

Vitamin D Deficiency: A New Risk Factor for Type 2 Diabetes?

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Key Words

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Abstract

Recent compelling evidence suggests a role of vitamin D deficiency in the pathogenesis of insulin resistance and insulin secretion derangements, with a consequent possible interference with type 2 diabetes mellitus. The mechanism of this link is incompletely understood. In fact, vitamin D deficiency is usually detected in obesity in which insulin resistance is also a common finding. The coexistence of insulin resistance and vitamin D deficiency has generated several hypotheses. Some cross-sectional and prospective studies have suggested that vitamin D deficiency may play a role in worsening insulin resistance; others have identified obesity as a risk factor predisposing individuals to exhibit both vitamin D deficiency and insulin resistance. The available data from intervention studies are largely confounded, and inadequate considerations of seasonal effects on 25(OH)D concentrations are also a common design flaw in many studies. On the contrary, there is strong evidence that obesity might cause both vitamin D deficiency and insulin resistance, leaving open the possibility that vitamin D and diabetes are not related at all. Although it might seem premature to draw firm

conclusions on the role of vitamin D supplementation in reducing insulin resistance and preventing type 2 diabetes, this manuscript will review the circumstances leading to vitamin D deficiency and how such a deficiency can eventually independently affect insulin sensitivity.

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Introduction

The increasing prevalence of obesity [1] is turning type 2 diabetes into one of the most frequent causes of death [2]. Similarly, vitamin D deficiency has recently been recognized as a worldwide concern [3], still linked to obesity. It is widely known that the pathophysiology of type 2 diabetes involves progressive impairment of insulin secretion associated with a coexisting insulin resistance [4]. Along with the classic role of 1,25(OH)₂D in calcium homeostasis and bone metabolism [5, 6], several studies have found an association between vitamin D deficiency and a cluster of metabolic abnormalities called the ‘meta-

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bolic syndrome', including abdominal obesity, insulin resistance, dyslipidemia, and hypertension, with the consequent risk of developing cardiovascular diseases and/or type 2 diabetes [7]. Furthermore, other studies have suggested an intriguing involvement of vitamin D in the impairment of β -cell secretion [8, 9]. The concomitant association of vitamin D deficiency with insulin resistance, impaired insulin secretion, and their important metabolic consequences has generated the hypothesis of a possible role of vitamin D in the pathogenesis of type 2 diabetes. The purpose of our review is to summarize the current knowledge and possible mechanisms.

Determinants of 25(OH)D Homeostasis

Dietary vitamin D is a fat-soluble vitamin which is absorbed in the small intestine and incorporated into chylomicrons. Dietary vitamin D travels to the liver, bound to vitamin D-binding protein and in continued association with chylomicrons and lipoproteins, where it and endogenously synthesized cholecalciferol are metabolized [10, 11]. The association of oral vitamin D with chylomicrons and lipoproteins permits a more rapid hepatic delivery when compared to endogenously synthesized or parenterally administered hormones, which circulate exclusively on vitamin D-binding protein. This difference results in a rapid but less sustained increase in plasma 25-hydroxyvitamin D (25OHD) levels obtained with oral as opposed to parenteral administration or endogenous synthesis. In various tissues cholecalciferol undergoes a hydroxylation reaction with the formation of 25-hydroxycholecalciferol [25(OH)D], which in turn enters the general circulation bound to a specific protein carrier (vitamin D binding protein) [12]. In the kidney, the 25(OH)D can undergo two different hydroxylation reactions (catalyzed by different hydroxylases: 1α -hydroxylase and 24-hydroxylase), generating the active 1,25(OH)₂D (calcitriol), and 24,25(OH)₂D, the inactive form [13]. 1,25(OH)₂D plays a pivotal role in calcium and phosphorus homeostasis, increasing intestinal calcium absorption and regulating bone mineralization [14]. Measurement of serum 25(OH)D is widely accepted to be the most useful marker for assessment of the individual vitamin D status. Several factors are involved in regulating levels of 25(OH)D; in particular, it is influenced by the dietary intake [15] and ultraviolet B exposure [16] which transforms 7-dehydrocholesterol into vitamin D. The serum 25(OH)D concentration tends to fall with age as a consequence of an age-related decline in 7-dehydrocho-

lesterol production in the skin [17, 18]. Other factors known to influence 25(OH)D levels include race and physical activity [19–21]. During exposure to sunlight, the solar UVB photons with 290- to 315-nm wavelengths are absorbed by 7-dehydrocholesterol in the skin, which is then converted into previtamin D which is converted by a thermal reaction into vitamin D. Since there are seasonal variations in UVB exposure, 25(OH)D serum concentrations can accordingly vary, i.e. adequate 25(OH)D concentrations in the summer and the beginning of fall but suboptimal concentrations in winter and spring [22–24]. To confirm this assumption, Bolland et al. [25] conducted a cross-sectional study evaluating healthy older men and postmenopausal women living in New Zealand, showing seasonal (and latitudinal) variations in 25(OH)D concentrations. This observation was also confirmed by evidence of a high prevalence of vitamin deficiency and by the seasonal variation of vitamin D levels in a healthy Thai population in which the winter sunlight was hypothesized to be insufficient to induce cutaneous 25(OH)D synthesis [26]. Thus, sun exposure and time spent outdoors are important predictors of serum 25(OH)D values [27]. Increased skin pigmentation, application of sunscreen, aging, and clothing have dramatic effects on vitamin D production in the skin [28]. It is interesting that seasonal variations have also been reported in terms of metabolic control in diabetic children with type 1 diabetes [29, 30]; for example, better metabolic control was shown by a decrease in the required dose of insulin during a summer camp. In addition, patients with type 2 diabetes experienced seasonal variations in terms of fasting glucose and HbA1c [31, 32], as did patients with type 1 diabetes [33]. Though intriguing, the seasonal variation of vitamin D and its association with diabetes determinant factors can generate only pure speculation.

Observational Study Evidence

Prospective follow-up studies on this topic have not shown conclusive results yet [34–44] (table 1). In particular, the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study [45] showed that vitamin D deficiency was associated with an increased risk of developing diabetes and metabolic syndrome at the 5-year follow-up. This study was performed in an Australian population and this ethnicity-selected cohort can limit the generalization of these results to other race/ethnicity. In the same manner, Pittas et al. [35] found that vitamin D deficiency is a predisposing factor for developing diabetes. However,

Table 1. Prospective and cross-sectional studies evaluating the association of vitamin D status and the risk of developing type 2 diabetes

Study (year)	Study design	Follow-up years	Characteristics/age	Sample size	Conclusion
Scragg et al. [56] (2004)	Cross-sectional	–	Non-Hispanic whites, Mexican-Americans/ ≥20 years	6,228	Inverse association between vitamin D status and diabetes, probably involving insulin resistance
Knekt et al. [40] (2008), Finnish Mobile Clinic	Nested case-control	22	Nondiabetic adults/ 40–74 years	Cases 230/ controls 452	High vitamin D status provides protection against type 2 diabetes
Forouhi et al. [42] (2008), Ely study	Cohort	10	European adults/ 63.5 years	Cases 37/ noncases 740	Inverse associations between baseline serum 25(OH)D and future glycemia and insulin resistance
Pittas et al. [35] (2010), Nurses' Health Study	Nested case-control	14	Women/56.4 years	Cases 608/ controls 599	Plasma 25-OHD concentration was associated with a lower risk of incident type 2 diabetes in women
Grimnes et al. [38] (2010), Tromsø Study	Cohort	11	Nondiabetic adults/ 59.6 years	Cases 247/ noncases 5,872	Serum 25(OH)D was inversely associated with subsequent type 2 diabetes, but not after adjustment for BMI
Liu et al. [41, 43] (2010–2012), Framingham Offspring Study	Cohort	7	Nondiabetic adults/ 54.2 years	2,571	Higher vitamin D status is associated with decreased risk of type 2 diabetes
Dalgard et al. [36] (2011)	Cross-sectional	–	Faroese residents/ 72.5 years	668	No significant relationship of vitamin D status with fasting glucose, insulin, or HOMA
Gagnon et al. [37] (2011), Australian Diabetes, Obesity and Lifestyle study	Cohort	5	Nondiabetic Australian adults/55 years	Cases 199/ noncases 5,001	Higher serum 25(OH)D levels, but not higher dietary calcium, were associated with a significantly reduced risk of diabetes
Robinson et al. [34] (2011), Women's Health Initiative	Nested case-control	7.3	Older women/66.3 years	Cases 317/ controls 4,823	No association between vitamin status and risk of developing type 2 diabetes
Kayaniyil et al. [44] (2011)	Cohort	3	Nondiabetic patients/ 50.1 years	Cases 131/ noncases 358	Higher baseline 25(OH)D independently predicted better β -cell function and lower AUC glucose
Pilz et al. [46] (2012), Hoorn study	Prospective	7.5	Nondiabetic older subjects/67.9 years	Cases 45/ noncases 280	No significant association of vitamin D status with the incidence of diabetes, but a significant association with follow-up HbA1c levels

this study was performed only in white women and the results cannot be directly extrapolated to men or non-white women.

A role of vitamin D in glucose derangements is also suggested by evidence provided by Need et al. [17], who found an association between serum 25(OH)D and fasting glucose levels in postmenopausal white women; in particular, they found a dramatic deterioration in blood glucose in the presence of 25(OH)D levels below 40 nmol/l.

On the contrary, some studies showed no significant association between 25(OH) levels and incident diabetes [34–38, 40–44]. In particular, recently the Hoorn study [46] confirmed the lack of a significant association of baseline vitamin D levels and glucose metabolism and

incident diabetes, but suggested a trend towards an inverse association of 25(OH)D with prospective changes in HbA1c.

The controversial results of these studies are mostly due to their experimental design. In fact, they are cross-sectional and observational studies in which it can be hypothesized that there is an association between two or more variables without explaining the causality that links them; in addition, confounding factors related to dietary factors but also unmeasured nondietary factors cannot be excluded [34, 35, 40, 43, 44, 46]. The results of the studies may also differ because of the different populations included with different serum 25(OH)D status and diabetes risk profiles [40–43].

Some studies are also limited by single measurements of vitamin D status [36–38, 40, 42, 46], which may not reflect the long-term vitamin D status. Furthermore, possible changes in dietary habits during the follow-up period may have altered the vitamin D status over time, thus weakening the association between vitamin D status and type 2 diabetes incidence [40, 44].

Recently, meta-analyses and systematic reviews [14, 47–49] tried to clarify the evidence already published on the interesting association between vitamin D deficiency and abnormal glucose tolerance. Forouhi et al. [47] reviewed in the systematic reviews and meta-analysis only prospective studies, and they found strongly inverse associations between vitamin D circulating levels and incidence of type 2 diabetes. However, a causal effect cannot be stated based on the current epidemiological evidence; randomized trials of vitamin D supplementation were recently analyzed by George et al. [48], and the results suggested that there is no evidence to recommend vitamin D supplementation in patients with type 2 diabetes or impaired glucose intolerance in order to prevent and/or improve glycemic control. Finally, evidence for the association between type 1 diabetes risk and VDR polymorphisms was recently provided in a meta-analysis [49].

Role of Vitamin D in Insulin Resistance

Recently, there has been a growing interest in the non-classical effects of vitamin D, based on findings showing the presence of vitamin D receptors in tissues other than bone, gut, and kidneys [50]. Furthermore, several studies have suggested the involvement of vitamin D in the pathogenesis of cardiovascular diseases [51], cancer [52], and the metabolic syndrome [6].

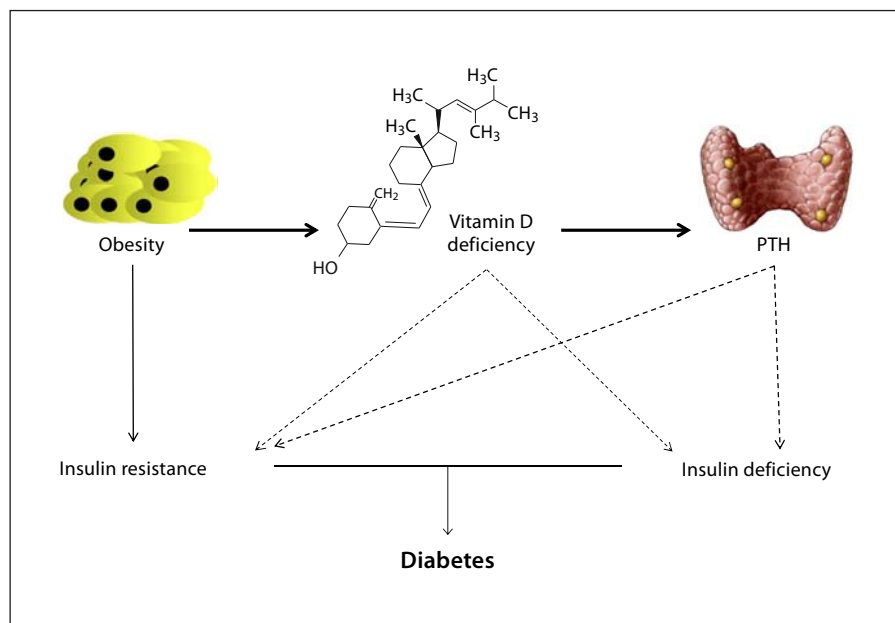
Various cross-sectional studies have largely, but not consistently, shown a significantly increased risk of type 2 diabetes and impaired glucose metabolism in vitamin D deficiency conditions [53, 54]. In the same manner, Oosterwerff et al. [55] suggested that subjects with serum 25(OH)D below 50 nmol/l, in community-dwelling older persons in The Netherlands, have a higher risk of the metabolic syndrome. Data from the cross-sectional survey NHANES (National Health and Nutrition Examination Survey) III [56] found an inverse relationship between vitamin D status and the incident type 2 diabetes, hypothesizing a role of vitamin D in the pathogenesis of insulin resistance; on the other hand, a recent prospective study [57] on the general Denmark population stated that low 25(OH)D status was not significantly associated

with incident diabetes after adjustment for confounders, although it suggested that low vitamin D status could be related to deterioration of glucose homeostasis.

Role of Obesity

Several of the above reported studies suggested that the association between low 25(OH)D levels and metabolic syndrome was more pronounced in overweight and obese people than in normal-weight individuals [58], highlighting a still open issue, i.e. are 25(OH)D levels directly related to insulin resistance or through obesity? Fat mass acts as a reservoir of 25(OH)D and its metabolites [59, 60]; in addition, obese people have been reported to have less exposure to sunlight because of less exercise and less mobility [61]. This strict correlation was also confirmed by Blum et al. [59] who measured 25(OH)D concentrations in serum and subcutaneous adipose tissue collected from obese subjects undergoing gastric bypass surgery, showing an inverse association of 25(OH)D with body weight and adiposity. Attempting to explain the mechanism for the subnormal concentration of 25(OH)D in obesity, Wortsman et al. [60] assessed whether obesity could alter the cutaneous production of 25(OH)D or intestinal absorption. Both processes were similar to those in lean subjects, confirming that the low 25(OH)D concentration is most probably due to its increased sequestration in the enlarged pool of subcutaneous fat tissue and its consequent reduced bioavailability. To confirm that 25(OH)D levels were not causally related to obesity, Manco et al. [62] found that although there was a rapid improvement in insulin sensitivity after bariatric surgery, this change did not correlate with 25(OH)D levels. Similarly, to investigate a cause-effect relation between 25(OH)D status and insulin sensitivity, we performed a cross-sectional study showing lower 25(OH)D levels in obese compared to lean subjects; 25(OH)D levels were associated with the degree of insulin sensitivity, BMI, PTH, total cholesterol, HDL cholesterol, and triglycerides. However, in our population, body size was the most powerful predictor of 25(OH)D levels, as shown by multivariate regression analysis. Therefore, to further test the hypothesis that insulin resistance might depend on hypovitaminosis and not on obesity, we considered the obese subjects in our cohort and divided them into two subgroups, according to their insulin sensitivity (low and high). The two subgroups showed similar results for BMI, age, and sex, but did not show any difference in 25(OH)D concentration, thus confirming the hypothesis that the most important determinant of hypovitaminosis D is the adipose tissue. In obesity, both low 25(OH)D con-

Fig. 1. Obesity is an important feature in the pathogenesis of type 2 diabetes (solid arrows). Vitamin D deficiency is an important feature of obesity mostly due to the storage of 25(OH)D vitamin in adipose tissue because of its lipophilic properties, causing, in turn, a compensatory increase in PTH (bold arrows). The decrease in 25(OH)D levels may occur through several mechanisms, resulting in worsening of insulin resistance and secretion and augmenting the risk of developing type 2 diabetes. Furthermore, hypovitaminosis D may increase insulin resistance indirectly, through the compensatory increase in PTH levels. In addition, hypovitaminosis D-induced secondary hyperparathyroidism has been shown to inhibit insulin synthesis and secretion from β -cells and reduce insulin sensitivity (dotted arrows). Solid and bold arrows indicate cause and effect relationships; dotted ones indicate not firmly established evidence.



centration and insulin resistance appear to be dependent on the increased body size [63]. Accordingly, in a recent study we demonstrated a strong relationship between 25(OH)D and obesity in PCOS patients; in particular, our data showed that vitamin D deficiency does not directly affect the development of insulin resistance in PCOS, but the presence of obesity was considered the best predicting factor of 25(OH)D levels [64]. Although vitamin D deficiency and insulin resistance appear to be unrelated, it cannot be excluded that vitamin D deficiency may play a role in worsening obesity-associated insulin resistance. In fact, Zhou et al. [65] reported a protective effect of vitamin D on insulin resistance induced by free fatty acids in cultured C2C12 cells.

Several mechanisms have been proposed to explain the role of vitamin D in the pathogenesis of insulin resistance: vitamin D may act on insulin action by stimulating the expression of insulin receptors and amplifying glucose transport [66]; furthermore, since 25(OH)D regulates the intracellular cytosolic calcium pool, it may indirectly contribute to peripheral insulin resistance in insulin target tissue [67–69], again impairing insulin signaling transduction [70] and decreasing glucose transporter-4 activity [71].

The adipokine adiponectin is highly abundant in human serum and is secreted by adipose tissue in an inverse proportion to the body mass index [72]. Making an attempt to find a link between hypovitaminosis D and insulin resistance, adiponectin has been proposed as a *trait*

d'union; in fact, hypovitaminosis D and lower circulating adiponectin are associated in subjects with impaired glucose tolerance, independently of adiposity [73]. Adiponectin and glucose homeostasis are both regulated by osteocalcin, an osteoblast hormone linked to vitamin D metabolism [74, 75]. 1,25(OH)₂D also indirectly regulates adiponectin secretion affecting adipogenesis through a vitamin D receptor-dependent mechanism, although an additive direct action of vitamin D on adiponectin transcription in adipocytes cannot be entirely ruled out [76]. Again, although based only on cross-sectional studies, it might be at least suggested that hypovitaminosis D and insulin resistance are primarily caused by obesity; still, hypovitaminosis D might worsen obesity-induced insulin resistance (fig. 1).

Role of PTH

It is well known that severe hypovitaminosis D causes a compensatory increase in the secretion of PTH; this inspired the hypothesis that low 25(OH)D levels exert their action on insulin resistance indirectly through PTH. For example, a cross-sectional study revealed that the PTH level, but not the 25(OH)D level, is an independent predictor of the 'metabolic syndrome' in morbidly obese men and women [77]. Poor vitamin D levels induce higher PTH concentrations to finally increase calcium reabsorption from the skeleton and reabsorption in the kidneys. Elevated PTH concentrations have been shown to inhibit insulin synthesis and secretion from β -cells [78]

and to reduce insulin sensitivity [79, 80]; thus, hypovitaminosis D-induced secondary hyperparathyroidism may contribute to the development of metabolic syndrome. In accordance with this hypothesis, Reis et al. [81] failed to find any evidence of an association between vitamin D deficiency and the metabolic syndrome in either sex; on the contrary, elevated PTH levels were associated with an increased prevalence of metabolic syndrome in older men, partly associated with insulin resistance as estimated by HOMA-IR. Recently, Soares et al. [82] suggested an intrinsic inverse relationship between PTH and insulin sensitivity in obesity, independent of vitamin D. The significant decrease in PTH during weight loss (the most powerful approach to reduce insulin resistance) did not cause demonstrable differences in vitamin D status. In addition, PTH correlates with several of the features included in the metabolic syndrome, such as systolic and diastolic blood pressure, waist circumference, BMI, and insulin sensitivity, as estimated by HOMA [83].

The mechanisms underlying the relationship between PTH and insulin resistance are still unclear; some authors [84, 82] again hypothesized a correlation between intracellular calcium affected by PTH levels and insulin resistance, while others suggested that increase in PTH levels encourage intracellular flux of calcium within adipocytes, leading to increased lipogenesis and, therefore, weight gain [85]. Based on these considerations and data, the PTH concentration can therefore be inscribed as another possible mechanism linking hypovitaminosis D and insulin resistance; however, the differentiation among the three associated possible mechanisms (calcium, vitamin D, and PTH) remains difficult to investigate (fig. 1).

Role of Vitamin D in Insulin Secretion

Several epidemiological studies suggested an interesting involvement of vitamin D in the impairment of β -cell secretion [79]. Since the description of impaired pancreatic insulin secretion in vitamin D-deficient rats 30 years ago [86], many observational studies in animal models have shown that vitamin D deficiency inhibits rat pancreatic insulin synthesis and secretion; although limited to animal models, in these experiments the supplementation of vitamin D corrected the observed defect, thus confirming a possible mechanism [87, 88]. Furthermore, the prevalence of diabetes is doubled in NOD mice when they are fed a vitamin D-deficient diet in early life [89, 90].

Vitamin D was reported to be essential for insulin secretion from pancreatic β -cells [8] in both in vitro and in vivo studies [91–93]. The mechanisms by which vitamin D acts on insulin secretion are thought to be both direct and indirect [14]; in particular, the direct effect of vitamin D on insulin synthesis and secretion is suggested by the demonstrated binding of the active form 1,25(OH)₂D to the vitamin D receptor on β -cells, by the identification of vitamin D response elements in the human insulin gene promoter [94], and by the transcriptional activation of the human insulin gene caused by 1,25(OH)₂D [95]. Instead, the indirect effects of vitamin D on β -cell secretory function seem to be mediated by alterations in calcium flux through the β -cell membrane, as suggested by a study conducted by Beaulieu et al. [96] in rats affected by vitamin D deficiency or associated with hypocalcemia, showing that the latter had significantly higher glucose concentrations ($p < 0.0005$) and lower insulin response during GTT compared to all other groups ($p < 0.001$).

Observational studies have described a link between geographical latitude, vitamin D intake, and the incidence of type 1 diabetes [97, 98]. The European Community-sponsored Concerted Action on the Epidemiology and Prevention of Diabetes study found a 33% reduction in the risk of developing childhood-onset type 1 diabetes in children who received vitamin D supplementation compared with nonsupplemented children [99]. Cod liver oil, taken during the first year of life, reduced the risk of childhood-onset type 1 diabetes [100]. A further study found that an intake of 2,000 IU of vitamin D during the first year of life diminished the risk of developing type 1 diabetes by 80% and showed that the incidence of childhood diabetes was three times higher in subjects with suspected rickets [101]. More recently, the Diabetes Autoimmunity Study in the Young (DAISY) reported that the presence of islet auto-antibodies in offspring was inversely related to maternal dietary vitamin D intake during pregnancy [102]. It was found that cod liver oil, an important source of vitamin D taken often by pregnant women, was associated with a reduced risk of type 1 diabetes in their offspring [103].

A recent meta-analysis by Zipitis and Akobeng [104] concluded that vitamin D supplementation might be protective against the development of type 1 diabetes during infancy. In adult patients with recent-onset type 1 diabetes, an open-label randomized trial also found a benefit in supplementation with 1,25(OH)₂D which temporarily reduced the required insulin dose [105].

The apparent reduction of type 1 diabetes may be due to the immunomodulatory effects of vitamin D, thereby

protecting from or arresting the immune process which contributes to its development [50]. In fact, 1,25(OH)D suppresses adaptive immunity by inhibiting the maturation of dendritic cells, reducing their capacity to present antigen to CD4 cells. Furthermore, 1,25(OH)D inhibits the proliferation and differentiation of CD4 cells into Th1 and Th7 and promotes the production of Th2 and T reg cells.

These findings therefore suggest that vitamin D administration may play an important role in the suppression of the adaptive immune system and may consequently have a beneficial effect on the prevention and treatment [50].

Intervention Studies

The challenge to confirm the evidence of several observational studies suggesting that vitamin D deficiency is associated with glucose metabolic derangements are the intervention studies. Kumar et al. [106] showed that the replacement of physiological 25(OH)D levels in vitamin D-deficient subjects improved glucose tolerance. In the same manner, Nagpal et al. [107] performed a randomized controlled trial administering three doses of 120,000 IU vitamin D or placebo in centrally obese but nondiabetic Indian subjects, finding that vitamin D supplementation improved insulin sensitivity derived from measures of the indirect index of insulin resistance. In a randomized, placebo-controlled trial, von Hurst et al. [108] demonstrated that supplementation with vitamin D enhanced insulin sensitivity in South Asian women who were both insulin resistant and vitamin D deficient, but only if the dose was large enough and continued over a sufficient length of time. These findings suggest the importance of the long-term maintenance of adequate vitamin D levels to have some impact on glucose metabolism [109]. The same authors suggested in a recent study that South Asian women are at high risk of hypovitaminosis D, in part due to deliberate sun avoidance and an indoor lifestyle [110]. Taking into account diabetic patients, vitamin D oral supplementation for 12 weeks in subjects with type 2 diabetes increased insulin secretion but had no effect on insulin resistance as suggested in a recent placebo-controlled trial [111] administering daily two capsules of calcitriol (0.25 µg 1,25-dihydroxy cholecalciferol per capsule).

The use of different doses and isoforms of vitamin D along with different times of supplementation does not allow drawing of firm conclusions and establishment of a real beneficial effect of vitamin D. Some authors hy-

pothesized that the positive effect of vitamin D is mediated by calcium, and in order to investigate this hypothesis they performed supplementation studies using both vitamin D and calcium [112]. This hypothesis was suggested by observational studies that reported that intakes of calcium and dairy products seem to be associated with a lower prevalence of the 'metabolic syndrome' in middle-aged and older women [113]. In the Nurses' Health Study [113], the investigators showed that a combined daily intake of >1,200 mg calcium and >800 IU vitamin D was associated with a 33% lower risk of type 2 diabetes compared with an intake of <600 mg and 400 IU calcium and vitamin D, respectively. These findings also agreed with reported findings from a randomized, controlled trial conducted on healthy, older adults with impaired fasting glucose [114], showing that daily supplementation with 500 mg calcium citrate and 700 IU vitamin D for 3 years prevented increases in plasma glucose and insulin resistance that usually occur with aging.

On the other hand, de Boer et al. [115] found that supplementation with 1,000 mg elemental calcium plus 400 IU vitamin D did not reduce the risk of developing diabetes over 7 years of follow-up in the Women's Health Initiative intervention trial, a trial based on a well-characterized, large, ethnically diverse cohort of women. In agreement with this evidence, the oral administration of 800 IU vitamin D and 1,000 mg calcium in older people at high risk of another osteoporotic fracture did not suggest a protective effect against the development of type 2 diabetes or use of medication for type 2 diabetes [116]. Other small trials have reported no change in insulin secretion after vitamin D supplementation among insulin-resistant [109] or healthy obese adults [108].

Tai et al. [117] failed to find effects on blood glucose or insulin secretion during OGTT performed after 2 weeks of supplementation with two oral doses of 100,000 IU of vitamin D in adults with vitamin D deficiency and without diabetes; in the same manner, supplementation with vitamin D for 6 months in diabetic subjects with normal serum 25(OH)D did not provide any improvement in terms of glycated hemoglobin levels, insulin secretion, or resistance [118].

These findings suggest that higher doses of vitamin D may be required to affect the diabetes risk, and/or that associations of calcium and vitamin D intake with improved glucose metabolism observed in nonrandomized studies may be the result of confounding or of other components of foods containing these nutrients. Intervention studies in subjects with type 2 diabetes showed no overall improvement in β -cell function or insulin resistance

Table 2. Interventional studies evaluating the effect of vitamin D supplementation on insulin sensitivity/insulin secretion

Study	Study population	Age, years	Control	Supplement	Duration	Primary endpoints
Borissova et al. [121] (2003)	10 females with type 2 diabetes	17–60	placebo	1,332 IU cholecalciferol	1 month	No significant improvement in insulin resistance
Grant et al. [116] (2005)	5,292 people at high risk of further fractures	>70	placebo	800 IU cholecalciferol ± 1,000 mg calcium	24–62 months	No effect on development of type 2 diabetes
Pittas et al. [114] (2007)	314 Caucasian adults without diabetes	>65	placebo	500 mg calcium citrate and 700 IU cholecalciferol	3 years	Attenuation of increase in glycemia and insulin resistance in subjects with IFG
de Boer et al. [115] (2008)	33,951 healthy postmenopausal women	50–79	placebo	1,000 mg elemental calcium plus 400 IU cholecalciferol	7 years	No reduction in the risk of developing diabetes
Tai et al. [117] (2008)	32 adults with vitamin D insufficiency and without diabetes	55 (mean)	placebo	two oral doses of 100,000 IU cholecalciferol, 2 weeks apart	2 weeks	No effect on blood glucose, insulin concentration, or insulin sensitivity
Nagpal et al. [107] (2009)	100 healthy male volunteers, centrally obese	43.8 (mean)	placebo	three doses of 120,000 IU oral cholecalciferol	6 weeks	Improvement in postprandial insulin sensitivity
Jorde et al. [118] (2009)	36 subjects with type 2 diabetes	21–75	placebo	4,000 IU cholecalciferol (weekly)	6 months	No effect on glucose metabolism
von Hurst et al. [108] (2010)	81 South Asian women with insulin resistance	42 (mean)	placebo	4,000 IU cholecalciferol	6 months	Significant improvements in insulin sensitivity
Mitri et al. [39] (2011)	92 adults with glucose intolerance or early diabetes	57 (mean)	placebo	2,000 IU cholecalciferol ± 800 mg calcium carbonate	16 weeks	Improvement in β -cell function
Nazarian et al. [122] (2011)	8 subjects with VDD and prediabetes	18–60	NA	10,000 IU cholecalciferol	4 weeks	Improvement in insulin sensitivity
Harris et al. [124] (2012)	89 overweight African-Americans with prediabetes or early diabetes	56.7 (mean)	placebo	4,000 IU cholecalciferol	12 weeks	No effect on the disposition index or glycemia

[119–121], but these trials were limited by low therapeutic exposure to vitamin D and a variable duration of type 2 diabetes in the study populations. To overcome these limitations, a recent study [122] evaluating subjects with impaired fasting glucose and submitted to the administration of 10,000 IU of vitamin D daily for 4 weeks showed a significant improvement in insulin sensitivity. Recent results have suggested that vitamin D supplementation may have a role in delaying the natural history of type 2 diabetes [115]. In the same manner, Mitri et al. [123], in an interventional study on subjects at high risk for diabetes, supplemented with vitamin D [2,000 IU once per day with or without calcium carbonate (400 mg twice daily) for 16 weeks], showed an improvement in pancreatic β -cell function assessed as the disposition index, i.e., the change of disposition index was due to increased insulin secretion without a significant change in insulin sensitiv-

ity. On the other hand, Harris et al. [124] recently suggested that supplementation with vitamin D for 3 months did not change the pathophysiology of prediabetes in overweight or obese African-Americans, although they observed that supplementation decreased insulin sensitivity and increased insulin secretion with early diabetes or prediabetes, but it did not have effect on the disposition index or on the fasting glucose (table 2).

Several ongoing trials are currently trying to evaluate the effect of vitamin D supplementation on β -cell function and insulin sensitivity in patients at high risk for type 2 diabetes [Vitamin D and Calcium Homeostasis for Prevention of Type 2 Diabetes (CaDDM) NCT00436475] and patients affected by prediabetes or newly diagnosed diabetes mellitus type 2 [Effects of Vitamin D on Beta Cell Function and Insulin Sensitivity in Pre-diabetes and Diabetes Mellitus Type 2 (EVIDENS) NCT01497132].

Conclusion

Based on the excursus of the several studies described above, vitamin D deficiency is strongly associated with obesity mostly due to the storage of 25(OH)D vitamin in adipose tissue because of its lipophilic properties. The decrease in 25(OH)D levels may occur through several mechanisms such as a decrease in the calcium concentration, an increase in PTH, or a direct effect of vitamin D on worsening insulin resistance and secretion, augmenting the risk of developing type 2 diabetes. Interventional

studies have provided conflicting and inconclusive results due to the different populations studied, chemical formulations of vitamin D, doses, and time frame of supplementation. Further studies are required especially in subjects that are affected by a high risk of developing diabetes (impaired fasting glucose and/or glucose tolerance, possibly without obesity). Based on the hypothesized mechanism of action of vitamin D, these subjects may be the main beneficiaries of the effects of vitamin D on the prevention of type 2 diabetes.

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