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REVIEW

Conundrum of vitamin D on glucose and fuel homeostasis

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Abstract

As an endocrine hormone, vitamin D plays an important role in bone health and calcium homeostasis. Over the past two decades, the non-calcemic effects of vitamin D were extensively examined. Although the effect of vitamin D on beta cell function were known for some time, the effect of vitamin D on glucose and fuel homeostasis has attracted new interest among researchers. Yet, to date, studies remain inconclusive and controversial, in part, due to a lack of understanding of the threshold effects of vitamin D. In this review, a critical examination of interventional trials of vitamin D in prevention of diabetes is provided. Like use of vitamin D for bone loss, the benefits of vitamin D supplementation in diabetes prevention were observed in vitamin D-deficient subjects with serum 25-hydroxyvitamin D < 50 nmol/L (20 ng/mL). The beneficial effect from vitamin D supplementation was not apparent in subjects with serum 25-hydroxyvitamin D > 75 nmol/L (30 ng/mL). Furthermore, no benefit was noted in subjects that achieved serum 25-hydroxyvitamin D > 100 nmol/L (40 ng/mL). Further studies are required to confirm these observations.

Key Words: Vitamin D; Glucose metabolism; Diabetes mellitus; Insulin sensitivity; Beta

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cell function

Core Tip: Vitamin D deficiency is a well-recognized health issue and contributes to bone loss and calcium dysregulation. Evidence suggests that excess vitamin D is not in and of itself of therapeutic benefit. Available clinical data suggests that vitamin D supplementation appears to limit the development of diabetes in vitamin D deficient subjects. However, no benefit was observed in non-vitamin D deficient subjects. Furthermore, overreplacement of vitamin D is of no beneficial effect and could possibly be harmful.

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INTRODUCTION

The potential role of vitamin D deficiency induced by migration of human beings has been suggested to be involved in human evolution and various modern health conditions[1]. The history prospective of vitamin D evaluation will enhance our understanding of the development in this field. The role of dietary deficiency in the pathogenesis of rickets was established by Platt[2] in 1919. Although it was thought to be caused by vitamin A deficiency initially, McCollum *et al*[3] identified a vitamin deficiency other than vitamin A that caused rickets in 1922. Since vitamin A, B, and C were already identified, the new molecule was named as vitamin D[4].

Beginning with its discovery in 1922, scientific publications focusing upon vitamin D numbered no more than some 10 per year but this increased to 35 per year by 1945 (Figure 1). As knowledge of the structure, molecular biology and function of vitamin D increased[5,6], there was a concurrent increase in vitamin D-specific publications. With the observations of the non-calcemic effects of vitamin D[7], vitamin D-focused publications peaked at 5152 in 2017. Recently, the role of vitamin D deficiency in relation to coronavirus disease 2019 (COVID-19) infection attracted attention[8].

Vitamin D on bone health

The role of vitamin D on calcium and bone metabolism was well-summarized[9]. There is no doubt about the association between rickets and vitamin D deficiency and the reversal and prevention of rickets with vitamin D supplementation. However, controversy still surrounds the efficacy of vitamin D supplementation upon bone mineral density and fracture prevention. Multiple studies failed to demonstrate any benefit from vitamin D supplementation[10-12] and a systematic review and meta-analysis also failed to confirm any beneficial effect on bone density or fracture prevention from vitamin D supplement[13]. Nevertheless, placebo-control randomized clinical trials revealed a threshold effect of vitamin D[14,15] with no benefit observed on the subjects with baseline 25-hydroxyvitamin D level ≥ 75 nmol/L (30 ng/mL). Furthermore, possible detrimental effects on bone mineral density were observed in subjects who received a higher dose of vitamin D (250 μg or 10000 IU daily) with a mean 25-hydroxyvitamin D of 200 nmol/L or 80 ng/mL[12]. While not conclusive, these data suggest that the optimal effects of vitamin D are found at a 25-hydroxyvitamin D level of 75 nmol/L (30 ng/mL).

Vitamin D as a hormone

Vitamins are defined as micronutrients that cannot be self-synthesized and that necessary for the proper function of key enzymatic processes. Consequently, vitamins must be obtained through the diet. Vitamin D is synthesized from cholesterol to 7-dehydrocholesterol, also known as pro-vitamin D_3, in the skin through the action of ultraviolet radiation[16]. In addition, the liver forms 25-hydroxyvitamin D_3, also

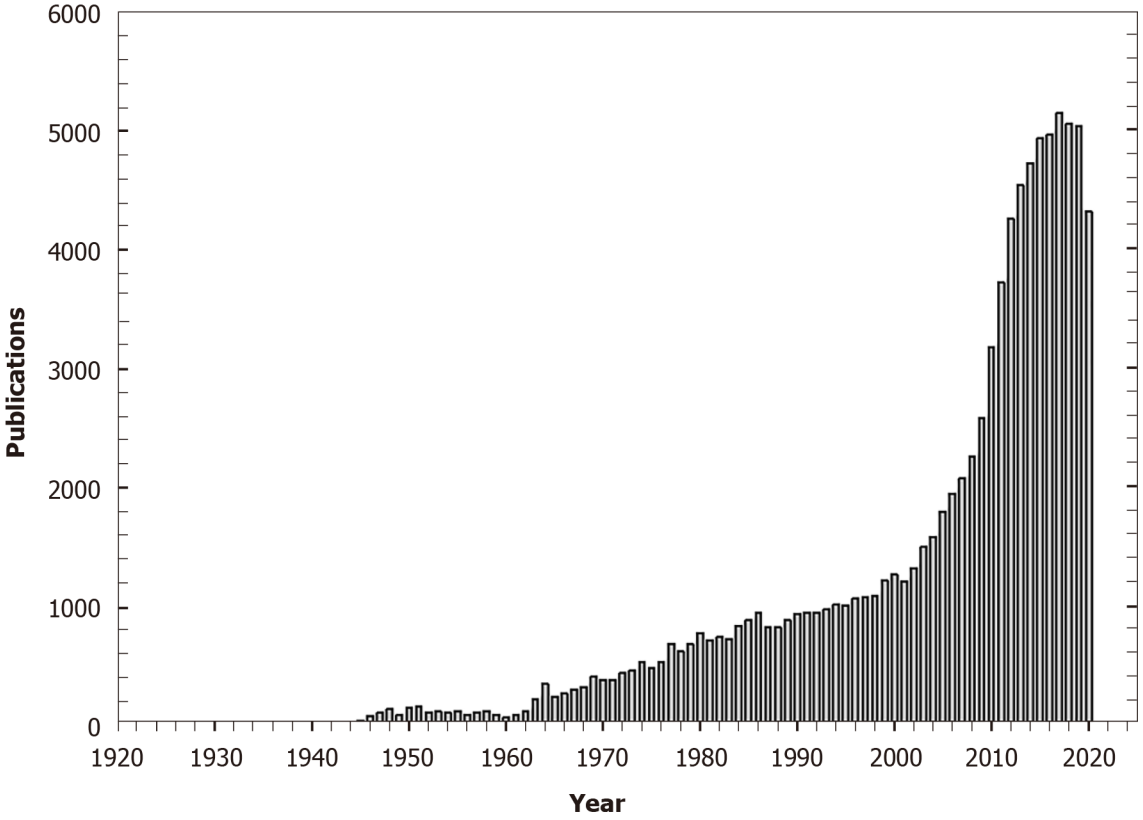

Figure 1 Vitamin D publications from 1922 to 2020. Data were obtained from PubMed (https://pubmed.ncbi.nlm.nih.gov/) accessed on October 20, 2020.

known as pre-vitamin D_3. To become an active compound, further hydroxylation in the kidney is required to form 1,25-dihydroxyvitaomin D_3, which is a biologically active vitamin D. Then, 1,25-dihydroxyvitamin D is released into circulation to exert its effects on the target cells and promote calcium and bone homeostasis. Thus, vitamin D is a hormone and, like the pituitary-thyroid axis, has a complex natural history in the body (Table 1).

The half-life of thyroid hormone depends upon thyroid status[17]. The half-life for levothyroxine (T4) is 6-7 d in euthyroid subjects, 9-10 d in subjects with hypothyroidism, and 3-4 d in subjects with hyperthyroidism. The half-life of liothyronine (T3) is 18-24 h in euthyroid subjects, 12-16 h in hyperthyroid subjects, and 26-32 h in hypothyroid subjects. The half-life of vitamin D averages 15 h but depends upon of the type of vitamin D (cholecalciferol or vitamin D_3 *vs* ergocalciferol or vitamin D_2) and vitamin D binding protein concentration[18]. The half-life of 1,25-dihydroxyvitamin D is 10-20 h[19], while there is no information regarding the half-life of 1,25-dihydroxyvitamin D_3 *vs* D_2. Since 1,25-dihydroxyvitamin D is released into the blood and exerts its effects upon osteocytes to promote mineralization and on the gastrointestinal epithelium to increase calcium and phosphorus absorption, it is appropriate to classify vitamin D as a hormone.

EVIDENCE OF NON-CALCEMIC EFFECTS

In addition to the target organs, both the vitamin D receptor and 1alpha-hydroxylase (CYP27B1) are expressed in various other tissues[20], suggesting additional functions of vitamin D beyond bone metabolism and calcium homeostasis. Interestingly, the vitamin D receptor is expressed in the pancreatic islets[21], liver[22], muscle[23], and adipose tissue[24]. 1alpha-hydroxylase (CYP27B1) is expressed in pancreatic islets[25], liver[26], muscle[27], and adipose tissue[28]. Thus, it is possible that vitamin D could take part in glucose and fuel homeostasis.

In contrast to calcemic effects of vitamin D which is primary mediated by circulating 1,25-dihydroxyvitamin D produced in the kidney, the non-calcemic effects of vitamin D are mediated by circulating 25-hydroxyvitamin D through a paracrine or autocrine function[29]. Within the target cells or its vicinity, circulatory 25-hydroxyvitamin D

Table 1 Vitamin D as a hormone: Comparison of the pituitary-thyroid and parathyroid hormone-vitamin D axes

	Pituitary-thyroid axis	Parathyroid-vitamin D axis
Organ(s)	Thyroid glands	Skin/liver/kidney
Source compound	Iodine, tyrosine	Cholecalciferol (cholesterol), ergocalciferol
Prehormone	Levothyroxine, $T_{1/2}$ = 6-7 d	25-hydoxyvitamin D_2/D_3, $T_{1/2}$ = 13-17 d
Active hormone	Triiodothyronine, $T_{1/2}$ = 14-24 h	1,25-dihydroxyvitamin D_2/D_3, $T_{1/2}$ = 10-20 h
Transportation	Thyroxine binding globulin	Vitamin D binding protein
Receptor	Thyroid hormone receptor	Vitamin D receptor
Stimulating factor	Thyroid stimulating hormone	Parathyroid hormone
Effect	Energy homeostasis	Calcium homeostasis

enters cells and is converted to 1,25-dihydroxyvitamin D by the locally existing 1alpha-hydroxylase (CYP27B1). Hence, 25-hydroxyvitamin D is the key circulatory element for the non-calcemic effects of vitamin D whereas 1,25-dihydroxyvitamin D the promotes the calcemic effects.

EFFECTS UPON CELL DIFFERENTIATION AND CELL PROLIFERATION

Colon, prostate, breast, and ovarian cancer

A role for vitamin D in the pathogenesis of cancer was proposed in 1980[30] after it was observed that colon cancer rates were higher in the northern rather than the southern United States. The association of vitamin D deficiency with cancer, including breast[31], prostate[32], and colon cancer[33] was attributed to the ability of vitamin D to differentiation cells[34] and to suppress cell proliferative[35] along with other effects [36,37].

Immunity, autoimmunity, and inflammation

The risk of type 1 diabetes was reduced by vitamin D supplement in a birth-cohort study from Finland[38]. Furthermore, a polymorphism in the vitamin D receptor was associated with increased risk of type 1 diabetes[39]. Not unexpectedly, a role of vitamin D deficiency in the pathogenesis of type 1 diabetes was proposed[40]. In addition, the association of vitamin D deficiency with multiple sclerosis[41], systemic lupus erythematosus[42], and other autoimmune diseases[43] was attributed to the immunomodulatory and anti-inflammatory effects of vitamin D[44]. Furthermore, vitamin D plays an important role in the maintenance of B cell homeostasis[45], and vitamin D replacement may reduce B cell-mediated autoimmune disorders.

The role of vitamin D in the treatment of tuberculosis was appreciated with the observation that sun exposure altered the clinical presentation of tuberculosis[46]. Subsequently, vitamin D was administered as part of the treatment of tuberculosis [47]. Vitamin D deficiency was frequently observed in patient with untreated tuberculosis[48]. It is now known that Toll-like receptors up-regulate expression of the vitamin D receptor and the vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin and killing of intracellular Mycobacterium tuberculosis[49]. Thus, the role of vitamin D in fighting infection is established[50]. Further, vitamin D deficiency is associated with acute respiratory tract infection[51], bacterial vaginosis[52], pneumonia[53], foot infection in diabetics[54], chronic hepatitis C infection[55], and human immunodeficiency virus infection[56]. Recently, vitamin D deficiency was recognized as a risk factors for COVID-19 infection[57-61]. Thus, vitamin D could play a role in fighting infection.

An association between vitamin D receptor polymorphism and the severity of coronary artery disease was reported[62]. Deficiency was also noted to associate with an increased risk of myocardial infraction[63], hypertension[64], and stroke[65]. The mechanism proposed to account for these associations included activation of the renin-angiotensin system[66], coronary calcification[67], platelet activation and aggregation [68], increased proinflammatory cytokines[69], and vascular endothelial dysfunction [65].

Fuel metabolism

In patients with vitamin D deficiency and diabetes, vitamin D supplementation improved beta cell function and glucose tolerance[70]. An association between vitamin D deficiency and glucose intolerance and beta cell dysfunction was observed in east London Asians[71]. Similarly, alternations in vitamin D metabolism in obese subjects manifesting as low 25-hydroxyvitaimin D is well-recognized[72]. This topic will be reviewed in this article.

Neuropsychiatric disorders

Vitamin D deficiency was reported to be associated with depression[73], schizophrenia [74], autism[75], and Parkinson's disease[76]. Various mechanisms have been reported to support a role of vitamin D in neuropsychiatric disorders. Vitamin D has a protective effect on dopaminergic neurons[77]. Vitamin D deficiency could result in altered synaptic plasticity through its effect on perineuronal nets leading to cognitive deficits[78]. Vitamin D deficiency alters brain protein expression in rats[79]. Furthermore, immunohistochemical study revealed the expression of vitamin D receptor and 1alpha-hydroxylase (CYP27B1) in various regions of human brain with the strong expression in the hypothalamus and in the large (presumably dopaminergic) neurons within the substantia nigra[80]. Thus, vitamin D deficiency could play a role in the pathogenesis of various neuropsychiatric disorders.

VITAMIN D REPLACEMENT THERAPY

Source of vitamin D

Vitamin D is available in two forms: ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Ergocalciferol comes from plants in the form of ergosterol (provitamin D_2). Ergosterol is an important component of mushrooms. Through ultraviolet b (UVB) irradiation, which can occur within mushroom or artificially, it becomes ergocalciferol [81]. Cholecalciferol comes from animals and people through the biosynthesis of cholesterol to 7-dehydrocholesterol (Provitamin D_3). Again, through UVB irradiation, this intermediate becomes cholecalciferol. Thus, dietary intake and sun exposure are the major determinants of serum 25-hydroxyvitamin D levels.

Sun, mainly UVB irradiation, plays an important role in biosynthesis of vitamin D. Since 7-dehydrocholesterol can be synthesized from cholesterol, theoretically vitamin D supplementation is not required once sun exposure is adequate. Skin color is a key determinant of vitamin D synthesis[82]. Vitamin D has been proposed to play a role in human evolution and migration away from equator by affecting skin color through the development of depigmented and tannable skin *via* genetic pathways under positive selection[1,83]. Sun exposure is highly effective in raising serum 25-hydroxyvitamin D concentration, while its effects diminish significantly on donning clothing and using sun screen[84]. In this regard, more body surface area exposure is more effective than longer exposure time[85]. However, the efficacy of sun exposure to increase serum 25-hydroxyvotamin D concentrations diminishes with the degree of skin tanning[86]. Thus, minimized sun exposure time for 5 min to 30 min (depending on time of day, season, latitude, and skin pigmentation) with maximize body surface exposure is recommended[9]. However, increased risk of sun-mediated skin cancer makes this approach to prevent vitamin D deficiency less optimum[87].

Vitamin D can be obtained through dietary intake. However, except for cod liver oil, vitamin D content in naturally occurring food is relatively low, even in mushrooms (Table 2). Although ergosterol is highly abundant in the membrane of mushrooms, mushroom are cultivated under shadow without UVB irradiation[81]. Thus, dietary intake of vitamin D is inadequate and vitamin D supplement is often needed to avoid deficiency.

Comparison of metabolism of vitamin D_2 vs vitamin D_3

It is estimated that 65% of vitamin D is present as vitamin D while 35% is in the form of 25-hydroxyvitaomn D. As well, almost 75% of vitamin D is in adipose tissue, while 25-hydroxyvitamin D is distributed 20% in muscle, 30% in serum, 35% in fat, and 15% in other tissues[88]. The metabolism of vitamin D_3 and vitamin D_2 is summarized in Table 3. Vitamin D binding protein transports the various forms of vitamin D in circulation, including vitamin D, 25-hydroxyvtamin D, and 1,25-dihydroxyvitamin D [89]. Each vitamin D binding protein molecule has one binding site for vitamin D and/or its metabolites. The relative affinity of vitamin D binding protein to vitamin D_3

Table 2 Vitamin D content of selected foods

Food	Per serving		Percent DV
	IU	μg	
Cod liver oil, 1 tablespoon	1360	34.00	170
Trout (rainbow), farmed, cooked, 3 ounces	645	16.13	81
Salmon (sockeye), cooked, 3 ounces	570	14.25	71
Mushrooms, white, raw, sliced, exposed to UV light, 1/2 cup	366	9.15	46
Milk, 2% milkfat, vitamin D fortified, 1 cup	120	3.00	15
Soy, almond, and oat milks, vitamin D fortified, various brands, 1 cup	100-144	2.50-3.60	13-18
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 1 serving	80	2.00	10
Sardines (Atlantic), canned in oil, drained, 2 sardines	46	1.15	6
Egg, 1 large, scrambled (Vitamin D is in the yolk)	44	1.10	6
Liver, beef, braised, 3 ounces	42	1.05	5
Tuna fish (light), canned in water, drained, 3 ounces	40	1.00	5
Cheese, cheddar, 1 ounce	12	0.30	2
Mushrooms, portabella, raw, diced, ½ cup	4	0.10	1
Chicken breast, roasted, 3 ounces	4	0.10	1
Beef, ground, 90% lean, broiled, 3 ounces	1.7	0.04	0

Adapted from: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/#en25. The Food and Drug Administration developed daily values (DVs) to help consumers compare the nutrient contents of foods and dietary supplements within the context of a total diet. The DV for vitamin D on the new Nutrition Facts and Supplement Facts labels used for the values in Table 2 is 20 μg (800 IU) for adults and children aged 4 years and older. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet. DV: Daily value.

Table 3 Comparison of transportation and metabolism of vitamin D_3 *vs* D_2

Ref.	Symbol	Name (chromosome location)	Function	D3/D2
Haddad *et al*[90], 1993	VBP	Vitamin D binding protein (4q12-q13)	Vitamin D transportation	1.14
Holmberg *et al*[91], 1986	*CYP2R1*	25-hydroxylase (11p15.2)	Conversion of vitamin D to 25-hydroxy vitamin D	5.0
Zarei *et al*[93], 2016	*CYP27B1*	1alpha-hydroxylase (12q13.1-q13.3)	Conversion of 25(OH)D to 1,25(OH)2D	2.4
Jones *et al*[94], 1980	VDR	Vitamin D receptor (7q36)	Receptor for vitamin D	1.3

is 1.14 times stronger than to vitamin D_2[90]. 25-hydroxylase (CYP2R1) catalyzes 25-hydroxylation of vitamin D_3 5 times more efficiently than vitamin D_2[91]. Thus, after administration of a single oral dose of vitamin D_3 and vitamin D_2, a more sustainable and prolonged increase in serum 25-hydroxybitamin D_3 concentration is observed compared to serum 25-hydroxybitamin D_2 concentration[92]. 1alpha-hydroxylase (CYP27B1) coverts 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 2.4-time more efficiently than 25-hydroxyvitamin D_2[93]. In receptor binding assays, 1,25-dihydroxyviramin D_3 has 1.3 times more receptor affinity than 1,25-dihdroxyvitamin D_3[94]. These data indicate that vitamin D_3 is more biologically potent than vitamin D_2.

Comparison of biological potency of vitamin D_2 vs vitamin D_3

Vitamin D_2 and vitamin D_3 were reported to have similar efficacy in raising serum 25-hydroxyviramin D concentration[95]. However, other studies demonstrated that vitamin D_3 was more efficacious at raising serum 25(OH)D concentrations than vitamin D_2[96-100]. This finding was confirmed by a meta-analysis of the randomized

control trials[101]. Furthermore, 25-hydroxyvitamin D_3 has a longer half-life compared to 25-hydroxyvitamin D_2 (15.1 ± 3.1 d *vs* 13.9 ± 2.6 d, P = 0.001, mean ± STD)[18]. In comparison to oral vitamin D_2, oral vitamin D_3 achieves a higher serum concentration of 1,25-dihydroxyvitamin D[100,102] and a more effective suppression of serum parathyroid hormone concentration[97]. Physicians preferring use of vitamin D_2 should be aware of its markedly lower potency and shorter duration of action when compared to vitamin D_3. Thus, vitamin D_3 is the preferred form of vitamin D for replacement therapy.

OPTIMAL SERUM 25-HYDROXYVITAMIN D CONCENTRATION

Minimal serum 25-hydroxyvitamin D concentration

The primary function of vitamin D is to maintain calcium homeostasis. The minimal serum 25-hydroxyvitamin D concentration for health was defined based on the serum parathyroid hormone response to replacement therapy with ergocalciferol[103]. A serum 25-hydroxyvitamin D concentration of 50 nmol/L (20 ng/mL) was recommended since no further changes in serum parathyroid hormone levels were found in subjects with a serum 25-hydroxyvitamin D level of 50 nmol/L (≥ 20 ng/mL). In 2010, the United Sates Institute of Medicine adapted this value as a target for ensuring good bone health[104]. However, based on a larger observational study with 1569 subjects in France, serum parathyroid hormone concentration were noted to still decrease when the serum 25-hydroxyvitamin D rose to 78 mmol/L (31 ng/mL)[105]. Furthermore, a serum 25-hydroxyvitamin level of 75 nmol/L (30 ng/mL) is a recognized threshold for intestinal calcium absorption[106]. As shown in Table 4, many professional organizations and agencies have since adapted 75 nmol/L (30 ng/mL) as the minimal acceptable serum 25-hydroxyvitamin D concentration recognizing this may have beneficial effects beyond bone health, targeting beyond bone health while the Institute of Medicine define the minimal 25-hydroxyvitamin D concentration 50 nmol/L (20 ng/mL) on bone health with a public health interest.

Maximal serum 25-hydroxyvitamin D concentration

The maximal allowed serum 25-hydroxyvitamin D concentration is defined by the appearance of adverse effects. Although the Institute of Medicine dose not define maximal serum 25-hydroxyvitamin D concentration[104], a warning against elevated serum 25-hydroxyvitamin D concentrations is stated. This warning is based upon the observed association of increasing mortality with serum 25-hydroxyvitamin D concentration > 125 nmol/L (50 ng/mL)[107] by limiting the maximal daily vitamin D allowance (Table 4). This notion was further supported by the finding of increased cardiovascular mortality with serum 25-hydroxyvitaminD > 125 nmol/L (50 ng/mL)[108]. In addition, a progressive decline in bone mineral density with serum 25-hydroxyvitamin D greater than 125 nmol/L (50 ng/mL) was observed in a United States population[109]. Conversely, bone mineral density improved after discontinuation of vitamin D supplementation in patients with a serum 25-hydroxyvitamin D concentration greater than 50 ng/mL[110]. Although vitamin D supplementation increased calcium absorption without a threshold effect[111], reanalysis of the data revealed a diminished response (per 1000 IU of vitamin D in Table 5) with increasing dose of vitamin D supplement suggesting a threshold effect of vitamin D on calcium absorption[112], something noted by others[106]. We reported lack of improvement in insulin sensitivity in individuals with a serum 25-hydroxyvitamin D concentration > 125 nmol/L (50 ng/mL)[113]. Although hypercalcemia from vitamin D intoxication occurs mainly when the serum 25-hydroxyvitamin D concentration is > 374 nmol/L (150 ng/mL)[114], serum 25-hydroxyvitamin D concentrations > 75 nmol/L (50 ng/mL) could be either harmful or lack beneficial effect.

Comparison of daily replacement vs intermittent replacement of vitamin D

The observation that a single oral dose of vitamin D_3 2.5 mg (100000 IU) can maintain serum 25-hydroxyvitamin D above the target goal[115] provides a unique dosing strategy of vitamin D replacement therapy with greater adherence. It could even ensure 100% compliance if given by or under the direct supervision of a health care provider. Weekly[103], monthly[116], biyearly[117], and even yearly[118] schedules were reported in various trials leading to initiation of more convenient dosing schedule at less frequent intervals in clinical practice. To reduce the dosing frequency, a much higher dose of vitamin D is required which is predicted to cause a short-term spike (> 75 nmol/L or 50 ng/mL) in serum 25-hydroxyvitamin D concentration shortly

Table 4 Recommended daily vitamin D intake as promulgated by selected organizations and agencies

Organization	Daily intake		Goal	
	IU	μg	ng/mL	nmol/L
Institute of Medicine	600-800	15-20	> 20 (20-50)	> 50 (50-125)
Agency of Healthcare Research and Quality, Department of Health and Human Services	> 1000	> 25	> 30	> 75
Office of Dietary Supplements, NIH	600-800	15-20	20-50	50-125
National Osteoporosis Foundation	800-1000	20-25	> 30	> 75
American Association of Clinical Endocrinologists	1000-2000	25-50	30-60	75-150
Endocrine Society	1500-2000	37.5-50	30-100	75-250

Table 5 Diminished response of intestinal calcium absorption in response to increasing vitamin D supplementation

Daily vitamin D supplementation		Observed increase in calcium absorption	Estimated increase in calcium absorption per 1000 IU (25 μg)
IU	μg		
800	20	3.90%	4.88%
2000	50	5.00%	2.50%
4000	100	6.70%	1.68%

after oral administration. In addition to the adverse effects as described in the above section 4.2, increased falls and fracture are observed with annual vitamin D replacement therapy. These mainly occur within the first 3 mo after oral administration of 12.5 mg vitamin D_3[118]. Furthermore, the associations of high-dose vitamin D treatment with gastrointestinal complaints[119], increased bone turnover markers [120], hypercalcemia[121], hypercalciuria[122], and increased urinary magnesium loss [123] have been reported. Similar levels of serum 25-hydroxyvitamin D concentration were achieved at the end of a 56-d trial from daily (1500 IU/d), weekly (10500 IU/wk), and monthly (45000 IU/4 wk) replacement therapy. Excessive serum 25-hydroxyvitamin D concentration was not observed in those on the daily regimen but was observed in individuals on the weekly regimen and was still more common in those on monthly regimen[124]. Thus, high-dose vitamin D replacement therapy results in excessive serum 25-hydroxyvitamin D concentration.

A Lysine (K) amino acid polymorphism, in replacement of Threonine (T), at position 436 of vitamin D binding protein is associated with increased affinity of vitamin D and is associated a 416% elevation in serum 25-hydroxyvitamin D concentration if high-dose (4000 IU) vitamin D_3 replacement therapy if given as opposed to low-dose (600 IU) vitamin D_3 replacement therapy. Individuals carrying the TT SNP showed only a 136% increase in circulating vitamin[125]. Since the K allele is a minor allele and KK genotype accounts for less than few percent of population, the KK subjects may account for the excessive serum 25-hydroxyvitamin D-associated complications noted in certain studies. Given the above, daily vitamin D supplementation would seem to be most physiological and safest way to correct vitamin D deficiency and avoid the possible adverse effects associated with the excessive serum 25-hydroxyvitamin D concentration.

Factors affecting serum 25-hydroxyvitamin D concentration

Various genetic loci are associated with serum 25-hydroxyvitamin D concentration [126] with 4 major loci identified (Table 6). These are all key proteins involved in the transportation and metabolism of vitamin D. Race and ethnicity were noted to have significant impact on serum 25-dihyrdroxyvitamin D concentration[127], again implicating a genetic influence[126] including skin color[128].

Seasonable variations in serum 25-hydroxyvitanim D concentrations related to sun exposure are well described[126]. Consistent with this, latitude has a significant impact on serum 25-dihydrocyvitamin D concentration[129]. Living closer to the equator and increasing sun exposure can improve vitamin D levels. However, the increased risk of skin cancer from sun exposure should be balanced employing maximum skin

Table 6 Major loci associated with changes in serum 25-hydroxyvitamin D concentration

Chromosome	SNP	Gene symbol	Protein	*P* value
4p12	rs2282679	GC	Vitamin D binding protein	1.9×10^{-109}
11q12	rs12785878	DHCR7	7-dehydrocholsterol reductase	2.1×10^{-27}
11p15	rs10741657	CYP2R1	1-alpha-hydroxylase	3.3×10^{-20}
20q13	rs6013897	CYP24A1	1,25-dihydroxyvitamin D3 24-hydroxylase	6.0×10^{-10}

Adapted from Wang *et al*[126]. SNP: Single nucleotide polymorphism.

exposure area with decreased exposure time[85]. Dietary supplementation also corrects deficiency. Obesity is associated with a lower serum 25-hydroxyvitamin D concentration[72] while weight reduction with loss of adipose tissue is associated with improvement in serum 25-hydroxyvitamin D concentration[130]. These findings indicate that vitamin D status may be improved through modification of lifestyle.

Practical recommendations for vitamin D replacement therapy

As showed in Table 4, the recommended vitamin D supplement varies between organizations and agencies. The reasons for this relate to the purpose of vitamin D supplementation, visive calcemic *vs* non-calcemic effects. For calcemic effects, bone health is the goal of supplementation and is maximized through using a conservative daily vitamin D to achieve the minimal serum 25-hydroxyvitamin D concentration while avoiding possible adverse effects associated with overreplacement. A public health approach to this is displayed in Table 7. In contrast, a more personized approach is rationale when the target is to promote the non-calcemic effects of vitamin D.

We recommend using vitamin D_3, instead of vitamin D_2, for the rationale as discussed in the sections 3.2 and 3.3. We are in favor of daily replacement therapy and against intermittent mega dose replacement. This is supported by the recommendations of the Endocrine Society for indefinitely intermittent mega dose replacement [131]. It has been estimated that supplement with cholecalciferol 1000 IU (50 μg) daily will increase serum 25-hydroxyvitamin D concentration by 10 ng/mL[132]. Since vitamin D is a fat soluble, replacement therapy can be further enhanced by taking it with the largest meal of day[133]. We recommend vitamin D_3 1000 IU daily for achievement of an initial serum 25-hydroxyvitamin D concentration between 51 nmol/L (21) ng/mL and 75 nmol/L (30 ng/mL); 2000 IU daily for between 26 nmol/L (11 ng/mL) and 50 nmol/L (20 ng/mL); and 5000 IU for equal or less than 25 nmol/L (10 ng/mL). Serum 25-hydroxyvitamin concentration should be measured within 3 mo for assessment and, if indicated, dose adjustment. We are targeting serum 25-hydroxyvitamin D concentration between 75 nmol/L (30 ng/mL) and 125 nmol/L (50 ng/mL).

VITAMIN D AND DIABETES PREVENTION

Vitamin D diabetes prevention trials

To date, eight clinical trials employed vitamin D to reduce prediabetes progression to overt diabetes (Table 8). Only two studies[134,135] demonstrated positive results. Although these two studies had small sample size, they recruited true vitamin D deficient (25-hydroxyvitamin D < 50 nmol/L or 20 ng/mL) subjects and achieved final 25-hydroxyvitamin D concentration at 89-90 nmol/L, after intervention for 1 year and 6 mo, respectively. Of note, the study in India[134] was a randomized open label study demonstrating an odds ratio of 0.31 [95% confidence intervals (CI): 0.11-0.90]. The study in Iran was a randomized placebo control study[135] revealing an odds ratio of 0.06 (95%CI: 0.01-0.51). Because of relatively small sample sizes of both studies, the CI were very wide. Additional studies with similar initial and final 25-hydroxyvitamin D concentration (< 50 nmol/L and 90-100 nmol/L, respectively) and much larger sample sizes are required to confirm these data.

Two negative studies[136,137] were noted to have similar initial 25-hydroxyvitamin D concentrations (25-42 nmol/L). The negative results could be due to the relatively short interventions (8-16 wk) and small sample sizes. The study in Holland only

Table 7 Vitamin D supplementation versus vitamin D replacement therapy

	Vitamin D supplement	Vitamin D replacement therapy
Target goal	Bone health	Beyond bone health
Target 25-hydroxyvitamin D level	> 20 ng/mL (50 nmol/L)	> 30 ng/mL (75 nmol/L)
Initial testing for 25-hydroxyvitamin D level	No	Yes
Concern of over-replacement	Yes	Yes
Follow-up testing for 25-hydroxyvitamin D level	No	Yes
Dose adjustment	No	Yes
Approach	Public health	Individualized

Table 8 Preventive trials of vitamin D supplementation to prevent the development of type 2 diabetes

Ref.	Country Race/ethnicity	Placebo control			Intervention			Dose	Frequency	Duration	Diabetes prevention
		n	25(OH)D nmol/L		*n*	25(OH)D nmol/L					
			Initial	Final		Initial	Final				
Dutta *et al*[134], 2014[1]	IndiaAsian Indian	49	45	44	55	43	89	1500 μg	Weekly X 8, monthly	1 yr	Positive[2]
Niroomand *et al* [135], 2019	IranIranian	83	32	40	83	31	90	1250 μg	Weekly for 3 mo, monthly	6 mo	Positive[3]
Wagner *et al* [136], 2016[4]	Sweden	22	47	46	21	42	83	750 μg	weekly	8 wk	Negative
Oosterwerff *et al* [137], 2014	HollandNon-Western	65	22	23	65	25	60	30 μg	daily	16 wk	Negative
Barengolts *et al* [141], 2015[5]	United States African American	86	35	50	87	37	120	1250 μg	weekly	12 m	Negative
Davidson *et al* [139], 2013[6]	United States Latino and African American	53	55	60	56	55	167	2222 μg	weekly	12 mo	Negative
Jorde *et al*[140], 2016	Norway	255	61	64	256	60	110	500 μg	weekly	5 yr	Negative
Pittas *et al*[138], 2019	United States mixed	1212	70	72	1211	69	136	100 μg	daily	24 mo	Negative

[1]This study was an open label randomized design, instead of randomized placebo-control design as other studies.
[2]Intervention is associated with significantly lower progression to diabetes (11% *vs* 27%; $P = 0.04$) and higher reversal to normoglycemia (43% *vs* 20%; $P = 0.02$).
[3]The rate of progression toward diabetes was significantly lower in the intervention group (3% *vs* 28%; $P = 0.002$).
[4]Meadian 25-hydroxyvitamin was provided, rather than mean 25-hydroxyvitamin D as in other studies.
[5]Ergocalciferol was used, rather than cholecalciferol in other studies.
[6]Weekly dose of cholecalciferol was adjusted to titrate serum 25-hydroxyvitamin D between 162 nmol/L and 200 nmol/L.

achieved a final suboptimal 25-hydroxyvitamin D concentration of 60 nmol/L.

The other four studies[138-141] had a final 25-hydroxyvitamin D concentration > 100 nmol/L which might not be optimal for glucose metabolism. Among them, the study in African American[141] was the only study that recruited true vitamin D deficient subjects (initial 25-hydroxyvitamin D 37 nmol/L). Of note, ergocalciferol was used which could be less effective biologically as discussed above in 3.2 and 3.3. Enrollment of non-vitamin D deficient (25-hydroxyvitamin D < 50 nmol/L) subjects [138-140] could further reduce the chance of finding any effect. Furthermore, the study in Norway had a significant dropout rate in the interventional group with only 45% of participants completing the planned 5-year visit. The largest intervention trial[138] included more than 1000 subjects in each group. To be able to apply to the general population in the United States, this study did not target vitamin D deficient subjects and allowed the participants to take additional vitamin D up to 25 μg daily. Therefore, it had the highest initial 25-hydroxyvitamin D among these studies, 70 nmol/L in the

control group and 69 nmol/L in the interventional group, which might diminish the power of this study to detect the beneficial effect of vitamin D. Regardless of the negative results in most studies, the beneficial effect of vitamin D supplementation cannot be completely excluded, especially in subjects with vitamin D deficiency (25-hydroxyvitamin D < 50 nmol/L).

The effects of vitamin D supplement on parameters of glucose metabolism

Various parameters of glucose metabolism were reported in most of above-mentioned studies, except one[138]. After vitamin D intervention for 1 year, the study from India [134] observed improvement in fasting and 2-hr post-challenge glucose concentrations, insulin sensitivity by Homeostasis Model (HOMA) insulin resistance index, QUICKI, and 1/fasting insulin concentration while no impact on HbA1c and beta cell function by HOMA. Following vitamin D supplement for 6 mo, the study from Iran[135] reported the improvement in the HOMA insulin resistance index and marginal improvement in fasting insulin concentration (P = 0.05) and 2-hour post-challenge blood glucose concentration (P = 0.07) with no impact on fasting blood glucose concentration.

After an 8-wk intervention, the study from Sweden[136] assessed insulin sensitivity and beta cell function using the hyperglycemic clamp. They observed a significant improvement in deposition index based on the first phase insulin response (P = 0.005) and marginal improvement in first phase insulin response (P = 0.06), insulin sensitive index (P = 0.09), deposition index based on the second phase insulin response (P = 0.06), and A1c (P = 0.06) but no impact on the second phase insulin response and fasting and 2-hr post-challenge blood glucose concentration.

In contrast, the study from Holland[137] evaluated glucose metabolism parameters based on the 75-g glucose tolerance test following intervention for 16 wk. They reported negative results, finding no effects upon insulin area under curve, glucose area under curve, insulin sensitivity by composite insulin sensitivity index, Stumvoll index, insulin resistance index by HOMA, and beta cell function by insulinogenic index. Of note, the final 25-hydroxyvitamin D concentration was only 60 nmol/L which could be suboptimal for glucose metabolism. Similarly, after the vitamin D supplementation for 5 years, the study from Norway[140] observed no impact on fasting and 2-hr post-challenge serum glucose concentration, fasting and post challenge serum insulin concentration, fasting serum C-peptide concentration, HbA1c, and insulin sensitivity by HOMA insulin resistance index and QUICKI.

Following a 12-mo intervention, the study involving Latino and African Americans [139] observed a significant improvement in HbA1c but no effects on fasting and 2-hr post-challenge blood glucose concentration, beta cell function by the ratio of insulin and glucose area under curve, Stumvoll first and second insulin response, insulinogenic index, insulin sensitivity index by HOMA insulin resistance index and composite insulin sensitivity index, and oral disposition index. However, a significant improvement in composite insulin sensitivity index but not Matsuda index, insulinogenic index, C-peptidogenic index, and HbA1c was noted.

Excepting two studies[137,140] with negative results, favorable outcomes on parameters of glucose metabolism were reported in five studies[134-136,139,141] suggesting some benefits to supplementation under these conditions.

Summary of vitamin D and diabetes prevention

In vitamin D deficient (25-hydroxyvitamin D < 50 nmol/L) prediabetic subjects, vitamin D supplement appears to be effective in reduction of the development of overt diabetes. However, there appears to be no benefit in vitamin D sufficient subjects, which was noted in a study from Norway[142]. Based on pooled data from four intervention trials, in subjects without vitamin D deficiency there is no improvement in glucose metabolism with high dose vitamin D supplementation and if anything, the effect is negative[143]. This notion is consistent with the observed threshold effect of vitamin D on bone health and lack of benefit in subjects with baseline 25-hydroxyvitamin D level ≥ 75 nmol/L (30 ng/mL)[14,15].

LABORATORY EVIDENCE SUPPORTING THE EFFECT OF VITAMIN D ON GLUCOSE AND FUEL HOMEOSTASIS

Beta cell function

Functional beta cell studies: The important role of vitamin D on insulin secretion has

been noted in laboratory animals since 1980. Insulin secretion was reduced by about 50% in isolated perfused islets from vitamin D-deficient rats compared to controls [144]. Interestingly, 1,25-dihydroxyvitamin D_3 was noted in cell nuclei in the islets of langerhans[145]. Furthermore, administration of 1,25-dihydroxyvitamin D3 to vitamin D-deficient rats improved insulin secretion significantly when compared to controls [146]. Vitamin D deficiency impaired both phases of insulin release in rats while correction of hypocalcemia failed to reverse the defect in insulin release[147]. Vitamin D, but not calcium, was essential for normal insulin secretion from the perfused rat pancreas[148]. The positive effect of single dose of 1,25-dihydroxyvitamin D_3 on insulin secretion was apparent at 8 h in perfused rat pancreata, peaked at 14 h, and then decreased to pretreatment baseline values by 36 h[149]. Dietary vitamin D3 supplementation improved impaired glucose tolerance and insulin secretion in the vitamin D-deficient rats[150]. A dose-dependent effect from parenteral 1,25-dihydroxyvitamin D on insulin secretion and glucose metabolism was observed within 3 h and remained effective up to 20 h in the vitamin D-deficient rats[151]. The role of vitamin D on insulin synthesis and secretion was supported by studies in vitamin D receptor knockout mice. Insulin secretory capacity was reduced by 60% in vitamin D receptor knockout mice[152] with increased post-challenged blood glucose but normal fasting blood glucose concentration and reduced insulin mRNA levels in pancreatic islets but normal pancreatic beta cell mass, islet architecture, and islet neogenesis when compared to wild type mice. Thus, vitamin D plays an important role in pancreatic insulin synthesis and secretion in vivo.

Mechanistic studies of beta cell function: Although the essential role of vitamin D on insulin secretion has been established in vitamin D depleted laboratory animal, details of the underlying molecular mechanism remain to be defined. Employing a proteomic approach, treatment with 1,25-dihydroxyvitamin D_3 resulted in 31 differentially expressed proteins in INS-1 beta-like cells[153] with 29 upregulated, some of which were implicated in insulin granule motility and insulin exocytosis as well as regulation of ions. Pretreatment of INS1E cells with 1,25-dihydroxyvitamin D or 25-hydroxyvitamin D and glucose resulted in 526 and 181 differentially expressed genes, respectively[154].

Several molecular mechanisms were proposed to account for the effects of vitamin D on beta cells, including changes in the local pancreatic islet renin-angiotensin system [155], restoration of GLUT2 expression[156], enhancement of IP3 and AMPA receptor expression[157], vitamin D-binding protein-induced beta cell dedifferentiation[158], reduction of oxidative damage[159], reduced cholinergic pancreatic effects[160], enhanced transcriptional regulation of voltage-gated calcium channels[161], and elevation of PPAR-γ expression[162]. However, further studies are required to confirm the proposed mechanisms.

Insulin sensitivity

Functional studies of insulin sensitivity: In contrast to beta cell function, there are fewer studies of insulin sensitivity. Dietary supplementation of vitamin D improved insulin sensitivity, hepatic steatosis, and myocardial fibrosis in Western diet fed rats [163]. In dietary-induced obese mice, vitamin D receptor activation in liver macrophages improved insulin sensitivity with reduction of hepatic inflammation and steatosis[164]. Vitamin D treatment improved insulin resistance index in a nongenetic model of type 2 diabetes[165]. However, vitamin D status were not reported in these studies.

Mechanistic studies of insulin sensitivity: Chronic central administration of 1,25-dihydroxyvitamin D_3 dramatically reduced body weight, putatively by lowering food intake, in obese rodents[166]. Treatment with vitamin D increased mitochondrial function and insulin sensitivity, in part, through upregulation of perilipin 2, a perilipin protein upregulated with 1,25-dihydroxyvitamin D treatment[167]. In skeletal myocytes, vitamin D reduced insulin resistance by altering lipid partitioning and lipid droplet packaging in favor of lipid turnover[168]. FGF-23 knockout mice are hypoglycemic with profoundly increased peripheral insulin sensitivity and improved subcutaneous glucose tolerance. Ablation of vitamin D signaling in these mice normalized subcutaneous glucose tolerance tests and insulin sensitivity[169]. Caveolin-1 protein, which is necessary for vitamin D signaling, could play a role in vitamin D-induced insulin sensitivity in skeletal muscle[170]. In cultured rat osteoblasts, 1,25-dihydroxyvitamin D_3 treatment increased expression of the insulin and vitamin D receptors, and elevated osteocalcin levels under high glucose exposure [171], which may in turn improve insulin sensitivity.

However, the results of vitamin D receptor knockout mice were less uniform. Skeletal muscle-specific vitamin D receptor knockout mice developed insulin resistance and glucose intolerance accompanied by increased expression and activity of FOXO1[172]. Deletion of macrophage vitamin D receptor promoted insulin resistance and monocyte cholesterol transport and accelerated atherosclerosis[173]. In contrast, deletion of the vitamin D receptor gene in endothelial cells improved glucose tolerance and insulin sensitivity in skeletal muscle and reduced expression and secretion of insulin in pancreatic islets[174]. Together these data indicate that vitamin D has positive and negative effects on insulin sensitivity that are cell and organ specific.

CONCERNS ARISING WITH REPORTED STUDIES

Lack of true vitamin D deficient subjects

Due to publicity and potential non-calcemic benefits of vitamin D supplementation, the sale of vitamin D supplements increased significantly and taking vitamin D supplements is common. Thus, there are less true vitamin D deficient subjects available for inclusion in clinical trials. As well, a general lack of funding support for large trials impedes addressing the ability of researchers to address the gaps in knowledge surrounding vitamin D and its beneficial effects.

Lack of beneficial effects from suboptimal replacement and detrimental effects of over-replacement

To obtain the maximal effect of vitamin D, serum 25-hydroxyvitamin D concentration should be maintained in an optimal range, namely between 75 nmol/L (30 ng/mL) and 125 nmol/L (50 ng/mL). Inadequate vitamin D replacement therapy will reduce the chance to observe the expected beneficial effect of vitamin D while adverse effects associated with excessive serum 25-hydroxyvtamin D concentration will also cloud data interpretation. Although mega doses of vitamin D given intermittently could improve compliance in a study protocol, the predicted wide swings in serum 25-hydroxyvitamin D concentrations will confound outcomes. It is important in clinical studies to use a proper daily dose to avoid these pitfalls.

Inadequate sample size

The Diabetes Prevention Program demonstrated a 58% (95%CI: 48%-66%) reduction in the incidence of diabetes in the lifestyle intervention group (cumulative incidence of diabetes 14.4% in 1079 participants) and a 31% reduction in diabetes (95%CI: 17%-43%) in the metformin treated group (cumulative incidence of diabetes 21.7% in 1073 participants) when compared to the placebo (cumulative incidence of diabetes 28.9% in 1082 participants)[175]. Insulin sensitivity improved by 61.8% in the lifestyle intervention group and 28.3% in the metformin group[176]. This study can be employed to calculate a sample size sufficient for assessing the effects of vitamin D intervention.

Based on the non-linear relationship of serum 25-hydroxyvotamin D concentration and insulin sensitivity index as we reported[113], we constructed Table 9. Assuming a linear relationship between improvement in insulin sensitivity and reduction of diabetes from the Diabetes Prevention Program[175,176], we calculated the required sample size to detect the reduction of diabetes incidence after vitamin D replacement therapy in a population similar to that of the Diabetes Prevention Program[175] with a power of 0.80 to detect the proposed difference and a type I error rate, alpha, of 0.05 in a clinical trial of 3 years. Starting with a baseline serum 25-hydroxyviyamin D of 25 ng/mL (10 ng/mL), 170 subjects would be needed. Such a study cohort size is not excessive. However, if the baseline serum 25-hydroxyvitamin D is equal or greater than 50 nmol/L (20 ng/mL) the cohort size needed increases markedly. These calculations suggest that all studies to date are flawed secondary to inadequate sample size.

It has been frustrating to confound the published negative reports while ample evidence supports the benefit of vitamin D. Accordingly, we propose these guidelines [177]. Future studies into the effects of vitamin D supplementation need to ensure the proper selection of study subjects, adequate vitamin D replacement to achieve an optimal serum 25-hydroxyvitamin D concentrations, avoidance over-placement to eliminate detrimental effects, and adequate sample size to detect the proposed effects.

Table 9 Calculated sample size requirement to detect an improvement in insulin sensitivity based on a baseline serum 25-hydroxyvitamin D concentration of 40 ng/mL (100 nmol/L) and a power of 0.80 and alpha of 0.05

Initial serum 25-hydroxy-vitamin D concentration		Estimated insulin sensitivity index(μM/min/m²/pM)	Improvement in insulin sensitivity index with postintervention Serum 25-hydroxyvitamin D concentration 40 ng/mL (100 nmol/L)	Diabetes reduction based on the Diabetes Prevention Program	Sample size
ng/mL	nmol/L				
10	25	4.1326	0.8664	0.4361	340
15	37	5.4144	0.4246	0.2118	1602
20	50	6.2812	0.2280	0.1121	5934
25	62	6.8674	0.1232	0.0589	21878
30	75	7.2638	0.0619	0.0278	99260
35	87	7.5319	0.0241	0.0086	1041162

THE ISSUES THAT NEED TO BE ADDRESSED BY THE FUTURE STUDIES

Optimal serum 25-hydroxyvitamin D concentration for glucose metabolism

Table 4 summarizes the recommended serum vitamin D concentrations from several institutions and agencies. As appreciated, studies on bone health[14,15] showed no additional benefit in the subjects with serum 25-hydroxyvitmanin D > 75 nmol/L (30 ng/mL) and this agrees with the effects upon diabetes prevention. However, increased all-cause mortality[107] and cardiovascular mortality[108] occurred prior to the 125 nmol/L (50 ng/mL) threshold, implying a much lower maximum dose for optimal serum 25-hydroxyvitamin D concentration. The question remains whether the same relationship applies to glucose homeostasis.

Detrimental effects on glucose metabolism for serum 25-hydroxyvitamin D concentrations above a maximum threshold

The detrimental effects noted in individuals with serum 25-hydroxyvitamin D concentration above a maximum threshold was observed in a cross-sectional study[109]. Further, improvement in bone density after discontinuation of vitamin D supplementation in osteoporotic patients with elevated serum 25-hydroxyvitamin D concentration was reported[110]. Elevated serum 25-hydroxyvitamin D concentrations were also associated with increased falls and fracture[118]. These reports suggest that assessment of negative effects from elevated serum 25-hydroxyvitamin D concentration may be uncovered with additional study.

Diabetes prevention in vitamin D deficit subjects

Although various evidence suggests the benefit of vitamin D on glucose metabolism, published diabetes prevention trails are not convincing and suffer from improper designed and execution. To address this issue, a well-designed and well-conducted randomized, placebo-control trial to test the effects of vitamin D to limit development of diabetes is warranted, by selecting true vitamin D deficient subjects, achieving optimal but not excessive serum 25-hydroxyvitamin concentration, and enrolling adequate number of subjects. Properly monitoring serum 25-hydroxyvitamin D concentrations is required during the study.

CONCLUSION

The role of vitamin D in glucose metabolism and fuel homeostasis is supported by a number of observational studies. We reported that serum 25-hydroxyviatmin D concentration accounted for 21.2% of the variation in insulin sensitivity index in univariate analysis and 6.1% by itself among 42% with other covariates in multivariate analysis[178]. We also reported that serum 25-hydroxyviatmin D concentration accounted for 8.2% of the variation in beta cell function in univariate analysis and 4.5% by itself among 25.5% with other covariates in multivariate analysis[179]. Although the intervention studies have failed to provide concordant data for multiple reasons, laboratory studies revealed a number of molecular mechanisms that underlie the effect

of vitamin D supporting the important role of the vitamin in glucose metabolism and fuel homeostasis. Since the independent contributions of vitamin D to insulin sensitivity[178] and beta cell function[179] are relatively small, vitamin D deficiency could be the last straw that breaks camel's back in polygenetic and multifactorial diseases, such as diabetes, obesity, and hyperlipidemia.

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