MECHANISMS IN ENDOCRINOLOGY

Vitamin D as a potential contributor in endocrine health and disease

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Abstract

Objective: It has been suggested that vitamin D may play a role in the pathogenesis of several endocrine diseases, such as hyperparathyroidism, type 1 diabetes (T1DM), type 2 diabetes (T2DM), autoimmune thyroid diseases, Addison's disease and polycystic ovary syndrome (PCOS). In this review, we debate the role of vitamin D in the pathogenesis of endocrine diseases.
Methods: Narrative overview of the literature synthesizing the current evidence retrieved from searches of computerized databases, hand searches and authoritative texts.
Results: Evidence from basic science supports a role for vitamin D in many endocrine conditions. In humans, inverse relationships have been reported not only between blood 25-hydroxyvitamin D and parathyroid hormone concentrations but also with risk of T1DM, T2DM, and PCOS. There is less evidence for an association with Addison's disease or autoimmune thyroid disease. Vitamin D supplementation may have a role for prevention of T2DM, but the available evidence is not consistent.
Conclusions: Although observational studies support a potential role of vitamin D in endocrine disease, high quality evidence from clinical trials does not exist to establish a place for vitamin D supplementation in optimizing endocrine health. Ongoing randomized controlled trials are expected to provide insights into the efficacy and safety of vitamin D in the management of endocrine disease.

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Introduction

The main physiologic role of vitamin D is to regulate calcium and phosphorus homeostasis and to promote bone health. However, accumulating evidence from animal and human studies suggests that vitamin D may also be important for a variety of nonskeletal actions that may be important in the pathogenesis of several endocrine diseases. The increased appreciation of the pleiotropic effects of vitamin D and the high prevalence of hypovitaminosis D in the general healthy population have generated very high interest in vitamin D among researchers, clinicians and the lay public. Vitamin D has been implicated in the pathogenesis of several endocrine

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conditions, including primary hyperparathyroidism, type 1 diabetes (T1DM) (1), type 2 diabetes (T2DM) (2, 3), autoimmune thyroid, (4) adrenal diseases (5), and polycystic ovary syndrome (PCOS). The present review focuses on the reported association between vitamin D status and endocrine diseases and the potential role of vitamin D supplementation in the treatment of endocrine disease.

Vitamin D homeostasis

Humans derive vitamin D from cutaneous synthesis (in the form of cholecalciferol (D_3)), diet (in the form of D_3), and nutritional supplements (in the form of D_3) or ergocalciferol (D_2) (6). Upon exposure to u.v B radiation (UVB), 7-dehydrocholesterol in the skin is converted to pre-vitamin D_3, which is immediately converted to vitamin D_3 in a heat-dependent process. After ingestion or synthesis, vitamin D is hydroxylated in the liver to form 25 hydroxyvitamin D ($25(OH)D_2$ or $25(OH)D_3$, its major circulating form, which has little biological activity. 25(OH)D is converted in the kidney by 25(OH)D-1α-hydroxylase (CYP27B1), to its bioactive hormonal metabolite 1,25 dihydroxy-vitamin D ($1,25(OH)_2D$ or calcitriol). The primary action of $1,25(OH)_2D$ is through the nuclear vitamin D receptor (VDR), which heterodimerizes with the retinoid X receptor and binds to vitamin D-responsive elements near target genes (6, 7). The primary action of $1,25(OH)_2D$ is to enhance intestinal calcium absorption and to promote osteoclast function, thereby maintaining calcium and phosphorus homeostasis and bone health. However, the discovery that nearly all tissues in the body express the VDR and that several tissues also express CYP27B1, thereby allowing for local production of $1,25(OH)_2D$ with a paracrine effect, has provided important insights into the pleiotropic effects of vitamin D and its potential role in a variety of extra-skeletal tissues (7), including many that affect endocrine disease.

Classification of vitamin D status and vitamin D intake requirements

Blood concentration of 25(OH)D is the biomarker used by clinicians and researchers to determine vitamin D status. However, there is no consensus on the 25(OH)D thresholds for defining vitamin D adequacy. The guidelines by the Institute of Medicine (IOM) and the Endocrine Society differ on classification of vitamin D status (8, 9). These differences are explained by the populations targeted by the guidelines and how the evidence was synthesized. Specifically, the IOM guidelines concentrated on the general healthy population and considered only trials and concluded that blood concentration of 25(OH)D >20 ng/ml is consistent with favorable skeletal outcomes. In contrast, the Endocrine Society clinical practice guidelines concentrated on people at high risk for vitamin D deficiency and considered both trials and observational (epidemiologic) studies in concluding that blood concentration of 25(OH)D >30 ng/ml is desirable for optimal skeletal outcomes without any upper limit that would be concerning for safety. Both guidelines agreed that recommendations will require reconsideration in the future as additional data from on-going randomized trials become available. Variability in vitamin D-binding protein and bioavailable 25(OH)D concentration may also be important when assessing vitamin D status, especially in certain populations such as African-Americans (10).

The recommended intakes by the two guidelines also differ. The IOM report on dietary reference intakes for calcium and vitamin D recommends 600 international units per day of vitamin D for individuals 9–70 years old and 800 international units for those older than 70 years as the recommended dietary allowance (RDA), which is defined as the intake that meets the needs of 97.5% of the healthy population. In contrast, the Endocrine Society clinical practice guidelines conclude that to raise the blood level of 25(OH)D consistently above 30 ng/ml, intakes of 1500–2000 IU/day are required. The IOM report recognized the lack of trials with vitamin D supplementation for nonskeletal outcomes as a major hurdle in establishing recommendations, while the Endocrine Society guidelines applied evidence from observational studies to develop its recommendations and considered blood 25(OH)D concentration as a clinically important surrogate outcome that correlates with health and disease.

Vitamin D and primary hyperparathyroidism

Ionized calcium is the most tightly regulated analyte in the circulation. This fine regulation is achieved through an interplay between parathyroid hormone (PTH), calcitonin, and $1,25(OH)_2D$. PTH is the major stimulator of renal CYP27B1, which increases biosynthesis of $1,25(OH)_2D$. In turn, PTH is downregulated both by 1, $25(OH)_2D$ and ionized calcium.

The seemingly inactive vitamin D metabolite, 25(OH)D, is an important regulator within parathyroid tissue. Parathyroid cells take up vitamin D-binding protein along with its 25(OH)D, which is the mechanism that

provides parathyroid tissue with better access to circulating 25(OH)D than most other tissues. Furthermore, the parathyroid glands possess the enzyme, CYP27B1, which produces $1,25(OH)_2D$ for local paracrine regulation. The combined effect of efficient access to circulating 25(OH)D and $1,25(OH)_2D$ plus the local production of $1,25(OH)_2D$ is suppression of both PTH secretion and parathyroid cell proliferation (11).

Larger parathyroid adenomas respond poorly to feedback by calcium or $1,25(OH)_2D$; consequently, in primary hyperparathyroidism, $1,25(OH)_2D$ levels often correlate positively with circulating 25(OH)D (12). If vitamin D supply is low, then primary hyperparathyroidism can remain latent, known as 'normocalcemic primary hyperparathyroidism' (13). Hypercalcemia develops once the 25(OH)D concentration increases and elevated PTH stimulates renal CYP27B1 relentlessly, which generates $1,25(OH)_2D$ in proportion to the supply of 25(OH)D. This relationship highlights a fundamental aspect of the vitamin D system: its operation under first-order reaction kinetics, namely, the yield of the product ($1,25(OH)_2D$) is proportional to the supply of the substrate (25(OH)D). Therefore, the enzymes of the vitamin D system need to modify their function according to the supply of 25(OH)D. Depending on severity, primary hyperparathyroidism can disrupt the adaptation, resulting in elevated $1,25(OH)_2D$ and increased intestinal calcium absorption. While this form of hypercalcemia, promoted by the underlying parathyroid adenoma, is not strictly a manifestation of vitamin D toxicity, it is a form of hypersensitivity to higher doses of vitamin D that is important to consider, given how common parathyroid adenomas are (14).

In healthy persons, the reference (normal) range for serum PTH is known to decline as serum 25(OH)D levels increase. Therefore, the theoretical plateau in PTH, as 25(OH)D increases, can be used as a determinant in establishing the adequacy of vitamin D status. That relationship breaks down in primary hyperparathyroidism, because with disease progression, PTH becomes an unregulated driver of 25(OH)D metabolism into $1,25(OH)_2D$, a powerful hypercalcemic hormone. Ongoing research (Table 1) will further clarify the effect of vitamin D supplementation on hyperparathyroidism.

Vitamin D and T1DM

T1DM is one of the first endocrine disorders where a potential role for vitamin D was reported. T1DM is characterized by an autoimmune destruction of the insulin producing pancreatic islet β-cells, rendering patients dependent on insulin administration for survival (15). Potential effects of vitamin D deficiency on T1DM are multiple, including alterations in the innate immune system, such as impaired macrophage function and also dysfunction of the β-cell itself (16). Caution, however, is warranted when postulating a direct effect of vitamin D deficiency on immune or β-cell function *in vivo*, as vitamin D deficiency leads to decreased calcium concentration, with calcium being a crucial ion both for immune function and insulin secretion. In nonobese diabetic (NOD) mice, the principal animal model of T1DM, severe vitamin D deficiency increases the risk for developing diabetes (17), but absence of any effect on T1DM presentation in VDR knockout NOD mice suggests a redundancy of the vitamin D system in the pathogenesis of T1DM (18). *In vitro*, the active form of vitamin D, $1,25(OH)_2D$, directly protects β-cells from the destructive effects of inflammatory cytokines and limits the inflammatory profile of macrophages (19, 20).

In NOD mice, administration of high doses of $1,25(OH)_2D$ from early life onward lowers incidence of T1DM (21, 22), highlighting vitamin D as a promising intervention in prevention of T1DM. To replicate the immune and metabolic effects of the active form of vitamin D seen in the mouse model, very high doses are required that would induce hypercalcemia and hypercalciuria and potentially bone decalcification (23). Synthetic analogs of $1,25(OH)_2D$ with immune modulatory function but lesser effects on calcium and bone have been developed to overcome such an obstacle. In NOD mice, such analogs can prevent the progression of the disease (24, 25), which has been postulated to be due to the direct β-cell protective effects of $1,25(OH)_2D$ combined with the blocking of inflammation, together with the regulator T lymphocytes, which may be partly a direct effect on T lymphocytes, but also via an effect on the central antigen presenting cells, the dendritic cells (26). *In vitro*, the presence of $1,25(OH)_2D$ or an analog results in the generation of dendritic cells with specific characteristics, such as less IL12 secretion, less CD80/CD86 expression, less MHC II expression, and most importantly less stimulation of effector T cells and specific generation of regulator T cells (27, 28). Thus, a second possible avenue to exploit the potential beneficial immune modulatory effects of vitamin D is the auto-transfer of *ex vivo* $1,25(OH)_2D$ (or analog)-exposed dendritic cells generated from peripheral blood monocytes from patients with T1DM. Upon transfer back into patients, these dendritic cells should be able to induce regulator T cells and shift the

Table 1 Summary of available evidence that links vitamin D to endocrine diseases.

Diseases	Putative mechanisms	Observational studies	Clinical trials	Examples of ongoing clinical trials
Hyperparathyroidism	Suppress both PTH secretion and parathyroid cell proliferation	✓✓✓✓✓	✓✓✓✓	NCT01329666: primary hyperparathyroidism (PHPT): early effect of vitamin D NCT00538720: effects of vitamin D replacement in patients with primary hyperparathyroidism (PHPT)
Type 1 diabetes	Improvements in insulin secretion and autoimmunity	✓✓		NCT01390480: effects of vitamin D supplementation in subjects with new-onset of type 1 diabetes NCT01785108: DIABGAD – trial to preserve insulin secretion in type 1 diabetes using GAD-Alum (Diamyd) in combination with vitamin D and ibuprofen
Type 2 diabetes	Improvements in insulin sensitivity, insulin secretion, and inflammation	✓✓✓✓	✓✓	NCT01942694: vitamin D and type 2 diabetes study NCT01633177: study of vitamin D and omega-3 supplementation for preventing diabetes NCT01736865: vitamin D for established type 2 diabetes (DDM2)
Autoimmune thyroid disease	Modulation of immune system by suppressing activated T cells and enhancing macrophages ability to phagocytize	✓	✓	
Addison's disease	Improvement in residual adrenal function and T-lymphocyte immune balance	✓		
Polycystic ovarian syndrome	Improvement in insulin sensitivity, cardiovascular risk factors, and reproductive function	✓✓✓	✓✓	NCT00907153: vitamin D for the treatment of women with polycystic ovary syndrome (PCOS) NCT00743574: health benefits of vitamin D and calcium in women with PCOS (polycystic ovarian syndrome)

Number of ✓ denotes degree of available evidence (✓=low; ✓✓✓✓✓=very high).

immune system from attack toward tolerance towards the β-cell. Clinical trials exploring this potential therapeutic avenue are underway.

In population-based studies, low vitamin D concentration, especially in early life, has been associated with a higher risk for T1DM (1). Lower concentrations of 25(OH)D were reported in North Indian (29), Italian (30), Swedish (31), and British (32) children or young adults with newly diagnosed T1DM compared with controls. An increased prevalence of vitamin D deficiency in children and adolescents with T1DM compared with nondiabetic individuals was also observed in American (33), Australian (34), and Qatari (35) populations. Of interest, there are also reported associations between polymorphisms of genes involved in the vitamin D system and metabolism and T1DM risk islet autoimmunity risk (32, 36).

Several observational studies have found that supplementation (based on self-reported data) with vitamin D in early life is associated with a lower risk of T1DM in later life (37, 38). In a retrospective case–control study in Norway, intake of cod-liver oil by children during infancy did not prevent T1DM, though there was a trend toward an inverse association (39). More recently, the ABIS study in Sweden reported that the use of vitamin D-containing supplements during pregnancy was associated with reduced development of autoantibodies to GAD or IA-2A in the offspring of T1DM parents at 1 year, but not at 2.5 years (40). In small intervention studies, data on the effect of vitamin D supplements in patients with established T1DM have been disappointing. For example, a study in Europe showed that administration of 0.25 μg $1,25(OH)_2D_3$ was safe but failed to reduce loss of β-cell function, even in patients with high C-peptide at diagnosis (41).

In summary, based on observational studies, vitamin D deficiency (defined as 25(OH)D <12 ng/ml) should probably be avoided in individuals at high risk of developing T1DM, specifically in early life. However, whether supplementation with high dose vitamin D or its analogs have a therapeutic role in prevention or treatment of T1DM is presently under investigation.

Vitamin D and T2DM

Among the multiple associations that have been reported between vitamin D status and chronic diseases, the link between vitamin D and T2DM stands as one of the most promising ones. The potential effect of vitamin D on glycemia appears to be mediated by direct and indirect effects on three different pathways: insulin secretion, insulin sensitivity, and systemic inflammation. A direct effect of vitamin D on insulin secretion may be mediated by activation of VDRs in the pancreatic β-cells. VDR is expressed in pancreatic cells and mice lacking VDR have impaired insulin secretion (42). In addition, the direct effect of vitamin D on insulin synthesis is supported by the presence of the vitamin D response element in the human insulin gene promoter (43). Importantly, pancreatic β-cells express CYP27B1, thereby generating $1,25(OH)_2D$ locally, which allows for a paracrine effect of vitamin D. A direct effect of vitamin D on insulin sensitivity may be mediated by stimulating the expression of insulin receptors in peripheral insulin target cells. In addition, vitamin D insufficiency is associated with increased fat infiltration in skeletal muscle, independent of body mass, which is thought to contribute to decreased insulin action. Vitamin D may also decrease the effects of systemic inflammation, known to play an important role in the pathogenesis of T2DM, in several ways, which include directly modulating the expression and activity of cytokines in addition to several other noncytokine-related immune-modulating effects (44). Finally, insulin secretion and insulin sensitivity are both calcium-dependent processes (45, 46); therefore, vitamin D could affect both pathways, indirectly, through alteration in calcium concentration and flux through the cell membranes of the pancreas and insulin-responsive tissues.

The data from observational studies strongly support an association between low vitamin D status and incident T2DM. Recently, two meta-analyses of observational studies have been published with nearly identical results. Song *et al.* (2) reported a 38% lower risk of developing T2DM in the highest reference category of 25(OH)D compared with the lowest one (relative risk 0.62 (95% CI 0.54–0.70), while Afzal *et al.* (3) reported an odds ratio for T2DM of 1.5 (95% CI 1.33–1.70) for the bottom vs top reference category of 25(OH)D.

Randomized studies have shown inconsistent results. In trials that included participants with normal glucose tolerance or established diabetes at baseline, vitamin D supplementation had no effect on glycemic measures or incident diabetes. It is crucial to note, however, that most studies were underpowered or were *post hoc* analyses of completed trials. In addition, the results differed based on the adherence to vitamin D supplementation. For example, in a post-analysis of the RECORD study, while supplementation with 800 IU/day of vitamin D_3 did not change the risk of self-reported T2DM, there was a notable trend toward reduction in T2DM risk with vitamin D_3 (odds ratio 0.68; 95% CI 0.40–1.16) among study participants who were highly compliant with supplementation (47).

Vitamin D supplementation appears to be more promising in patients who are at risk for diabetes. In the calcium and vitamin D for T2DM mellitus (CaDDM) study, a 2×2 factorial design trial in participants with prediabetes, vitamin D supplementation improved disposition index, a measure of β-cell function (48). However, in another trial of non-Caucasians, very high dose vitamin D supplementation had no effect on insulin secretion, insulin sensitivity, or incident diabetes in a population with impaired fasting glycemia or impaired glucose tolerance and low vitamin D levels (49).

In summary, vitamin D appears to have no role in prevention of T2DM in the general population; however, there might be a role for vitamin D for treatment of established T2DM or prevention of T2DM in persons at risk, although the evidence from available trials is inconsistent. There are several ongoing large randomized trials in well-defined populations (D2d (NCT01942694), VITAL (NCT01633177), DDM2 (NCT01736865)) to test the hypothesis that vitamin D deficiency is a contributor to the pathogenesis of T2DM and to define its role in prevention or therapy of T2DM.

Vitamin D and Addison's disease

Addison's disease is a rare condition resulting from autoimmune-mediated destruction of the adrenal cortex and may present as either isolated adrenal deficiency or part of an autoimmune polyendocrine syndrome. Although the etiology of Addison's disease is largely elusive, current concepts point to environmental factors acting as triggers in a background of genetic susceptibility

leading to destructive CD8-T-lymphocytic infiltration of the adrenal cortex and characteristic 21-OHase antibody production (50). Although the main genetic susceptibility is identified at the HLA locus (51), other susceptibility genes have been described, including in the VDR (52) and CYP27B1 (5, 53), similarly to other autoimmune endocrine diseases (e.g. T1DM) (32). This shared genetic association led to the assumption that the vitamin D system may be involved in critical pathophysiologic pathways in these immune-mediated inflammatory disorders because active $1,25(OH)_2D$ may suppress steroidogenesis by downregulating CYP21A2 and upregulating CYP11A1 and CYP17A1. In an adrenal cell model (NCI-H295R line) (54), vitamin D acts not only on the immune system but also on the adrenal tissue itself.

Whether 25(OH)D concentrations differ between patients with autoimmune Addison's disease and controls is not known and is currently under investigation. However, there is evidence of interaction between vitamin D status and predisposing gene loci, similar to findings in T1DM (34). In summary, preliminary evidence suggests that vitamin D may be important in the modification of genetic susceptibility in Addison's disease; however, much remains to be studied on its functional and clinical relevance in humans.

Vitamin D and Hashimoto's thyroiditis

Hashimoto's thyroiditis is predominantly a disease of cell-mediated immunity that is manifested by a genetic defect in suppressor T-cell function. Th1 cells secrete various cytokines, such as interferon (IFN)-γ, which induces thyrocytes to express major histocompatibility complex class II (MHC II) surface HLA-DR antigens and renders them susceptible to immunologic attack. Although HLA-DR antigens are not physiologically expressed on thyrocytes, in Hashimoto's thyroiditis, they are on the surface of thyrocytes, which may trigger the autoimmune process. Activated by T lymphocytes, B lymphocytes produce autoantibodies that react to thyroid antigens (4, 55, 56, 57).

In Hashimoto's thyroiditis, the autoimmune process may be suppressed at various stages by $1,25(OH)_2D$. At first, vitamin D might suppress dendritic cell-dependent T cell activation, then, it might decrease proliferation of Th1 cells and the synthesis of Th 1 cell cytokines such as IFNγ. Vitamin D may also inhibit the expression of MHC II surface HLA-DR antigens on thyrocytes by inhibiting the synthesis of IFNγ, which induces thyrocytes to express those antigens. Furthermore, after being activated by T cells, B cells' ongoing proliferation may be suppressed and B cell apoptosis may be induced by $1,25(OH)_2D$. In this way, vitamin D might decrease autoantibodies that react with thyroid antigens (4, 55, 56).

Recently, studies have suggested that low vitamin D concentrations and other conditions which may result in reduced vitamin D function (e.g. certain *VDR* gene polymorphism, pathologies of vitamin D-binding protein and its gene) may increase the risk of Hashimoto's thyroiditis (56, 58, 59, 60, 61, 62). However, additional data are needed to clarify whether there is a link between vitamin D status and Hashimoto's thyroiditis and whether vitamin D supplementation might reduce the risk of Hashimoto's thyroiditis.

Vitamin D and Graves' disease

Graves' disease is an autoimmune thyroid disorder in which TSH receptor autoantibodies cause hyperthyroidism. Given the increasing interest in the role of vitamin D role in determining susceptibility to autoimmune diseases, it has been hypothesized that Graves' disease may also be affected by vitamin D, based upon its ability to modulate the immune system by suppressing the proliferation of activated T cells and enhancing the phagocytic ability of macrophages (63, 64).

Polymorphism in the *VDR* gene and vitamin-binding protein gene has been reported to be associated with Graves' disease's etiology (65, 66), probably via a reduction in vitamin D function, which may have an inhibitory effect on regulatory steps within the immune system. The reported effects appear to differ markedly among different ethnicities, e.g. ApaI, BsmI and FokI polymorphisms in the *VDR* gene are associated with higher susceptibility to Graves' disease in Asian populations, but do not appear to play a role in the Caucasian population (67). Furthermore, Feng *et al.* (68) have recently reported that BsmI and TaqI polymorphisms are significantly associated with autoimmune thyroid disorder risk, while the ApaI or FokI polymorphisms are not.

Women with new-onset Graves' disease have decreased 25(OH)D concentration, which is also associated with thyroid volume measured by ultrasonography (69). Furthermore, it has been reported that 25(OH)D concentration is higher in patients who achieve remission compared with those who do not (70). The current evidence to support a role of vitamin D in Graves' disease is preliminary but is worth investigating further in observational and intervention studies.

Vitamin D and PCOS

Accumulating evidence from several studies suggest that vitamin D may be involved in several features of PCOS, such as infertility, hirsutism, insulin resistance, and cardiovascular risk (71, 72). Wehr *et al.* (72) reported that women with normal ovulation had higher vitamin D levels than women with PCOS. In addition, 25(OH)D deficiency was found to be associated with lower rates of follicle development and pregnancy after stimulation in PCOS women (73). Vitamin D supplementation may improve reproductive function in women with PCOS by restoring normal menstrual cycles (74, 75). Women with PCOS and hirsutism have lower 25(OH)D levels than BMI matched controls (72, 76), which may be explained by an association of vitamin D with androgens or SHBG (71, 77). Vitamin D deficiency seems to also have an impact on insulin sensitivity in PCOS women, as evaluated by HOMA-IR (71, 72, 75). However, a more accurate evaluation of insulin sensitivity by hyperinsulinemic euglycemic clamp in PCOS women did not confirm such an association (78). In addition to insulin resistance, vitamin D deficiency in PCOS women has been associated with cardiovascular risk factors, such as high total cholesterol, systolic and diastolic blood pressure, C-reactive proteins and triglycerides, and low HDL cholesterol (72). Small uncontrolled intervention studies of vitamin D supplementation in women with PCOS have shown improvements in fasting and stimulated glucose and dyslipidemia (triglycerides and HDL) (75, 79).

An inverse association between vitamin D status and metabolic and hormonal disturbances has been reported in PCOS. However, due to the variability of the PCOS phenotype and the heterogeneity of available studies, it is difficult to draw any conclusions. Ongoing randomized trials in well-defined populations will help in defining the role of vitamin D in PCOS (Table 1).

Limitations in the study of vitamin D

The inverse association between vitamin D status and endocrine disease in observational studies may be confounded by several factors. Most importantly, good vitamin D status is generally a marker of good health, as high 25(OH)D concentration is associated with young age, normal body weight, and a healthy lifestyle, including good dietary and exercise habits. Similarly, a low vitamin D status may reflect chronic illness, which prevents outdoor activities and sun exposure. Importantly, vitamin D is rarely ingested in isolation, more often, it is ingested as part of a specific food (e.g. milk), a food group (e.g. dairy), or as part of a health dietary pattern (e.g. Mediterranean diet). Therefore, additional nutrients co-ingested with vitamin D (e.g. fish or fortified dairy products) may have independent or synergistic effects on cardiometabolic disease or, alternatively, foods rich in vitamin D may replace other foods that increase risk of cardiometabolic disease (e.g. fortified milk replacing soda). Nearly all available observational studies used single measurements of blood 25(OH)D as a proxy of vitamin D status, which may not reflect vitamin D status over long periods as risk factors for vitamin D deficiency increase with time (aging, declining physical activity, etc.). Therefore, inaccurate assessment of the exposure (vitamin D status) and uncontrolled or residual confounding may explain the results of the observational studies, which needs to be confirmed in controlled trials. An additional challenge in the study of vitamin D is that there is no consensus on the 25(OH)D thresholds for vitamin D adequacy.

Conclusions

Several observational studies have reported an association of low 25(OH)D concentration with endocrine diseases. However, due to a paucity of intervention studies, a causal link between vitamin D deficiency and endocrine diseases is far from proven, thus no guidance can be provided for or against recommending vitamin D supplementation for prevention or therapy of endocrine conditions, outside of the current recommendations by the IOM for the general populations (600–800 IU/day depending on age and gender). Ongoing and future trials are expected to provide answers to whether vitamin D supplementation holds promise for endocrine health and disease.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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