Vitamin D Correlation with Hypertension and Diabetes Mellitus

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Abstract

Background: The correct determination of volume status is a fundamental component of clinical evaluation as both hypovolaemia (with hypoperfusion) and hypervolaemia (with fluid overload) increase morbidity and mortality in critically ill patients. As inferior vena cava (IVC) accounts for two-thirds of systemic venous return, it has been proposed as a marker of volaemic status by indirect assessment of central venous pressure or fluid responsiveness. Although ultrasonographic evaluation of IVC is relatively easy to perform, correct interpretation of the results may not be that simple and multiple pitfalls hamper its wider application in the clinical setting. In the present review, the basic elements of the pathophysiology of IVC behaviour, potential applications and limitations of its evaluation are discussed.

Keywords: Inferior Vena Cava, Ultrasonography, Volume Status

Introduction

Observational reports have noted higher blood pressure trends in winter months and locations further from the equator, suggesting that low ultraviolet radiation and thus decreased capacity for cutaneous vitamin D synthesis are associated with hypertension. The most notable mechanism implicating vitamin D with hypertension is its role as a negative regulator of the RAS other notable hypotheses have suggested that vitamin D influences vascular endothelial function or vascular smooth muscle intracellular calcium concentrations **(1).**

Because inappropriately elevated activity of the RAS contributes to hypertension and cardiovascular risk, many observational and interventional studies have focused on investigating the role of vitamin D metabolites in the development of hypertension. The most convincing mechanistic studies linking vitamin D with RAS activity and blood pressure regulation were conducted in animal models. **Li et al. (2)** showed that VDR knockout (KO) mice had significant elevations in renin activity and circulating plasma angiotensin II concentrations **(3).** These mice developed hypertension and cardiac hypertrophy that could be attenuated with the administration of RAS antagonist pharmacotherapy, and also exhibited increased activity of the local cardiac tissue RAS **(4)**.

In parallel, a mouse model of 1α-hydroxylase deficiency (inability to synthesize 1,25[OH]2D) also exhibited a phenotype of enhanced RAS activity, hypertension, and cardiac hypertrophy that was attenuated with the administration of 1,25(OH)2D or RAS antagonists **(5).**

Corollary human physiology studies have shown that lower levels of 1,25(OH)2D and 25(OH)D are associated with higher plasma renin activity, higher angiotensin II concentrations, and higher systemic vascular-tissue RAS activity. Most human clinical studies evaluating the role of vitamin D on blood pressure have been cross-sectional analyses. The majority of these yielded results that were consistent with the animal data in showing an inverse association between vitamin D and blood pressure or prevalent hypertension. In contrast, at least 2 cross-sectional studies demonstrated no detectable association between vitamin D and blood pressure or the prevalence of hypertension; however, in addition to the traditional limitations of cross-sectional analyses, these conflicting results may have been confounded by comparatively high 25(OH)D concentrations and prevalent use of antihypertensive medications that could obscure potential associations **(6).**

Longitudinal and prospective studies evaluating 25(OH)D levels have similarly shed mixed results. In a prospective longitudinal analysis of 613 men from the Health Professionals' Follow Up Study and 1198 women from the Nurses'

Health Study followed for 4 to 8 years, **Forman et al. (7)** observed a pooled adjusted relative risk for incident hypertension of 3.18 (95% confidence interval [CI], 1.39-7.29) in individuals with lower (<15 ng/mL) vs higher (30 ng/mL) concentrations of 25(OH)D. The same authors subsequently performed a nested case-control analysis with normotensive women from the Nurses' Health Study and observed an adjusted odds ratio for incident hypertension of 1.66 (P trend = .01) when comparing thosewith 25(OH)D levels in the lowest vs highest quartiles

In the longitudinal Michigan Bone Health and Metabolism Study, **Griffin et al. (8)** evaluated the risk for systolic hypertension over 14 years in 559 white women who had 25(OH)D and blood pressure measures in 1993 and again in 2007. Although they observed no cross-sectional association between 25(OH)D concentrations and concurrent blood pressure in 1993, 25(OH)D concentrations of less than 32 ng/mL in 1993 were significantly associated with an increased risk for systolic hypertension in 2007 (adjusted odds ratio, 3.0; 95% CI, 1.01-8.7). In contrast, **Jorde et al. (9)** reported conflicting observations from the Tromso study that followed individuals for 14 years (1994-2008) who were naive to antihypertensive therapy. Although an inverse cross-sectional association between systolic blood pressure and quartiles of 25(OH)D was noted at baseline in 1994, 25(OH)D concentrations from 1994 did not predict incident hypertension or future blood pressure.

Interventional studies evaluating controlled ultraviolet exposure have also shown mixed results; **Krause et al. (10)** observed mild blood pressure reductions in untreated hypertensives, whereas **Scragg et al. (11)** observed no change in a largely normotensive population. Both of these studies were well designed, with significant increases in 25(OH)D levels following ultraviolet therapy; however, they may have been limited by durations of follow-up that were too short to detect pathological changes in arterial function (6 and 12 weeks, respectively) and by relatively small sample sizes.

The majority of interventional studies did not find a significant relationship between vitamin D supplementation and blood pressure or incident hypertension. The largest of these studies was the Women's Health Initiative (n = 36 282), designed to evaluate whether 400 IU of daily vitamin D3 with calcium supplementation reduced fracture and cancer risk when compared with placebo in a population of largely vitamin D–insufficient women. After 7 years of follow-up, no change in blood pressure or incident hypertension was observed. The interpretation of these results was limited by modest vitamin D3 supplementation in the intervention arm and a high rate of non–study-related vitamin D supplementation in the placebo group **(12).**

The second largest of these studies (n = 438) was designed to evaluate the effect of vitamin D3 supplementation on weight loss and included overweight and obese individuals, but did not exclude the use of antihypertensive medications. After 1 year of randomization to vitamin D3 40 000 or 20 000 IU/wk or to placebo, no change in blood pressure was observed. Because 25(OH)D levels in this study rose from a baseline of less than 30 ng/mL to greater than 50 ng/mL in the 40 000-IU/wk group, these data argued that reasonable elevations in 25(OH)D did not influence blood pressure. On the other hand, whether a 1-year follow-up was sufficient to detect blood pressure outcomes or whether a largely obese population with heterogeneous antihypertensive medication use was the ideal study population is debatable **(9)**

Witham et al. (13) were able to detect a blood pressure–lowering effect associated only when limiting their analyses to those studies that focused on hypertensive individuals, whereas **Pittas et al. (14)** were able to detect effects using studies with higher doses of vitamin D3 supplementation (>1000 IU/d). The meta-analysis by **Burgaz et al. (15)** detected a reduced odds of hypertension when comparing the highest category of 25(OH)D concentration to the lowest (odds ratio, 0.73; 95% CI, 0.63-0.84).

In contrast, **Elamin et al. (16)** detected no blood pressure–lowering effect in a meta-analysis evaluating cardiovascular outcomes. The Vitamin D and Omega-3 Trial (VITAL) (NCT 01169259) is a large randomized controlled trial (n = 20 000) in the United States that opened for recruitment in late 2010 and aims to evaluate the impact of vitamin D3 supplementation (2000 IU/d) on cardiovascular and cancer outcomes over 5 years. The size, duration of follow-up and higher vitamin D3 doses in this study design may allow sufficient power and effect size to examine the influence of long-term vitamin D3 supplementation on blood pressure.

Vitamin D and the pancreatic β cells, insulin secretion and sensitivity

T1DM is a chronic autoimmune disease that destroys pancreatic β cells, causing insulin insufficiency. One of the potentially important environmental factors underlie the development of T1DM is vitamin D. Vitamin D plays a protective role by regulating components of the immune system and regulating calcium homeostasis, which is important for immune function and insulin secretion **.** In vitro studies have suggested that the active form of vitamin D [1,25(OH)2D3] protects β cells against proinflammatory cytokines and chronic inflammation, which are involved in cellular stress and apoptosis. 1,25(OH)2D3, or its analogues, can inhibit lymphocyte and macrophage activation, abolish CD4+ expression by inhibiting interleukin 2 and interferon γ, and reduce expression of major

histocompatibility complex class II molecules. Administering high-dose 1,25(OH)2D3 (5 μg/kg of body weight on alternating days) from early life suppressed insulitis and reduced incidence of T1DM in NOD mice **(17)**.

An increasing number of epidemiological studies have associated low serum 25(OH)D levels with several autoimmune diseases. In particular, It Was demonstrated that children with multiple islet autoantibodies (pre-T1DM state) and children newly diagnosed with T1DM have lower 25(OH)D levels than children with negative autoantibodies. The authors showed that 25(OH)D serum levels in childhood were not associated with progression to T1DM.

Animal and in vitro studies provide compelling evidence that vitamin D may play a functional role in the preservation of glucose tolerance through its effects on insulin secretion and insulin sensitivity. Vitamin D deficient rabbits and mice present with impaired insulin secretion, and supplementation with vitamin D corrected the defect. In T2DM, several mechanisms could also explain the link between vitamin D and the risk of development T2DM. Indeed, vitamin D could influence β-cell function, insulin sensitivity, and systematic inflammation, all pathways that characterized T2DM. Moreover, numerous studies showed the expression of VDRs in pancreatic β-cells and in all insulin-responsive tissues **(18)**

Vitamin D may decrease systemic inflammation, which plays an important role in the pathogenesis of T2DM. In particular, vitamin D protects β cells from apoptosis and cytokine-induced insulin resistance by modulating the expression and activation of cytokines and inhibiting activation of NF-κB **(19).**

Pittas et al. (14) have summarized the biological evidence implicating a potential influence of vitamin D on glucose homeostasis. The inferences for the manifold roles of vitamin D include the presence of specific vitamin D receptors (VDRs) on pancreatic beta cells, the expression of 1α-hydroxylase enzyme in pancreatic beta cells which catalyzes the conversion of 25(OH)D to 1, 25-dihydroxyvitamin D, the presence of a vitamin D response element in the human insulin gene promoter, and the presence of VDR in skeletal muscle. In addition, directly activates transcription of the human insulin receptor gene, activates peroxisome proliferator activator receptor-, stimulates the expression of insulin receptor, and enhances insulin-mediated glucose transport in vitro.

Vitamin D may directly affect β-cell function via 1,25(OH)D binding to vitamin D receptors in β-cells and it may also have an indirect effect on calcium dependant insulin secretion through the regulation of calcium transport through the β-cells. It is now recognised that there are vitamin D receptors in the pancreatic β–cells and vitamin D dependant calcium binding proteins in pancreatic tissues**.** Consequently one of the major mechanisms facilitating the effect of vitamin D on insulin synthesis and secretion could involve the β–cell calcium dependant endopeptidases producing the cleavage that enables the conversion of proinsulin to insulin **(20)**

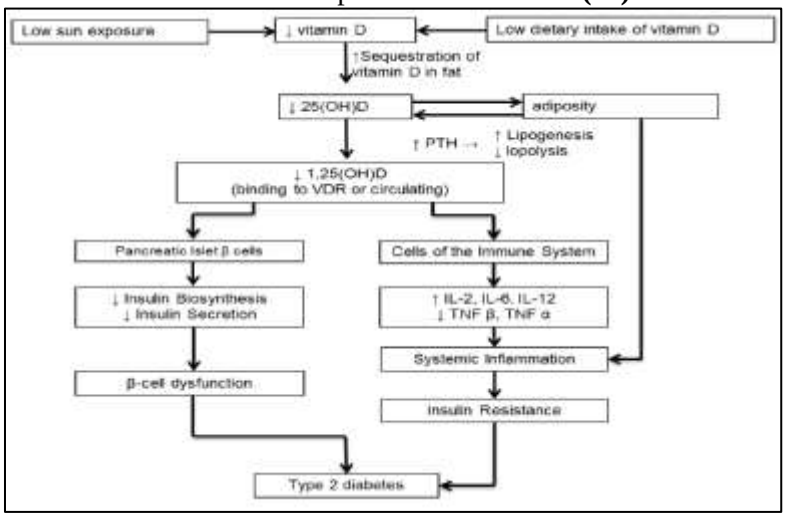

Figure 1: Hypothesized mechanisms underlying the interrelationships among vitamin D deficiency, insulin homeostasis and T2D (21).

1,25(OH)2D3 could direct stimulate insulin secretion because of the presence of VDRE, the vitamin D response element, in the insulin gene promoter of pancreatic β-cell. VDRE activates the transcription of insulin gene and of several other genes involved in cellular growth, cytoskeletar organization and intracellular junctions of β-cell. Therefore the expression of 1-α-hydroxylase in β cells generates a locally production of 1,25(OH)2D3, which creates a paracrine effect. Increased insulin secretion after vitamin D supplementation was shown in both in vitro and in vivo studies. A study on vitamin D–deficient rats showed a reduction of 48% in insulin secretion after 30 minutes of perfusion with glucose and arginine compared with rats supplemented with vitamin D before the procedure **(22).**

Therefore, an in vivo study showed that mice lacking VDR had impaired insulin secretion. Human studies demonstrated an increase of insulin secretion during OGTT (oral glucose tolerance test) in diabetic patients and in patients at high risk to development diabetes after administration of vitamin D. In contrast, It Was found an increase only in the first phase of insulin secretion during intravenous glucose tolerance test in diabetic women after supplementation of cholecalciferol for one month; no change was found in the second phase of insulin secretion. The major weakness of these clinical studies were the small cohort of evaluated patients and the short time of vitamin D treatment. **(22).**

A study on a larger cohort of patients with T2DM and deficiency level of 25(OH)D did not showed a correlation among overnight fast glucose, insulin and 25(OH)D level. However, the authors did not perform any stimulation test to assess a better evaluation of insulin secretion and did not implement vitamin D treatment. 1,25(OH)2D3 could activate the PKA that mediates the phosphorylation of different proteins, including the L-type voltage-dependent calcium channels and proteins necessary for the exocytotic mechanism, thus increasing the insulin secretion **(23)**.

Moreover, 1,25(OH)2D3 could activate phospholipase C (PLC), which cleaves phosphoinositides into inositol 1,4,5-trisphosphate (IP3), involved in calcium release from the endoplasmic reticulum, and diacylglycerol (DAG) that mediates the activation of the PKC. The activated PKC phosphorylates the KATP channels and the L-type voltage-dependent calcium channels. The activation of the KATP channels causes the depolarization of the cytoplasmatic membrane, which opens the T-type and the L-type voltage-dependent calcium channels resulting in an increase of the intracellular calcium level. The PKC also mobilizes the secretory vesicles that, together with the increase of calcium level, promotes insulin secretion**.** The increased calcium concentration causes the secretory response of insulin through the activation of calcium-calmodulin-dependent protein kinase II (CaMKII), a protein localized at the insulin secretory granules, which promotes the phosphorylation of several proteins involved in the mobilization and in the exocytosis of insulin granules. It has been suggested that the raised intracellular calcium level activates also the insulin gene expression via CREB (Calcium Responsive Element Binding protein) **(24).**

Furthermore, 1,25(OH)2D3 also regulates the expression of calbindin-D28k, a cytosolic calcium-binding protein expressed by β cells that stimulates insulin secretion by regulating intracellular calcium mobilization. An in vitro study showed that in calbindin- D28k transfected pancreatic β-cells, calbindin inhibited the free radical formation induced by cytokines and protected β-cells against degeneration. Insulin resistance is increased by systemic inflammation, and T2D and obesity are conditions of increased inflammatory reaction. In addition to effects on pancreatic β-cells, 1,25(OH)2D3 may target insulin-responsive tissues, such as liver, skeletal muscle and adipose tissue. Several studies associate vitamin D deficiency and insulin resistance **(20),** a condition in which peripheral tissues fail to respond to ordinary levels of circulating insulin to maintain normal glucose homeostasis. Vitamin D may directly influence insulin sensitivity by stimulating expression of insulin receptors (IRs) on target tissues **(25)**.

Through its immunomodulatory and anti-inflammatory effects, it is suggested that vitamin D may reduce the insulin resistance in these conditions. Both 1,25(OH)2D and its less calcemic analog 1,24(OH)2D have been shown to suppress TNFα expression in macrophages by increasing IkBα and decreasing NFkB activity. Contrasting data has been showed regarding the stimulation of IRs by vitamin D in the liver. It Was demonstrated an increased IRs expression in the liver of streptozotocin-induced diabetic rats after vitamin D supplementation. On the contrary, different studies in streptozotocin-induced diabetic rats and in mice model fed on a high-fat diet or low-fat diet did not found any alteration in liver expression of IRs after vitamin D treatment. **(25)**.

Several evidence supported that vitamin D plays an important role in skeletal muscle function. In VDR knockout (VDRKO) mice, the absence of the VDR is associated with atrophy fibers, poor musculoskeletal performance in behavioral tests, and marked changes in gait **(26).**

The activation of PPARδ by 1,25(OH)2D3 improve the free fatty acid-induced insulin resistance in skeletal muscle. Indirectly, vitamin D could decrease insulin resistance in skeletal muscle through the regulation of cellular calcium concentration. The increased calcium level in muscle cells enhanced the recruitment of Glucose transporter type 4 (GLUT4) to the cell membrane. However, in a recent study in mice fed on a high-fat diet or low-fat diet, the authors did not find any differences in IRs and GLUT4 gene expression after supplementation with vitamin D also in liver, muscle and adipose tissue **(27)**.

An important mechanism of action of 1,25(OH)2D3 in adipose tissues is the reduction of inflammation and the change of adipokine secretion, with a decrease of IL6, IL1β and TNFα. 1,25(OH)2D3 could also enhance insulin resistance through the inhibition of the renin-angiotensin-aldosterone system (RAAS), which is a well-known inhibitor of insulin action in peripheral tissues. Mice with mutations in the VDR have impaired insulin secretion and lower glucose tolerance than those with functional receptors. In vitro, induces the biosynthesis of insulin in rat pancreatic islet cells, and in another study, inhibited free fatty acid-induced insulin resistance (i.e., improved glucose

uptake) in cultured myocytes in a dose-dependent manner. The insulin sensitizing effects were mediated by a reduction in JNK activation **(5).**

Although the skeletal effects of vitamin D occur via an endocrine mechanism, there may be an autocrine/paracrine role of vitamin D in insulin target tissues. Pancreatic cells express the vitamin D receptor (VDR) as well as the pivotal enzyme 1α-hydroxylase. VDR is also expressed by both human skeletal muscle and adipose tissue, which are the main determinants of peripheral insulin sensitivity. These tissues were shown to express the 1α-hydroxylase gene in male Wistar rats **(2).**

Vitamin D deficiency may influence its effects on insulin secretion and sensitivity via its effects on intracellular calcium **(14).** Elevated intracellular calcium impairs postreceptor binding insulin action, such as the dephosphorylation of glycogen synthase and of insulin regulatable glucose transporter (GLUT-4) **(28).**

Vitamin D deficiency results in elevated parathyroid hormone (PTH), which in turn is known to elevate intracellular calcium. Sustained elevations of intracellular calcium may inhibit insulin-target cells from sensing the brisk intracellular calcium fluxes necessary for insulin action, such as glucose transport. Pancreatic beta cells also depend on an acute intracellular calcium increase for insulin secretion, which may also be attenuated with elevated cytosolic calcium **(29).**

Another possible mechanism is that elevated intracellular calcium enhances calmodulin binding to insulin receptor substrate-1 (IRS-1), which interferes with insulin-stimulated tyrosine phosphorylation and PI3-kinase activation **(2).** Indeed, PTH has been shown to be inversely associated with insulin sensitivity **(29).**

On the other hand, **Kamycheva et al. (30)** did not find significant differences in insulin or glucose metabolism in subjects with secondary hyperparathyroidism versus controls. Nevertheless, dichotomization based on serum 25(OH)D concentrations appeared to determine differences in insulin sensitivity. It is arguable that the insulin resistance seen in vitamin D deficient subjects is not fully explained by these aforementioned molecular mechanisms alone.

A number of cross sectional studies have shown inverse associations between serum 25(OH)D concentrations and the presence of T2D or measurements of glycaemia in a variety of different populations **(20)**

Evidence for vitamin D link with insulin resistance

Several trials have demonstrated an association between deficiency of vitamin D with increasing body mass index. One of those was a population trial from Norway with data from 10229 subjects, revealing an inverse association of 25(OH)D concentrations with BMI which was not only seen in summer, but also in winter months. So levels of 25(OH)D may change in seasons, but not body mass index **(9)**

Targher et al. (31) also observed lower 25(OH)D concentrations in participants with T2D when compared with controls (390 per group). However, **Liu et al. (32)** has also observed an inverse association with fasting glucose and fasting measures of insulin resistance (HOMA-IR) in a healthy population. A positive correlation has also been reported between 25(OH)D concentration and insulin sensitivity in 126 glucose tolerant subjects living in California **(32)**

In a study of adults from North America by **Devaraj et al. (33)**, prediabetic state (state of a fasting plasma glucose concentration of 6.1-6.9 mmol/L, a 2 h glucose concentration of 7.8-11 mmol/L, or glycosylated hemoglobin of 5.7%-6.4%), a form of insulin resistance presentation, was noted to be associated with serum 25(OH)D in the first quartile in comparison with the fourth quartile in association with an adjusted odds ratio of 1.47. The same study showed that in patients with metabolic syndrome, concentration of 25(OH)D was negatively associated with fasting glucose and homeostasis insulin resistance model of assessment.

Improvement in 25(OH)D status in T2DM patients was shown to be linked to some improvements in insulin sensitivity **(20)**, but still, other parameters of insulin resistance like obesity did not change significantly with vitamin D supplementations in other studies. The data from the Norwegian study (The Tromsø study), also included an intervention arm where 93 subjects of varying BMI values received vitamin D at 40000 IU weekly for a year. At the end of trial, increased vitamin D_3 doses were not associated with significant decrease in weight. The intervention showed that individuals with obesity needed bigger vitamin D doses than lean ones to achieve similar concentration of 25(OH)D **(9)**

A similar outcome to this was demonstrated in another study by **Lee et al. (34)**. At the end of the trial with non-significantly different 25(OH)D values at baselines and vitamin D treatment doses, subjects with higher BMIs had lower concentrations of 25(OH)D compared with those of lower BMIs indicating that possibly body composition and insulin resistance in higher BMI subjects have a regulatory influence on vitamin D absorption, metabolism and/or storage.

The negative association between body weight, together with evidence of increased adiposity and low adiponectin levels, and low 25(OH)D concentrations also were shown in different age groups including both children and adolescents. Deficiency of vitamin D was prevalent in young Norwegian subjects, African-American adolescents, in both black and Caucasian youth and tropical locations like Malaysia and Colombia **(35)**.

Vitamin D and diabetes

Vitamin D has been associated with β-cell function, peripheral insulin sensitivity, incident diabetes, and mortality in diabetes. However, definitive human clinical trial evidence to support vitamin D supplementation in improving glycemic control or delaying the onset of diabetes is lacking and is further hampered by inconsistent findings in human studies with limited study designs. As in the case of hypertension and kidney disease, one of the main putative mechanisms linking vitamin D to glucose control is its regulation of the RAS. The intrapancreatic and circulating RAS are known to negatively affect β-cell function and peripheral insulin sensitivity; it is speculated that the downregulation of the RAS by vitamin D may mediate its beneficial effects on glycemic control and diabetes. Experimental evidence highlights mechanisms by which vitamin D may influence glycemic control. These mechanisms include modulation of pancreatic RAAS activity and regulation of calcium ion traffic across β-cells that directly affect insulin synthesis and secretion. Furthermore, vitamin D deficiency results in aberrant immune responses that precipitate an inflammatory milieu and subsequent insulin resistance. However, discrepancies in experimental and clinical evidence underscore knowledge gaps in determining the relationship between vitamin D metabolism and glycemic control **(36).**

For example, although human adipocytes express membrane-bound VDR that modulates lipolysis and lipogenesis activity in vitro, VDR-null murine models exhibit a lean phenotype and increased energy expenditure, which are associated with adipose tissue atrophy. Furthermore, models heterozygous for VDR show a similar, albeit less severe phenotype. Alternatively, the increased adiposity and body fat mass observed in most insulin-resistant subjects may partly account for the lower 25-OH D levels seen in this population because lipid-soluble vitamin D may be sequestered in adipose tissue, thus decreasing 25-OH D bioavailability **(37).**

Observational, case control, and prospective evidence strongly suggests that supplementing infants with vitamin D may significantly reduce the future incidence of type 1 DM. Dosage and timing of therapy appear to modulate these protective effects. The evidence for type 2 DM is weaker. Results from the Women's Health Initiative (WHI), in which 33,591 post-menopausal women were randomized to both daily calcium and cholecalciferol (1 g and 400 IU, respectively) or placebo, demonstrated no primary prevention benefit of vitamin therapy in 2,291 incident cases of DM after 7 years of follow-up. Although the effect of supplementation on 25-OH D level was not reported in the WHI, this was estimated to be ~2 ng/ml, given the dosage used and reported compliance, which is thought to be of little clinical consequence. Nevertheless, participants with impaired fasting glucose at baseline showed attenuated progression of insulin resistance with vitamin D supplementation on subgroup analysis when compared with those subjects with normal glucose tolerance **(14).**

Other major limitations of the WHI study include study subjects' enrollment in additional dietary and hormonal interventions, dose of vitamin D administered, inclusion of subjects already taking vitamin D supplements, and the exclusion of men. Overall, although some smaller and nonrandomized clinical trials show promising improvements in glycemic control with vitamin D therapy in select patient populations (i.e., women with polycystic ovary syndrome or gestational diabetes), systematic reviews and meta-analyses of available randomized data demonstrate no beneficial effects of vitamin D supplementation on indexes of glucose metabolism. This finding is echoed in an Endocrine Society statement emphasizing the lack of solid evidence supporting benefits of vitamin D therapy in DM **(36).**

Cheng et al. (38) observed increased pancreatic islet RAS expression in VDR-KO mice. Furthermore, other investigation has shown that, in the presence of 1,25(OH)2D, islet cells from wild-type mice demonstrate attenuated local RAS production and improved insulin secretion. Together, these findings suggest that antagonism of the local pancreatic islet RAS may improve β-cell function and mass, and that VDR agonists may improve insulin secretion via negative regulation of renin expression **(38).**

The EUROpe and DIABetes (EURODIAB) EURODIAB case-control study found that vitamin D supplementation in infancy (by historical questionnaire) reduced the odds of developing type 1 diabetes mellitus (adjusted odds ratio, 0.67; 95% CI, 0.53-0.86). Similarly, in a Finnish birth cohort (n = 12 231) that was followed until age 30 years, infants who received the recommended vitamin D3 2000 IU/d during the first year of life had a relative risk of 0.22 (95% CI, 0.05-0.89) for developing type 1 diabetes mellitus when compared with those who received less. In contrast, longitudinal analyses in the Diabetes Autoimmunity Study in the Young study found no association between 25(OH)D levels or vitamin D intake with islet autoimmunity or progression to type 1 diabetes in 2644 children **(39).**

To date, large-scale prospective studies evaluating the effect of vitamin D therapy on the incidence of type 1 diabetes have not been performed. Cross-sectional studies evaluating type 2 diabetes mellitus have also provided inconclusive

results. **Scragg et al. (11)** evaluated more than 6000 individuals from the National Health and Nutrition Examination Survey and found that lowest-quartile 25(OH)D levels were associated with a diagnosis of diabetes by fasting blood glucose when compared with those in the highest quartile; however, this observation was only seen when excluding non-Hispanic blacks (n= 1736). Other analyses of large cohorts have demonstrated significant inverse associations between vitamin D metabolites and glycated hemoglobin, the prevalence of diabetes, and the 5-year incidence of developing diabetes **(40).**

Muscogiuri et al. (18) reported perhaps the strongest negative human mechanistic evidence to date. In 39 nondiabetic individuals who underwent hyperinsulinemic-euglycemic clamp, 25(OH)D concentrations were not associated with peripheral insulin sensitivity after adjustment for notable confounders, such as body mass index. This study highlights one of the 2 major confounders when evaluating for a true causal relationship between vitamin D and diabetes. The first is that body mass index is a critical predictor of both 25(OH)D and diabetes; thus, it may bias analyses toward rejecting the null hypothesis. The second is that dietary sodium intake acutely modifies insulin sensitivity and activity of the RAS (a putative mediator of the relationship between vitamin D and diabetes). **(40).**

Prospective and longitudinal studies have shed mixed results. In a Finnish cohort study following more than 4000 nondiabetic patients for 17 years, It WAs encountered 187 new cases of type 2 diabetes mellitus. Although the relative risk for developing diabetes between the highest and lowest quartile of 25(OH)D after multivariate adjustment was suggestive of a protective effect (relative risk = 0.70), the result was not statistically significant (P trend = .07). In contrast, several other longitudinal assessments have reported a significant inverse association between 25(OH)D concentrations and future severity of insulin resistance and/or incidence of diabetes **(14).**

To date, interventional studies have largely refuted the theory that vitamin D may benefit insulin sensitivity; however, it is important to note that they were not designed to specifically examine this question. In the Women's Health Initiative, postmenopausal women were randomized to receive a low dose of vitamin D3 (400 IU/d) or placebo. After a mean follow-up time of 7 years, the hazard for incident type 2 diabetes mellitus was 1.01 (95% CI, 0.94-1.10), suggesting a null effect. **(40).**

Diabetic neuropathy (DN) is the most common complication of DM and also a major cause of morbidity and mortality in diabetic patients. **Alamdari et al. (41)** in a cross-sectional study, observed reduction the levels of circulating 25(OH)-D was associated with an increased risk of large fiber neuropathy and FBG in type2 diabetic people.

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