



Review

Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome



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ABSTRACT

The aim of this study is to determine the relationships of vitamin D with diabetes, insulin resistance, obesity, and metabolic syndrome. Intra cellular vitamin D receptors and the 1- α hydroxylase enzyme are distributed ubiquitously in all tissues suggesting a multitude of functions of vitamin D. It plays an indirect but an important role in carbohydrate and lipid metabolism as reflected by its association with type 2 diabetes (T2D), metabolic syndrome, insulin secretion, insulin resistance, polycystic ovarian syndrome, and obesity. Peer-reviewed papers, related to the topic were extracted using key words, from PubMed, Medline, and other research databases. Correlations of vitamin D with diabetes, insulin resistance and metabolic syndrome were examined for this evidence-based review. In addition to the well-studied musculoskeletal effects, vitamin D decreases the insulin resistance, severity of T2D, prediabetes, metabolic syndrome, inflammation, and autoimmunity. Vitamin D exerts autocrine and paracrine effects such as direct intra-cellular effects via its receptors and the local production of 1,25(OH)₂D₃, especially in muscle and pancreatic β -cells. It also regulates calcium homeostasis and calcium flux through cell membranes, and activation of a cascade of key enzymes and cofactors associated with metabolic pathways. Cross-sectional, observational, and ecological studies reported inverse correlations between vitamin D status with hyperglycemia and glycemic control in patients with T2D, decrease the rate of conversion of prediabetes to diabetes, and obesity. However, no firm conclusions can be drawn from current studies, because (A) studies were underpowered; (B) few were designed for glycemic outcomes, (C) the minimum (or median) serum 25(OH) D levels achieved are not measured or reported; (D) most did not report the use of diabetes medications; (E) some trials used too little (F) others used too large, unphysiological and infrequent doses of vitamin D; and (G) relative paucity of rigorous clinical data on the effects of vitamin D sufficiency on non-calcium endpoints. Although a large number of observational studies support improving T2D, insulin resistance, obesity, and metabolic syndrome with vitamin D adequacy, there is a lack of conclusive evidence from randomized control clinical trials that, these disorders are prevented following optimization of serum levels of 25(OH)D. However, none of the currently conducted clinical studies would resolve these issues. Thus, specifically designed, new clinical studies are needed to be conducted in well-defined populations, following normalizing the serum vitamin D levels in vitamin D deficient prediabetes subjects, to test the hypothesis that hypovitaminosis D worsens these disorders and correction would alleviate it.

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Contents

1. Introduction	178
1.1. Vitamin D assay methodology and safety limits	178
1.2. Vitamin D status and diabetes in Asia, the middle east, and other areas	178
1.3. Geographical and regional variations in vitamin D and T2D relationship	179
2. Diabetes mellitus, obesity, and insulin resistance	180
2.1. Vitamin D deficiency and diabetes mellitus	180

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2.2.	T2D—data from longitudinal studies	181
2.3.	Association of serum vitamin D levels and diabetes	181
2.4.	NHANES data on vitamin D and diabetes	182
2.5.	Vitamin D and obesity	183
2.6.	Vitamin D status and bariatric surgery	183
3.	Hypovitaminosis D and pathogenesis of diabetes	183
4.	Discussion	184
5.	Conclusions	185
	Conflicts of interest	185
	References	185

1. Introduction

Severe vitamin D deficiency in adults results in osteomalacia; whereas in children, it manifests as rickets. Adequate vitamin D prevents osteomalacia and rickets and reduces the risk of falls and bone fractures [1,2]. Vitamin D is essential for calcium homeostasis for optimal skeletal health. Vitamin D status is best determined by measuring serum 25-hydroxy D [25(OH)D]; a level higher than 30 ng/mL contributes to the optimal calcium absorption, prevention of falls, and fracture prevention [3–5]. Below that level, circulatory parathyroid hormone (PTH) levels increase, causing secondary hyperparathyroidism and that increases the risk of osteoporosis and fractures [6–8] leading to bone loss. Thus, raised PTH levels in the absence of primary hyperparathyroidism or renal failure can be used as a surrogate marker of vitamin D insufficiency and vice versa [9]. Moreover, moderate elevations of PTH may also promote insulin resistance, weight gain, hypertension, left ventricular hypertrophy, and the acute phase response, while increasing risk for ischemic arrhythmias and cardiovascular mortality [10].

Active vitamin D is a seco-steroid hormone essential for calcium absorption, bone mineralization, calcium and phosphorus homeostasis, hormonal release, nerve conduction and neuromuscular function [5,11]. Serum 25(OH)D levels are positively associated with bone mineral density (BMD) [3]. Sub-optimal vitamin D status has been reported in many populations [3,12], but is a particularly troublesome for the elderly, disabled people, and hospitalized patients [2,6,13,14].

Deficiency of vitamin D can result from inadequate nutritional intake of vitamin D, increased catabolism of vitamin D, inefficient production in the skin, or inadequate exposure to sunlight. In addition, various health conditions affect vitamin D's bioavailability; whereas, gastrointestinal disorders limit its absorption, renal and liver diseases can prevent activation of the parenteral vitamin D or impair the conversion of vitamin D into its active metabolites.

Over the years, observational and ecological studies have been used to determine the risk-modifying effects of vitamin D on an epidemiological basis. Few randomized controlled trials (RCTs) are available; many studies, including the ongoing larger clinical trials, are not properly designed to determine whether replenishment of vitamin D alleviates extra-skeletal disorders, including diabetes, insulin resistance, cancer, and cardiovascular disease [15–20]. Moreover, the rigor of clinical data on the effects of vitamin D sufficiency on non-calcium endpoints are lacking. Overall, epigenetics and environmental factors have more impact on whether vitamin D causes diseases than do genetic factors.

1.1. Vitamin D assay methodology and safety limits

Although a serum 25(OH)D test using high pressure liquid chromatographic/mass-spectrometry (LS/MS/MS) methodology can cost less than \$3, commercial laboratories charge between \$75 and \$200 per test. The delay in reporting, assay variability, high cost and resultant inadequate insurance coverage and so forth are

hampering the diagnosis and treatment of vitamin D deficiency. There is a great need to develop a rugged, specific, point of testing method to determine the whole blood 25(OH)D levels in an outpatient clinic setting (i.e., similar to finger-stick, blood sugar testing) that costs no more than five dollars per sample.

Upper safe limit is 5000 IU a day [8,21,22] (and some considered it to be 10,000 IU) and the toxicity does not manifest serum levels below 120 ng/mL (300 nmol/L) [23]. To reach the latter levels, one must ingest vitamin D in excess of 50,000 IU daily for several months [24]. Thus, the safety of doses to 5,000 IU a day is assured [25–27] and for those who are taking doses below this, routine serum 25(OH)D testing is unnecessary, not cost effective and cannot be justified.

The best way to obtain vitamin D is through exposure to sunlight [28,29]. However, for the institutionalized persons and vulnerable and special populations who are unable to get adequate exposure to sun, supplements can be administered: one capsule of 50,000 IU vitamin D₃, once every 2 weeks (0.30 cents per capsule × 26 capsules over a year) would cost approximately, \$10 per year per person [30]. Considering the lack of adverse effects associated with such a dose and the potential benefit in decreasing morbidities, this is a cost-effective and practical approach for vulnerable groups of populations.

In addition to being a precursor for its active hormonal form for its endocrine/autocrine functions, 25(OH)D is also has independent physiological effects in the body [29,31]. In addition, the roles of affinity of vitamin D-binding protein, their circulating half-lives, and enzymatic transformations of vitamin D metabolites, and how these affect biological action in any given tissue determine its physiologic activities [32]. Based on emerging data from the laboratory, clinical trials, and data on circulating 25(OH)D levels during past few years, it is likely that for the optimal functioning of these systems, significant amount of vitamin D should be available on a “daily” basis for a longer duration, to ensure stable circulating concentrations and its health benefits [32–34].

When vitamin D is administered at intervals of more than a month, optimum target levels of serum 25(OH)D reached only for a short period; thus, is less beneficial [26,35,36]. However, the goal should be to maintain a steady state of desirable serum vitamin D levels throughout the year [37]. Allowing non-physiologic variations in vitamin D dosing schedules (i.e., infrequent high dose administration) may have negative effects on the outcomes on recipients. Because of the short circulating half-life and marked fluctuation of vitamin D levels, vitamin D intervention clinical trials which uses such infrequent and/or too high dosing regimens unlikely to generates useful or meaningful data [30,32,35,38].

1.2. Vitamin D status and diabetes in Asia, the middle east, and other areas

Vitamin D deficiency is common globally but predominate in Asia and in the middle east, where more than 50% of the population is vitamin D deficient [39] and approximately 75% is vitamin insufficient or deficient [40–42]. In a randomly selected 21,960

people in the Thai, 4th National Health Examination Survey in 2009, 5.7% were reported to have 25(OH)D concentrations less than 50 nmol/L, and in 45.2%, the levels were less than 75 nmol/L (75% of the women in Bangkok) [43,44]. In a similar study conducted in 541 women in Vietnam, the mean 25(OH)D level was 81 nmol/L; 7% had 25(OH)D levels less than 50 nmol/L, and 48% had levels less than 75 nmol/L. Overall, in 90% of women and children, 25(OH)D levels were less than 75 nmol/L (<30 ng/mL) [45].

Vitamin D deficiency is common in the middle-east. For example, in Omani population it is linked to sun avoidance, inadequate dietary vitamin D, and not taking supplemental vitamin D. Its capital, Muscat is located on latitude, 23.61°N, close to sea level. The mean serum 25(OH)D values of Omanis are lower than those reported for populations domiciled in higher latitudes [46]. To improve the vitamin status, author suggested people exposure of people to moderate amounts of sun; the governments should consider vitamin D₃ fortification of commonly consumed food; and people to take higher amounts of vitamin D₃ supplements.

In a study conducted in New Zealand, South Asian women with insulin resistance and baseline 25(OH)D levels below 20 ng/mL were treated with vitamin D₃ 4,000 IU/day. Those who achieved serum 25(OH)D levels above 32 ng/mL showed significant improvement in insulin sensitivity [47]. The study authors concluded that insulin resistance results in hyperglycemia, which can be reduced with appropriate doses of vitamin D supplements.

1.3. Geographical and regional variations in vitamin D and T2D relationship

Several studies have confirmed an association between vitamin D status with cardiovascular diseases and diabetes-related outcomes [15,18,48–59]. The rates of vitamin D deficiency increase as one moves away from the equator; so as and the risks for T2D and type 1 diabetes (T1D) [15,60]. Epidemiological data support that, the further people live from the equator, the greater the prevalence of diabetes (Fig. 1). Based on these data, one may conclude the existence of an inverse relationship between the vitamin D status (i.e., mean serum 25(OH)D levels) and the prevalence of diabetes [61].

Blood levels of vitamin D in humans vary by age [62,63], gender [64], body mass index [65], season [66,67], and their geographical location [64,67,68]. Those who live far away from the equator and around the equator, have low serum 25(OH)D levels, but due to different reasons [65,69]. People who live in areas away from the equator get too little exposure to UVB during most of the year, whereas those who live close to the equator that has plenty of sunshine throughout the year, but avoid sun-exposure because of high ambient temperatures [31,70]. The latter is true for most people living in South Asia and those in the Middle Eastern countries.

The amount of sunlight dermal-exposure is varied by type and the style of clothing, the use of sunscreen, latitude, institutionalization (pollution), condition and the color of the skin (that influence the dermal-generation of vitamin D), and thus, the blood

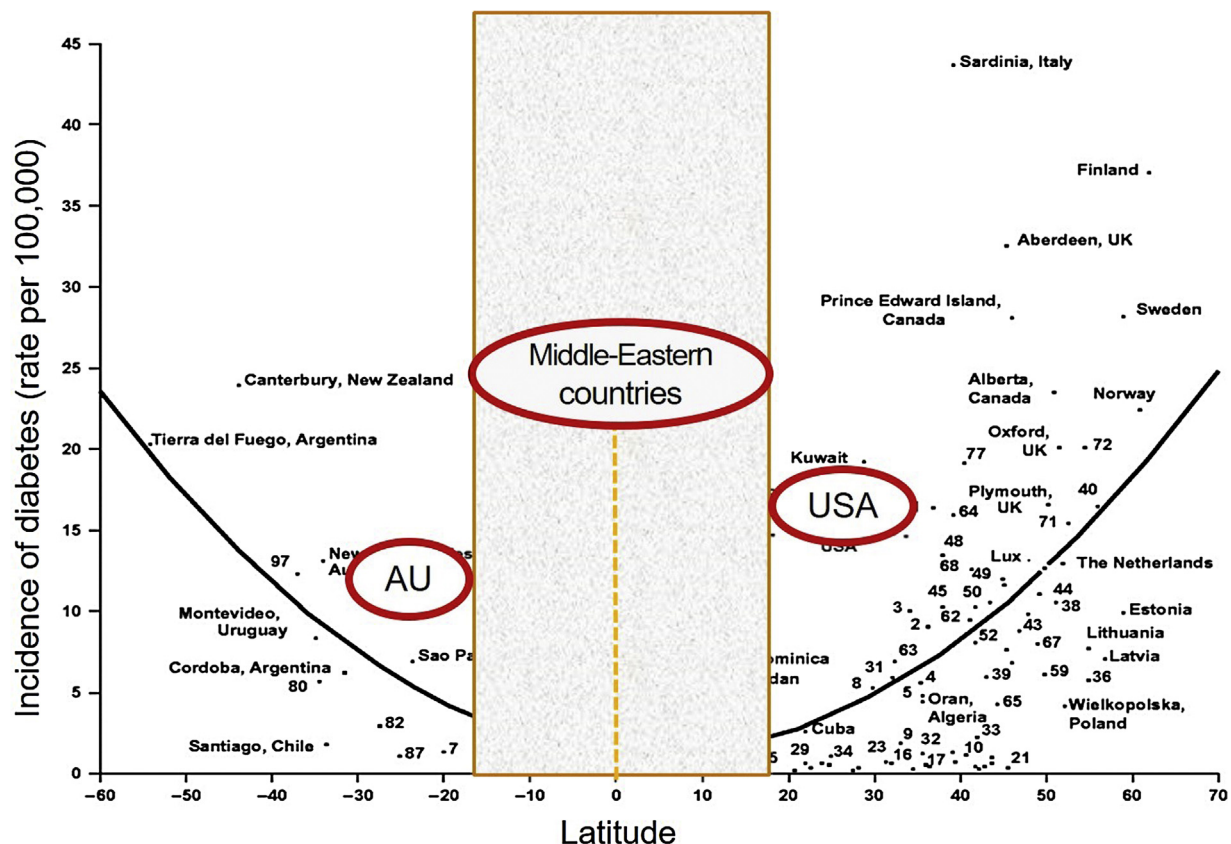


Fig 1. Incidence and the prevalence of diabetes increases with the distance people live away from the equator. Relationship between the incidence of type 1 diabetes (T1D) and the latitude of various countries. The incidence of T1D (also T2D and obesity) increases, as the distance from the equator increases [from Mohr et al. [216]].

vitamin D levels. So dietary, lifestyles, work environment, cultural habits, and demographic aspects all play a role, and need to take these into account, when planning to implement targeted interventions, including food fortification programs and executing public health policies.

Higher rates of diabetes are reported in countries that are located further from the equator (latitude) (Fig. 1), where people have less UVB exposure [71]. Similarly, those who live in higher altitudes also receive less exposure to UVB, and have a high prevalence of vitamin D deficiency, cardiovascular disease, and diabetes [18,72,73]. Many epidemiological and ecological studies have been published demonstrating close relationships between individual's sun-exposure and/or the vitamin D status with T1D [74–76], T2D [15,37,77–86], insulin resistance [17,19,20,47,61,79–82,87–92], hypertension [33,86,93–101], and metabolic syndrome [90,91,102].

2. Diabetes mellitus, obesity, and insulin resistance

Diabetes is not only about the inability to handle glucose properly but is also an inflammatory disease [103,104]. Because vitamin D has anti-inflammatory effects [71,105–108], it is not surprising that it has beneficial effects on improving islet-cell functions, insulin release, and decreasing insulin resistance [19,20,34]. Deficiency of vitamin D not only predisposes individuals to develop T1D and T2D but also leads to sub-optimal responses to therapy [109–113]. Vitamin D also plays a role in insulin signaling [114] and thus, modifies the risks of diabetes [115–117]. Although it is tempting to suggest, it is not known whether vitamin D adequacy would prevent age-related and glucotoxicity-induced death/apoptosis of islet-cells.

A population-based study from Norway, demonstrated a strong inverse association between elevated BMI and low serum 25(OH)D levels [118]. In addition, serum 25(OH)D levels inversely correlated with the mean blood sugar concentrations and severity of insulin resistance [37,119]. The finding of vitamin D receptors in the pancreatic β -cells [112,120] further supports the notion that vitamin D influences insulin synthesis and secretion. Fig. 2 illustrates the common pathways leading to destruction of β -cells and the development of diabetes and plausible effects of vitamin D in preventing it.

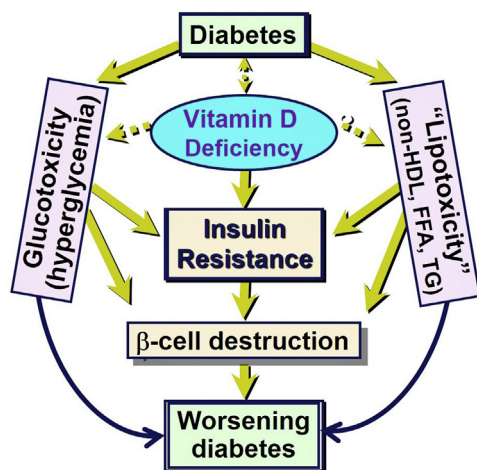


Fig. 2. Vitamin D deficiency enhance the risks of developing in diabetes. The role of vitamin D in the development of insulin resistance, and indirectly glucotoxicity and lipotoxicity. Vitamin D deficiency leads to a negative vicious cycle of worsening insulin resistance, β -cell distraction, and development of diabetes (FFA = free fatty acids; TG = triglycerides) [concept, was modified from Kahn SE [217] and Ludwig [218]].

Numerous observational studies have demonstrated a consistent, significant inverse association of low serum 25(OH)D levels with diabetes, prediabetes, obesity, and metabolic syndrome [81,121–124]. Micronutrient fortified milk is a reasonable source of vitamin D [192]. For example, those who consume more than three dairy servings per day are at a lower risk of developing diabetes [125]. Not only vitamin D but also daily consumption of calcium is also inversely associated with the risk of developing T2D [123,124,126,127] and blood pressure [33,34,86,128], which support this beneficial effects, but others disagree with these findings [129].

2.1. Vitamin D deficiency and diabetes mellitus

Diabetes mellitus is more than raised blood glucose; it is a syndrome with major long-term negative consequences. Among others, it is characterized by hyperglycemia, hyperlipidemia, and other metabolic abnormalities resulting in neurologic and small- and large-blood vessel complications. Experimental and epidemiologic studies have suggested beneficial effects of calcium and vitamin D supplementation in reducing the risk of developing diabetes. In recent years, many research studies have provided evidence on relationships between both T1D and T2D with vitamin D, as well as the beneficial effects of vitamin D supplementation in reducing the risk of diabetes and insulin resistance [83,130–133].

In addition, several observational and cross-sectional studies have also reported that people with higher serum 25(OH)D levels decreases elevated blood pressure [33,86,93–101], have reduced risk of developing T2D, and converting from prediabetes to diabetes [15,60,83,130–134]. Vitamin D seems to be particularly effective in reducing hypertension in those with T2D [86]. A cross-sectional study (n = 118 and n = 30) reported a negative correlation between 25(OH)D levels and insulin resistance (HOMA-IR; $r = -0.200$; $P = 0.032$) and glucose ($r = -2.95$; $P = 0.001$) but not with body mass index (BMI) [135]. Studies have also shown that vitamin D is more closely associated with glucose metabolism than obesity. Table 1 illustrates key correlations of vitamin D and diabetes.

Others have reported that daily supplementation of vitamin D and calcium over a 6 months, does not improve oral glucose tolerance-derived measures of insulin sensitivity, such as insulin secretion and β -cell function in adults with low vitamin D status at risk of type 2 diabetes [136]. However, same study reported that those with prediabetes, supplementation with vitamin D and calcium improve insulin sensitivity. A placebo control clinical study reported that a large doses of vitamin D₃ improves insulin sensitivity (based on HOMA-IR) and HbA1c in patients with T2D [137].

Vitamin D and calcium replacement in South Asian patients with T2D significantly decreased, both HbA1c and weight, which was attributed to the increased blood 25(OH)D levels [138]. In those with T2D who are calcium and vitamin D insufficient, vitamin D supplementation improved the glycemic status and lipid profiles [139]. Supplementation of vitamin D₃ and calcium was also reported to improve the body mass index and hip circumference, and systolic blood pressure in vitamin D insufficient people with T2D [140], but others have failed to conclude such [141].

Some who have re-analyzed the Women's Health Initiative study concluded that calcium plus vitamin D supplementation failed to reduce the risk of developing diabetes, and suggested that components of foods containing other nutrients may have confounded the results and higher doses of vitamin D may be required to affect diabetes risk [142]. Another groups reported that lower serum 25(OH)D levels per say did not associated with increased risk of developing T2D in the same cohort of postmenopausal women [143]. Nevertheless, using the same

Table 1

Relationships between vitamin D and diabetes.

(A) Scientific correlations between vitamin D and diabetes:

- Beta-cells contain vitamin D receptors
- 1,25(OH)₂D stimulates insulin release
- Insulin “release” is reduced in vitamin D-deficient animals (and in humans)
- 1,25(OH)₂D prevents development of diabetes in the NOD mouse
- Recent meta-analyses show association of low vitamin D status with increased risk of BOTH type 1 and type 2 diabetes

(B) Vitamin D and function of pancreatic β-cells:

- Association between vitamin D and physiological functions of pancreatic β-cells
- β-cells possess VDRs, and 1α-hydroxylase is expressed in pancreatic islet tissues
- Vitamin D deficiency impairs glucose-mediated insulin release
- Insulin secretion is calcium dependent and calcium homeostasis depends on vitamin D
- Vitamin D supplements improve insulin release in response to oral glucose load and reduce free fatty acid levels

(C) Vitamin D deficiency worsens diabetes:

- Diabetes is 5 times more common in non-equatorial areas
- Children getting 2000 IU of vitamin D are 8 times less likely to develop type 1 diabetes
- Sedentary and obese people get less sun exposure and thus have less vitamin D
- Worldwide, diabetes increases in parallel with vitamin D deficiency
- Elderly and those with dark skin get 3–6 times less vitamin D from the same amount of sun exposure

(D) Concerns related to clinical study data:

- Lack of adequately powered, randomized controlled, clinical studies
- Among the vitamin D intervention studies done, virtually none were designed for glycemic outcomes
- Measurements of minimum (or median) serum 25(OH)D levels achieved were not reported;
- Most did not report the use of diabetes (or even other) concomitant use of medications
- Some trials used too little doses of vitamin D (e.g., ≤800 IU) above to bring serum vitamin D levels beyond 30 ng/mL
- Others studies used too large, unphysiological and infrequent doses of vitamin D that will not maintain serum 25(OH)D concentrations throughout the study period
- Even the larger studies that are currently done are poorly designed to test vitamin D related hypotheses and hard endpoints
- Relative paucity of rigorous clinical data on the effects of vitamin D sufficiency on non-calcium endpoints.

cohort, other groups reported a favorable profiles [144], better health indices [145], and there is no adverse effects using the combination of calcium and vitamin D in postmenopausal women [146]. Calcium and/or vitamin D supplementation also shown to improve disease outcomes, particularly in those T1D-prone individuals that are calcium deficient [147].

2.2. T2D—data from longitudinal studies

Data from longitudinal, cohort studies demonstrated the relationships between the incidence of T2D and baseline serum 25(OH)D levels. For example, those with the highest serum 25(OH)D levels (e.g., above 30 ng/mL) had an approximate 20%–50% reduction in the risk of developing T2D [37,61,148]. Nevertheless, once a person developed T2D, vitamin D does not seem to make much difference to the course of the disease because other factors may override the benefits of vitamin D [33,149].

The mechanisms of vitamin D reducing the risk of T2D include, improved insulin sensitivity, reduced insulin resistance [16,17,92], and reduced inflammation that indirectly improves insulin resistance and pancreatic β-cell function [19,20,82,148] and survival. In addition, the mechanism of action of vitamin D may also mediate via the regulation of plasma ionized calcium levels,

which influence insulin synthesis and secretion [83,127,130–133], and thus have a direct beneficial effect on pancreatic β-cell functions [114,148].

The combined use of calcium and vitamin D supplements has also been shown to reduce the incidence of diabetes [150] (Fig. 3). In those who daily consume more than 800 IU of vitamin D and 1200 milligrams of calcium, risk for T2D was decrease by 33%, after controlled for age, BMI, hypertension, family history of diabetes, smoking physical activity, caffeine, alcohol, state of residence, type of fat (saturated, polyunsaturated, trans, etc.), cereal fiber, glycemic load, magnesium, and retinol [150].

2.3. Association of serum vitamin D levels and diabetes

Studies have consistently demonstrated that overweight children and adolescents have low serum 25(OH)D levels [118] that correlated with low adiponectin levels, obesity, and insulin resistance [151,152]. Similar data have been reported from many countries, including Malaysia, Spain, France, and Columbia, etc. [12,122,151–153]. A meta-analysis of observational studies confirms the association of low 25(OH)D with incidence of diabetes (OR, 0.82; 95% CI, 0.72–0.93) [122].

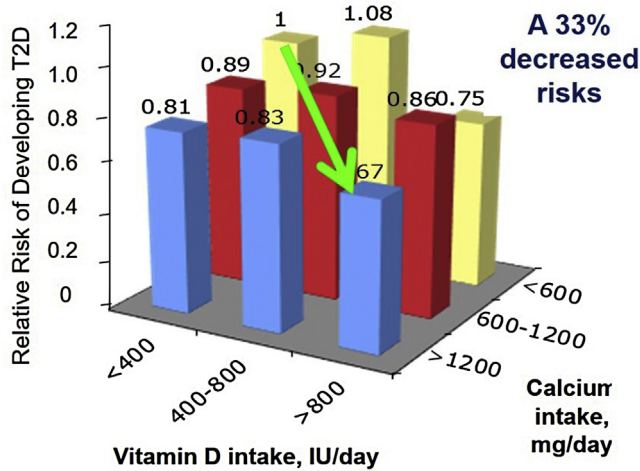


Fig. 3. Calcium and vitamin D adequacy, decreases the risks of diabetes. Relative risk for type 2 diabetes (T2D) based on total intake of vitamin D and calcium in the Nurses' Health Study. Women with vitamin D intake of 400 IU/day and total calcium intake of 600 mg/day served as the reference group. A 33% decrease in the incidence of diabetes was observed in those who consumed vitamin D together with a total calcium intake of 1.2 g of a day [data from Pittas et al., Diabetes Care, 2006, from Table 4 [150]].

Moreover, there is an inverse correlation between serum 25 (OH)D levels and cardiovascular diseases, metabolic syndrome, and their complications, such as glucose intolerance, hypertension, obesity, insulin resistance, ischemic heart disease, and stroke [15,154,155]. Indeed, analysis of the NHANES III database confirms a correlation of low serum 25(OH)D levels with increased obesity and metabolic syndrome [156–160]. Similar data have been

reported with other studies performed on different population [161].

Patients with metabolic syndrome have low serum 25(OH)D levels [162], and restoration of serum 25(OH)D levels improves insulin resistance [19,20,82]. Data suggest that in patients with T1D and T2D, hypovitaminosis D aggravates the macro-vascular complications, falls and osteoporotic fractures [1,84,113,148,163–167]. In addition, studies reported associations between the increased carotid intimal thickness and hypovitaminosis D [113,122]. Nevertheless, inconsistency of the calcium and other non-calcium endpoints vitamin D trials, as well as meta-analysis data are widespread [129,168,169].

Although there are no definitive RCTs, it is tempting to suggest that vitamin D supplementation could have a meaningful reduction of insulin resistance. Meanwhile, observational studies have reported decreased incidences of T1D after correction of vitamin D deficiency, with an overall incidence reduction of 25% [34,170]. Fig. 4 illustrates the relationship between vitamin D supplementation and T1D from several observational studies [171–175].

2.4. NHANES data on vitamin D and diabetes

The US population vitamin D status was reported by the National Health and Nutrition Examination Surveys (NHANES), a nationally representative, non-institutionalized sample [176,177]. The mean levels of 25(OH)D were highest in the youngest group (children 1–5 years old, mean 76.4 nmol/L) but decreased in each age category beyond that (6–11 years, 70 nmol/L; 12–19 years, 63.9 nmol/L; 20–49, 62 nmol/L; 50–60, 59.2 nmol/L; and 57.5 nmol/L in those who are over 70 years of age). Overall mean levels were slightly higher in men than women (62.9 nmol/L vs. 61.5 nmol/L);

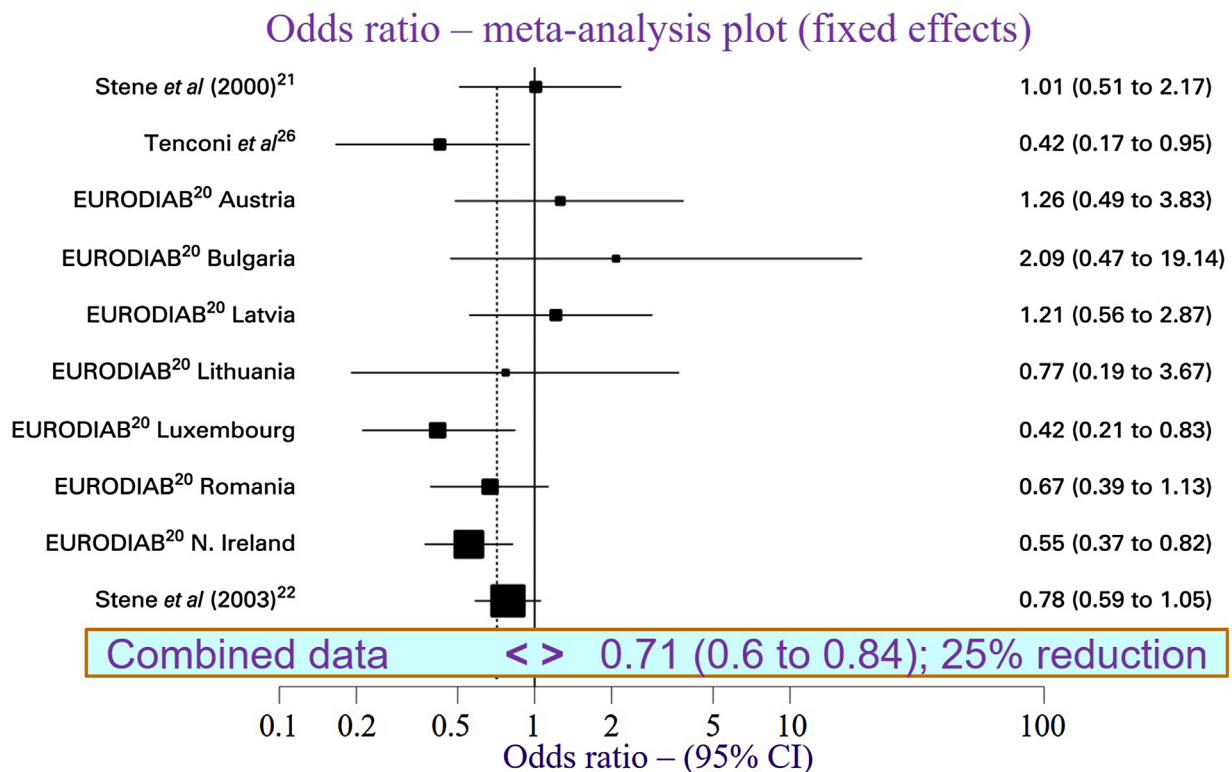


Fig. 4. Vitamin D supplementation reduces the incidence of Type 1 diabetes by 25%: Odds ratio—meta-analysis plot (fixed effects). Vitamin D supplementation and incidence of development of T1D. Odds ratios from several meta-analyses on decreasing the incidence of T1D in the presence of vitamin D supplementation [modified from Zipitis et al. [171] supported by other studies [172–175]].

however, as per the Endocrinology Society guidelines [27] indicate these levels are still suboptimal.

Not surprisingly, serum 25(OH)D levels were higher in blood samples taken during the summer, between the months of May and October, demonstrating the effects of being outdoors and exposure to UVB from the sunlight. Importantly, compared to the previous NHANES survey of 1988–1994, age-adjusted mean 25(OH)D levels were between 5 and 9 nmol/L lower in men. This can be explained in part by increased BMI and the widespread use of sun protection during this period.

A similar study, a nationally representative survey was conducted in Canada (Canadian Health Measures survey; n = 5306) conducted in individuals between 6 and 79 years of age, between 2007 and 2009 [178]. The mean concentration of 25(OH)D in this population was 67.7 nmol/L. Mean concentrations were lowest among men aged 20–39 years (60.7 nmol/L) and highest in men aged 6–11 years (76.8 nmol/L). An estimated 4.1% of the population had 25(OH)D levels less than 25 nmol/L, and 10% had levels less than 37.5 nmol/L [178]. Those who consumed milk frequently (vitamin D-fortified milk products are available in North America) and those with white ethnicity had higher blood concentrations of 25(OH)D [178].

Over a period of 10 years, data from the Canadian Multi-Centre Osteoporosis study (women, n = 1896 and men n = 829) showed serum 25(OH)D increased by 9.3 nmol/L in women and by 3.5 nmol/L in men. This was explained by the practice of increased use of supplements and food fortification. At baseline, 29.7% of participants had 25(OH)D levels less than 50 nmol/L; at the 10-year follow-up, the figure was 19.8% [179].

2.5. Vitamin D and obesity

Vitamin D receptor (VDR) is highly expressed in adiposities and is responsive to the fat soluble, 1,25(OH)₂D [180,181]. Increased body fat and higher BMI are inversely and strongly correlated with serum 25(OH)D levels [165,182,183]. Diabetes is a dual effect disease; precipitated in those with underlying genetic/epigenetics preponderance, in the presence of adverse environmental conditions (Fig. 5). A number of conceivable mechanisms including genetics, epigenetics and environmental have been proposed to explain these links between having sustained low serum 25(OH)D

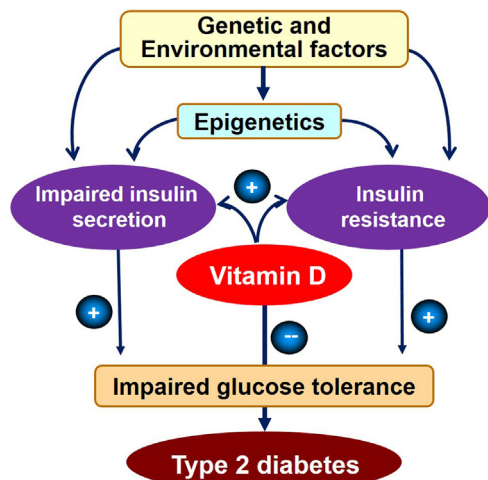


Fig. 5. Diabetes is a dual effect disease; hypovitaminosis D worsens it. Integrations and relationships between vitamin D and common metabolic disorders. Hypovitaminosis D influences the development and worsening of diabetes; hyperglycemia, hyperlipidemia, insulin resistance, hypertension, metabolic syndrome, obesity, as well as rickets, osteomalacia and osteoporosis.

levels with the pathophysiology of obesity, diabetes mellitus, and the metabolic syndrome [184,185]

Body fat is known to act as a storage for vitamin D in the body. While, obesity contributes to vitamin D deficiency, the latter contributes to gaining weight. Adiposity and the degree of skin pigmentation are associated with lower circulatory 25(OH)D concentrations than normal-weight and those with lighter skin [186]. As the skin pigmentation is non-modifiable, health education should be targeted in weight management, appropriate doses of micronutrient supplanting, age-appropriate physical activities, and gender based behaviors on safe sun exposure. Irrespective of the skin color and reporting a higher dietary vitamin D intake, half of the pregnant obese women are known to have suboptimal vitamin D status, compared to normal-weight women [187,188].

Since vitamin D metabolites are lipid soluble, the excess circulatory 25(OH)D is attracted to adipose tissue. Because of sequestration of 25(OH)D and its conversion to inactive metabolites, attributes at least in part, the exaggerated manifestation of hypovitaminosis in persons with obesity [189]. Therefore, for those with excess body fat, it is necessary to administer a higher doses of oral vitamin D supplements and/or longer sun exposure (i.e., body size and the adiposity should be considered when determining the dietary requirements for vitamin D in the obese [188–190].

2.6. Vitamin D status and bariatric surgery

Vitamin D deficiency is prevalent among patients with obesity and those presenting for bariatric surgery. These items need careful attention during the evaluation of patients before (and after) bariatric surgery, and provide them with adequate vitamin D and other micronutrient supplementation [191,192]. Most persons presenting for bariatric surgery have suboptimal vitamin D levels; African Americans and those with higher BMIs at the greatest risk for hypovitaminosis as well as surgery associated complications [193].

Nevertheless, the reverse is puzzling. For examples, in spite of this relatively large reservoir of vitamin D in persons with obese, following bariatric surgery it is quite common for people to develop significant hypovitaminosis D following bariatric surgery [194,195]. However, others reported no significant difference in 25(OH)D levels between obese patients before bariatric surgery and obese patients with no obesity surgery [196]. Authors concluded that the obesity itself is the link with vitamin D deficiency, independently from behavioral differences.

Considering the aforementioned, it is important to properly evaluate all bariatric patients coming for surgery prior to admitting them into a surgical program. Significant deficiencies of both fat- and water-soluble vitamins occur after malabsorptive bariatric surgery (decreased calorie absorption secondary to fat malabsorption) [194]. Patients who have undergone malabsorptive surgery are also at risk of late metabolic complications and thus, should be closely monitored, indefinitely. This is particularly important for those candidates conceding for malabsorptive gastrointestinal surgical procedures, such as duodenal switch and Roux-en-Y gastric bypass surgery [197]. The long-term nutritional monitoring is essential after any malabsorptive operations, especially for those with obesity.

3. Hypovitaminosis D and pathogenesis of diabetes

Many cellular, preclinical, and observational studies support a role for vitamin D in the pathogenesis of T1D and T2D [83,130–133,198]. Vice versa, persons with both type of diabetes has higher incidences of hypovitaminosis D. VDR and vitamin D-binding protein are abundantly expressed in β -cells in the pancreas and in

the immune system. Thus, it is not surprising to see pancreatic stimulation of insulin production in response to vitamin D. This could be another mechanism in preventing T2D and retard the conversion of those with prediabetes to diabetes, through its ability to decrease insulin resistance, insulin synthesis and secretion [199], and reduction of inflammation [16,17,107,108].

Vitamin D supplementation has been shown to increase insulin sensitivity and insulin release, as well as decrease inflammation in patients with T2D [92,170,200]. Moreover, lower the serum 25(OH)D level, higher the incidence of prediabetes among the normal, ambulatory, non-diabetic population [37,201] and higher the potential conversion of prediabetes to diabetes States [201]. Fig. 6 illustrates a statistically significant, 70% conversion rate from prediabetes to diabetes in those with hypovitaminosis D.

Vitamin D deficiency also affects other comorbidities related to insulin resistance. For example, in women with polycystic ovarian and metabolic syndrome, the incidence of vitamin D deficiency is three times greater than in women without those conditions [202]. Other epidemiological studies have suggested a link between vitamin D deficiency in early life and the late onset of T1D [120,203], perhaps related to the increased vulnerability for autoimmune diseases.

Low 25(OH)D levels may identify people at risk of T2D [9] and is a surrogate marker for having pathogenic visceral obesity, diabetes and metabolic syndrome [9]. One study showed that increasing the serum 25(OH)D levels from 25 to 75 nmol/L (from 10 to 30 ng/mL) led to a 60% improvement in insulin sensitivity. This improvement is greater than that generally achievable with any anti-diabetic medication, but this benefit occurs without adverse effects. Meanwhile, the relationship between vitamin D deficiency and other autoimmune diseases, such as rheumatoid arthritis is being explored [204–206].

4. Discussion

When a population is getting older, the prevalence of age-associated conditions, including cancer, T2D, and obesity, also increase; thus, populations with the largest numbers of older people will have the highest risks of these disorders. Nevertheless, micronutrient deficiencies such as vitamin D deficiency and associated illnesses can be decreased by correction of nutritional

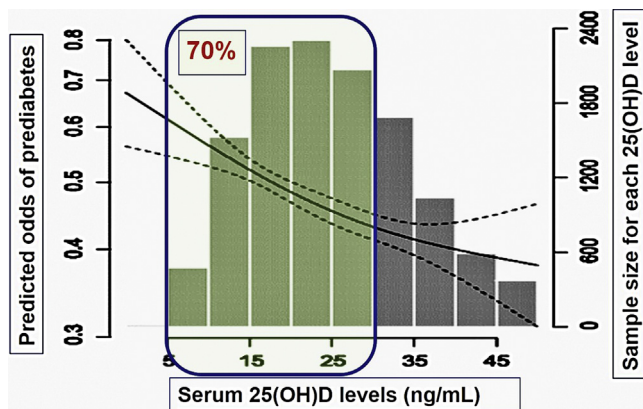


Fig. 6. Otherwise healthy people with low serum 25(OH)D have a higher prevalence of prediabetes.

Illustrate a multivariable adjusted odds of prediabetes, according to their serum 25(OH)D levels (ng/mL). Data of predicted odds of having prediabetes (solid line) is shown with 95% CI (dashed lines) using nonparametric logistic regression estimates. Adjusted logistic regression demonstrated a statistically significant inverse relationship between serum 25(OH)D levels and odds of sustaining prediabetes. Seventy percent of the occurrences of prediabetes were among those with serum vitamin D levels of less than 30 ng/mL [adapted from Shankar et al. [201]].

deficiencies cost-effectively. The latter include, the use of population-based supplementation and/or fortification of staple food, and lifestyle changes (e.g., increasing physical activities, consume less calorie-dense food, increased exposure to sunlight, and so forth).

Worldwide, malabsorption related disorders (e.g., secondary to medications, celiac disease, short bowel syndrome, Crohn's disease, Whipple's disease, etc.) are an important group of problems, that lead to the development of vitamin D deficiency. Because of the inability of activations steps from vitamin D to its active hormonal form 1,25(OH)₂D, hepatic and renal diseases directly disrupt the functions of vitamin D. Similarly, those who are taking long term supplements or medications (those that increase hepatic cytochrome P450 activation) reducing fat absorption or enhance catabolism of vitamin D, also leads to symptomatology associated with vitamin D inadequacy.

Low serum 25(OH)D concentrations are inversely associated with insulin resistance and metabolic syndrome, especially in those who are overweight and obese. They also are significantly associated with the development of T1D and T2D, insulin resistance, and worsening of existing metabolic syndrome. Moreover, having low vitamin D increased the risk for developing T2D and prediabetes, and markedly increases the rate of conversion from prediabetes to diabetes. Fig. 7 illustrates the tirade of negativity, demonstrating the plausible links between hypovitaminosis D with common metabolic disorders as well as musculoskeletal disorders that affecting approximately 3 billion people in the world.

As illustrated in Fig. 7, impaired insulin secretion and insulin resistance are common occurrence in patients with vitamin D deficiency. Although, vitamin D adequacy decreases the incidence and severity of T2D, insulin resistance, and metabolic syndrome, no firm conclusions can be drawn yet from the published observations and small RCT studies, because these studies were underpowered and poorly designed; only a few were specifically designed for glycemic outcomes; others were conducted for too short durations; most did not report the use of diabetes medications at baseline or during the study; and in some trials, investigators used too large but infrequently administered doses of vitamin D that are highly inefficient, compared with daily, weekly, or monthly doses of vitamin D (Table 1).

There is a paucity of RCTs and well-designed intervention studies to confirm the improvement of T2D and metabolic syndrome, following the increase of serum 25(OH)D above a predetermined level. Therefore, specifically designed, large-scale RCTs are needed in well-defined populations (those with early diabetes or prediabetes with documented hypovitaminosis) to test the hypothesis that low vitamin D levels directly contribute to the

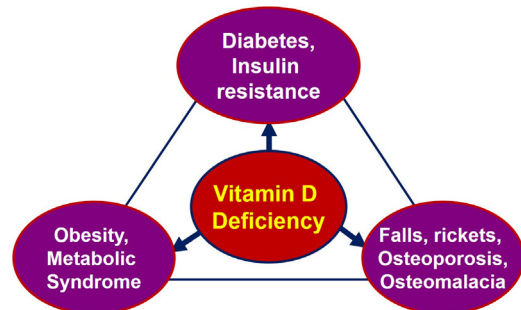


Fig. 7. Vitamin D deficiency is related to a number of important health conditions. "Tirade" of negativity. Figure illustration the links between hypovitaminosis D with common metabolic disorders (e.g., diabetes, insulin resistance, metabolic syndrome, obesity, etc.) as well as with increased risks of falls and musculoskeletal disorders.

pathogenesis of diabetes, insulin resistance, metabolic syndrome, and obesity, and that correction of such would be beneficial.

5. Conclusions

Recent studies indicate that vitamin D₃ is significantly more efficacious than is vitamin D₂ not only in increasing serum 25(OH)D concentrations, but also for maintaining serum vitamin D levels and its biological activities [207,208]. Thus, vitamin D₃ is the preferred choice for correcting vitamin D deficiency and maintenance with oral supplements. The majority of current evidence supports the hypothesis that adequate blood levels of vitamin D [i.e., above 30 ng/mL (>75 nmol/L)] improve the metabolic aspects of insulin sensitivity, diabetes, metabolic syndrome, and obesity [81,92].

The 1997 Dietary Reference Intake (DRI) values for vitamin D, initially established to prevent rickets and osteomalacia [209–211], are now considered too low by most clinical experts [212]. Studies suggest the intake of more vitamin D than currently suggested by the 2011 Institute of Medicine report is necessary to prevent most chronic diseases associated with low vitamin D levels. Food fortification programs are another logical approach to solve the global epidemic of vitamin D deficiency. Nevertheless, the amount of vitamin D (as well as several other micronutrients) added to staple food such as milk is inadequate, and can be safely double in most of the developing countries and emerging economies [192,213].

In the absence of adequate exposure to sunlight, oral intake of vitamin D (food plus supplements) doses between 1000 and 4000 IU per day together with maintaining the serum 25(OH)D levels above 30 mg/mL (75 nmol/L) over a longer period is necessary to have a meaningful impact in reduction of the incidence of the aforementioned metabolic disorders. Nevertheless, sensible exposure to sunlight is the best, cheapest and the safest way to obtain vitamin D, but for many, supplementation is the way forward [214].

Emerging research supports the conceivable role of vitamin D in protecting against many common diseases and disorders, such as cancer, heart disease, autoimmune diseases, musculoskeletal disorders, fractures, infections, and depression, diabetes, and insulin resistance. Consequently, many pro-active healthcare providers are using higher doses of supplementary vitamin D₃, to minimize aforementioned diseases in their patients [215]. The doses of vitamin D (not its analogies) that they generally prescribe are between 1000 and 5000 IU/day or 50,000 IU twice a month, which allow most of their patients to maintain serum 25(OH)D levels above 30 ng/mL (75 nmol/L).

Conflicts of interest

The author received no funds for this work and has no conflicts of interest.

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