Vitamin D as a potential contributor in endocrine health and disease

Giovanna Muscogiuri¹, Joanna Mitri², Chantal Mathieu³, Klaus Badenhoop⁴, Gonca Tamer⁵, Francesco Orio⁶,⁷, Teresa Mezza⁸, Reinhold Vieth⁹,¹⁰, Annamaria Colao¹, Anastassios Pittas²

1. Department of Clinical Medicine and Surgery, University “Federico II” Naples, Italy;
2. Division of Endocrinology, Diabetes and Metabolism, Tufts Medical Center, Boston, MA, USA;
3. Department of Endocrinology, UZ Gasthuisberg, 3000, Leuven, Belgium
4. Department of Medicine 1, Division Endocrinology & Diabetology, University Hospital of the Goethe-University Frankfurt, Frankfurt am Main, Germany
5. Division of Endocrinology and Metabolism, Department of Internal Medicine, Goztepe Training and Research Hospital, Medeniyet University, Istanbul, Turkey
6. Endocrinology, University “Parthenope” Naples, Naples, Italy;
7. Endocrinology of Fertile Age, University Hospital “S. Giovanni di Dio e Ruggi d’Aragona” Salerno, Italy
8. Endocrinology and Metabolic Diseases, Università Cattolica del Sacro Cuore, Roma, Italia
9. Department of Nutritional Sciences, University of Toronto, Toronto, Canada
10. Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

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Correspondence and reprint to: Giovanna Muscogiuri, MD - Via Sergio Pansini, 5 - 80131 Napoli – Italy; Tel. 0817464983; Fax 0815465443; e-mail: giovanna.muscogiuri@gmail.com.

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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, type 2 diabetes, autoimmune thyroid diseases, Addison’s disease, and polycystic ovary syndrome. 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 between not only blood 25-hydroxyvitamin D and parathyroid hormone concentrations but also with risk of type 1 diabetes, type 2 diabetes and polycystic ovary syndrome. 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 type 2 diabetes, 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 insight into the efficacy and safety of vitamin D in the management of endocrine disease.
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 non-skeletal 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 has 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 conditions, including primary hyperparathyroidism, type 1 diabetes (1), type 2 diabetes (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 \([D_3]\)), from diet (in the form of \([D_3]\)) and from nutritional supplements in the form of \([D_3]\) or ergocalciferol \([D_2]\) (6). Upon exposure to ultraviolet 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 \((25(OH)D_2 \text{ or } 25(OH)D_3)\), its major circulating form, which has little biological activity. 25(OH)D is converted in the kidney by 25(OH)D-1alpha-hydroxylase (CYP27B1), to its bioactive hormonal metabolite 1,25 dihydroxy-vitamin D \((1,25(OH)_2D \text{ or calcitriol})\). The primary action of 1,25(OH)_2D is through the nuclear vitamin D receptor, 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 vitamin D receptor 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 25OHD is the biomarker used by clinicians and researchers to determine vitamin D status. However, there is no consensus on the 25OHD 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 25OHD > 20 ng/mL is consistent with favourable 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 25OHD > 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 25OHD 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 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 25OHD consistently above 30 ng/mL, intakes of 1500 to 2000 IU/day are required. The IOM report recognized the lack of trials with vitamin D supplementation for non-skeletal 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 25OHD
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)\(_2\)D. Parathyroid hormone is the major stimulator of renal CYP27B1, which increases biosynthesis of 1,25(OH)\(_2\)D. In turn, PTH is down-regulated both by 1,25(OH)\(_2\)D 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)\(_2\)D for local paracrine regulation. The combined effect of efficient access to circulating 25(OH)D and 1,25(OH)\(_2\)D plus the local production of 1,25(OH)\(_2\)D is suppression of both PTH secretion and parathyroid cell proliferation (11).

Larger parathyroid adenomas respond poorly to feedback by calcium or 1,25(OH)\(_2\)D; consequently, in primary hyperparathyroidism, 1,25(OH)\(_2\)D 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)\(_2\)D 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]\(_2\)D) 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)\(_2\)D 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 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 type 1 diabetes (T1DM)**

Type 1 diabetes is one of the first endocrine disorders where a potential role for vitamin D was reported. Type 1 diabetes is characterized by an autoimmune destruction of the insulin producing pancreatic islet beta-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, but also dysfunction of the beta-cell itself (16). Caution, however, is warranted when postulating a direct effect of vitamin D deficiency on immune or beta-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 non obese 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 vitamin D receptor 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 beta-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 onwards lowers incidence of T1DM (21, 22), highlighting vitamin D as a promising intervention in preventing 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 analogues 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 analogues can prevent progression of the disease (24,25), which has been postulated to be due to the direct beta-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 analogue 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 analogue) -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 immune system from attack towards tolerance towards the beta-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 to controls. An increased prevalence of vitamin D deficiency in children and adolescents with T1DM compared with non-diabetic 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 type 1 diabetes risk islet autoimmunity risk (36,37).

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 (38,39). 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 towards an inverse association (40). 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 offspring of T1DM parents at 1 year, but not at 2.5 years (41). 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)₂D₃ was safe but failed to reduce loss of beta-cell function, even in patients with high C-peptide at diagnosis (42).

In summary, based on observational studies, vitamin D deficiency (defined as 25OHD < 12 ng/mL) should probably be avoided in individuals at high risk for 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 (Table 2).

**Vitamin D and Type 2 Diabetes (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 vitamin D receptors in the pancreatic beta cells. Vitamin D receptor is expressed in pancreatic cells and mice lacking vitamin D receptor have impaired insulin secretion (43). 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 (44). Importantly, pancreatic beta 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 non-cytokine related immune-modulating effects (45). Finally, insulin secretion and insulin sensitivity are both calcium dependent processes (46,47); 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 were
published with nearly identical results. Song et al. reported a 38% lower risk of developing
T2DM in the highest reference category of 25OHD compared to the lowest one (relative risk
0.62 [95% CI 0.54-0.70] (48) while Afzal et al. (49) reported an odds ratio for T2DM of 1.5
(95% CI 1.33-1.70) for the bottom versus top reference category of 25OHD.

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 D₃ did not
change the risk of self-reported type 2 diabetes, there was a notable trend towards reduction in
T2DM risk with vitamin D₃ (odds ratio 0.68; 95% CI 0.40-1.16) among study participants
who were highly compliant with supplementation (50).

Vitamin D supplementation appears to be more promising in patients who are at risk for
diabetes. In the Calcium and Vitamin D for type 2 Diabetes Mellitus (CaDDM) study, a 2x2
factorial design trial in participants with pre-diabetes, vitamin D supplementation improved
disposition index, a measure of beta cell function (51). 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 (52).

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], Table 2) 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 (53). Although the main genetic susceptibility is
identified at the HLA locus (54), other susceptibility genes have been described, including in
the vitamin D receptor (VDR) (55) and CYP27B1 (56,57), 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 since active 1,25(OH)2D may suppress
steroidogenesis by down-regulating CYP21A2 and up-regulating CYP11A1 and CYP17A1.
In an adrenal cell model (NCI-H295R line) (58), 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 modifying 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, the thyrocytes present HLA-DR antigens on their surface, which may trigger autoimmune process. Activated by T lymphocytes, B lymphocytes produce autoantibodies that react to thyroid antigens.

In Hashimoto’s thyroiditis, the autoimmune process may be suppressed at various stages by 1,25(OH)_{2}D. At first, vitamin D might suppress dendritic cell-dependent T cell activation, then, it might decrease proliferation of Th1 cells and the synthesis of Th1 cell cytokines such as IFN-γ. Vitamin D may also inhibit expression of MHC II surface HLA-DR antigens on thyrocytes by inhibiting the synthesis of IFN-γ, 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)_{2}D. In this way, vitamin D might decrease autoantibodies that react with thyroid antigens.

Recently, studies have suggested that low vitamin D concentrations and other conditions which may result with reduced vitamin D function (e.g., certain VDR gene polymorphism, pathologies of vitamin D binding protein and its gene) may increase risk of Hashimoto’s thyroiditis. 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.

Polymorphism in the VDR gene and vitamin binding protein gene have been reported to be associated to Graves’ disease’s etiology 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 Caucasian population (72). Further, Feng et al. (73), 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 (74). Furthermore, it has been reported that 25(OH)D concentration is higher in patients who achieve remission compared to those who do not (75). 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 polycystic ovary syndrome (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 (76,77). Wehr et al reported that women with normal ovulation had higher vitamin D levels than women with PCOS (77). In addition, 25(OH)D deficiency was found to be associated with lower rates of follicle development and pregnancy after stimulation in PCOS women (78). Vitamin D supplementation may improve reproductive function in women with PCOS by restoring normal menstrual cycles (79,80). Women with PCOS and hirsutism have lower 25(OH)D levels than BMI matched controls (77, 81), which may be explained by an association of vitamin D with androgens or SHBG (82,83). Vitamin D deficiency seems to also have an impact on insulin sensitivity in PCOS women, as evaluated by HOMA-IR (76,77,80). However, a more accurate evaluation of insulin sensitivity by hyperinsulinemic euglycemic clamp in PCOS women did not confirm such an association (84). 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 (77). 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) (80,85).

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 define 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 lower 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 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 Institute of Medicine for the general populations (600 to 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.
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References


8. Dietary Reference Intakes for Calcium and Vitamin D –Institute of Medicine of National Academies – November 30 2010


15. Atkinson MA. The Pathogenesis and Natural History of Type 1 Diabetes Cold Spring Harb Perspect Med. 2012 2(11)


27. Nikolic T, Roep BO. Regulatory multitasking of tolerogenic dendritic cells - lessons taken from vitamin d3-treated tolerogenic dendritic cells. *Front Immunol*. 2013**14**:4:113


47. Wright DC, Hucker KA, Holloszy JO, Han DH. Ca2+ and AMPK both mediate stimulation of glucose transport by muscle contractions. *Diabetes* 2004 53: 330-335.


51. Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in
adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr* 2011 **94**: 486-94

52. Davidson MB, Duran P, Lee ML, Friedman TC  High-Dose Vitamin D Supplementation in People With Prediabetes and Hypovitaminosis D. *Diabetes Care* 2013 **36**(2):260-6


82. Yildizhan R, Kuroglu M, Adali E, Kolusari A, Yildizhan B, Sahin HG, Kamaci M
   Serum 25-hydroxyvitamin D concentrations in obese and non-obese women with
   polycystic ovary syndrome. *Arch Gynecol Obstet*. 2009 280(4):559-63

83. Hahn S, Haselhorst U, Tan S, Quadbeck B, Schmidt M, Roesler S, Kimmig R, Mann
   K, Janssen OE. Low serum 25-hydroxyvitamin D concentrations are associated with
   insulin resistance and obesity in women with polycystic ovary syndrome. *Exp Clin

   S, Pontecorvi A, Giaccari A 2012 Low levels of 25(OH)D and insulin-resistance: 2

85. Kotsa, K., Yavropoulou, M.P., Anastasiou, O. Yovos JG Role of vitamin D treatment
   in glucose metabolism in polycystic ovary syndrome. *Fertility and Sterility*, 2009 92
   (3): 1053–1058
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<td>Polycystic ovarian syndrome</td>
<td>Improvement in insulinsensitivity, cardiovascular risk factors and reproductive function</td>
<td>✓✓✓</td>
<td>• NCT00907153: Vitamin D for the Treatment of Women With Polycystic Ovary Syndrome (PCOS)</td>
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<td>• NCT0743574: Health Benefits of Vitamin D and Calcium in Women With PCOS (Polycystic Ovarian Syndrome)</td>
<td></td>
</tr>
</tbody>
</table>


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