and metabolic disorders. A great body of literature highlights the strong association between vitamin D deficiency and adverse health outcomes across these domains. Low 25(OH)D concentrations have been linked to impaired muscle function, increased cardiovascular risk, insulin resistance, and metabolic syndrome. Hypovitaminosis D has been correlated with higher susceptibility to sarcopenia, with muscle regeneration being influenced by vitamin D-mediated T-cell modulation and mitochondrial function. Similarly, cardiovascular research underscores an inverse linear relationship between serum 25(OH)D concentrations and the risk of heart failure, with pronounced effects on left ventricular remodeling and adverse outcomes in post-myocardial infarction patients. Additionally, vitamin D deficiency appears to contribute to obesity through mechanisms involving adipose tissue metabolism and energy homeostasis, further exacerbating metabolic syndrome and its related complications.

Despite these well-documented associations, whether vitamin D supplementation mitigates these risks remains a subject of debate (Fig. 5), with the exception among adults with prediabetes, where vitamin D has been shown to reduce the risk of developing diabetes mellitus and improving the likelihood of regression to normal glucose regulation. While preclinical studies support its role in muscle repair and immune regulation, clinical trials have yielded inconsistent findings regarding improvements in muscle strength, physical performance, and fall prevention. Some studies suggest a U-shaped relationship between serum 25(OH)D concentrations and fall risk, indicating potential harm at both deficient and excessive levels. In the cardiovascular domain, although supplementation may aid in reducing LVAR and atrial fibrillation in specific populations, large, randomized trials have failed to demonstrate a significant reduction in ischemic heart disease risk in generally vitamin D older adults. Likewise, while vitamin D supplementation shows promise in improving glycemia and reducing T2DM incidence, particularly in prediabetic individuals, defining an optimal dosage remains a challenge.

These inconsistencies stem from variations in study design, heterogeneity in dosing regimens, and differences in baseline vitamin D status among participants. In some trials, beneficial effects may be masked when supplementation occurs in vitamin D-replete populations, highlighting the need for targeted, individualized interventions. Based on the evidence reviewed and previous recommendations stated in the 6th International Conference Controversies in Vitamin D, practical considerations regarding vitamin D dosing and vitamin D supplementation can be proposed. First, supplementation appears most effective in individuals with baseline serum 25(OH)D concentrations lower than 20 ng/mL, whereas benefits are inconsistent in vitamin D–replete populations. Daily doses in the range of 800–2000 IU are generally sufficient to preserve bone health and potentially improve muscle function, glycemic control, and reduce diabetes risk in deficient or high-risk adults, with doses up to 4000 IU/day being safe and beneficial in selected clinical contexts such as heart failure or obesity, where vitamin D metabolism is altered. Both daily and intermittent regimens (e.g., weekly or monthly administration of equivalent cumulative doses) are effective, provided that a stable 25(OH)D concentration is maintained. Importantly, the available data suggest a U-shaped relationship between serum 25(OH)D concentrations and falls, with the lowest risk observed around 20–40 ng/mL; therefore, according to the opinion of this Consensus Panel, excessive dosing that results in concentrations exceeding 60 ng/mL should be avoided. Overall, vitamin D supplementation should aim to maintain serum 25(OH)D concentrations within the range of 20–40 (up to 60) ng/mL, tailoring the dose to baseline status, comorbidities, and body weight as detailed in the previous Consensus [11]. However, recently, Holick [139] emphasized that, to achieve optimal extra-skeletal outcomes—including reduced risk of infections, autoimmune disorders, and cardiometabolic

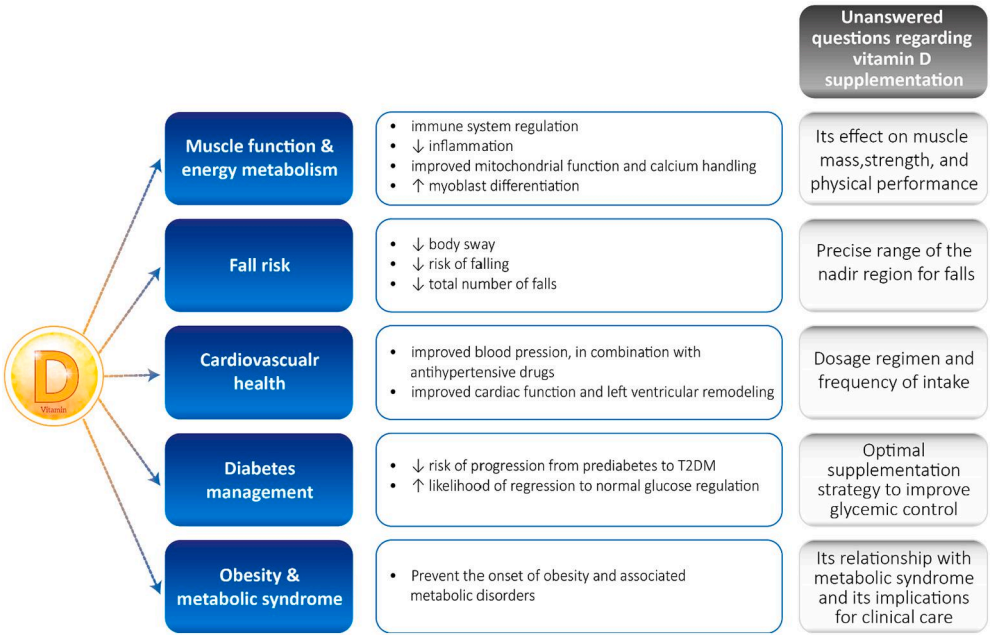


Fig. 5. The role and unanswered questions regarding vitamin D supplementation in metabolic conditions. Vitamin D supplementation has been proposed to improve outcomes in sarcopenia, cardiovascular disease, diabetes, obesity, and metabolic syndrome. While preclinical studies consistently demonstrate beneficial effects on muscle repair, mitochondrial function, and immune modulation [22–29], large, randomized trials in humans have yielded mixed or null results in cardiovascular disease, falls, and metabolic syndrome components [47,73–76,132,135]. Supplementation appears most effective in specific subgroups, particularly adults with prediabetes [105–109]. The figure highlights both the therapeutic promise and persisting uncertainties, stressing the need for individualized approaches. **Evidence base:** Summarized from preclinical in vitro/animal data [22–29] and in vivo clinical evidence from randomized trials and meta-analyses [47,73–76,105–109,132,135].

complications—circulating 25(OH) concentrations should ideally be between 40 and 60 ng/mL, with a minimum of 30 ng/mL, in line with the 2011 Guidelines critically appraising the 2024 Endocrine Society Guidelines and pointing out that it focus mainly on randomized controlled trials and largely overlook association studies supporting both skeletal and extra-skeletal benefits of vitamin D. Given the complex interplay between vitamin D metabolism, obesity, and cardiometabolic disorders, future research should focus on refining supplementation strategies, exploring vitamin D pathway metabolites, and integrating multi-disciplinary approaches to establish more conclusive evidence. The conference highlighted the urgent need for well-structured studies also based on national and international registries [121] to optimize vitamin D interventions and develop evidence-based recommendations tailored to different patient populations.

CRediT authorship contribution statement

Andrea Giustina: Writing – review & editing, Writing – original draft, Conceptualization. **Luigi di Filippo:** Writing – review & editing, Writing – original draft, Conceptualization. **Aneta Aleksova:** Writing – review & editing, Conceptualization. **Jens Bollerslev:** Writing – review & editing, Conceptualization. **Anna Maria Colao:** Writing – review & editing, Conceptualization. **Bess Dawson-Hughes:** Writing – review & editing, Conceptualization. **Lorenzo M. Donini:** Writing – review & editing, Conceptualization. **Peter R. Ebeling:** Writing – review & editing, Conceptualization. **Marise Lazaretti-Castro:** Writing – review & editing, Conceptualization. **Roberto Lorusso:** Writing – review & editing, Conceptualization. **Livio Luzi:** Writing – review & editing, Conceptualization. **Claudio Marcocci:** Writing – review & editing, Conceptualization. **Salvatore Minisola:** Writing – review & editing, Conceptualization. **Nicola Napoli:** Writing – review & editing, Conceptualization. **Anastassios G. Pittas:** Writing – review & editing, Conceptualization. **René Rizzoli:** Writing – review & editing, Conceptualization. **Patrizia Rovere Querini:** Writing – review & editing, Conceptualization. **Ferruccio Santini:** Writing – review & editing, Conceptualization. **Anne L. Schafer:** Writing – review & editing, Conceptualization. **Jyrki K. Virtanen:** Writing – review & editing, Conceptualization. **John P. Bilezikian:** Writing – review & editing, Conceptualization.

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Data availability

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