REVIEW

Vitamin D, Obesity and Risk of Diabetes

Short running head: Vitamin D, obesity and diabetes

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Abstract (English)

Vitamin D deficiency is newly recognized as a common condition of increasing prevalence worldwide. Clinically, vitamin D has an established role in calcium and bone metabolism, but lower vitamin levels are associated with obesity and an increased risk to develop type 2 diabetes, cardiovascular diseases and cancer. The molecular mechanisms of these associations are partially understood, but it is known that vitamin D stimulates lypolysis and inhibits adipogenesis in human adipocytes, and lower vitamin D may induce body fat accumulation. Vitamin D receptors are expressed in both pancreatic β-cells and skeletal muscle cells, and their activation results in increased insulin release and responsiveness to insulin for glucose transport. Vitamin D is also newly recognized for potent antiproliferative, prodifferentiative, and immunomodulatory effects in many tissues. Vitamin D deficiency is frequently unrecognized clinically and, although laboratory measurement is easy to perform and treatment of vitamin D deficiency is relatively well tolerated and inexpensive, physicians are not sufficiently informed about effects of vitamin D other than those on skeletal metabolism, and they rarely ask for plasma vitamin D measurement. The purpose of this Review is to examine the association between vitamin D deficiency, obesity and risk of type 2 diabetes.

Keywords: vitamin D, obesity, insulin, type 2 diabetes
Abstract (Italiano)

Il deficit di vitamina D è una condizione patologica in costante aumento nel mondo. È noto che la vitamina D ha un ruolo fondamentale sul metabolismo del calcio e dell’osso, ma recentemente è stato dimostrato che il deficit di vitamina D è associato con la obesità ed un maggiore rischio di sviluppare il diabete tipo 2, le malattie cardiovascolari ed il cancro. I meccanismi molecolari di queste associazioni sono parzialmente conosciute, ma è noto che la vitamina D favorisce la lipolisi e inibisce l’adipogenesi negli adipociti umani e che bassi livelli di vitamina D possono favorire l’accumulo di grasso corporeo. Recettori per la vitamina D sono espressi nelle cellule β-pancreatiche e nelle cellule del muscolo scheletrico e la loro attivazione favorisce la secrezione d’insulina ed un aumento della responsività all’insulina, per quanto concerne il trasporto del glucosio. Alla vitamina D viene anche attribuita una potente azione antiproliferativa, prodifferenziativa ed immunomodulatoria in molti tessuti. Seppure sia frequente, il deficit di vitamina D non è comunemente riconosciuto e, nonostante il dosaggio plasmatico sia facile da eseguire ed il trattamento con vitamina D sia ben tollerato e poco costoso, i medici sono poco informati sugli effetti non scheletrici della vitamina D, e raramente richiedono il dosaggio plasmatico della vitamina D. Lo scopo di questa Review è quello di esaminare le attuali informazioni sulle associazioni tra deficit della vitamina D, obesità e rischio di diabete tipo 2.
Introduction

Vitamin D deficiency (<75 nmol/l) is common in all age groups, with a dramatic increase in prevalence (74%) and severity over the last decade (1,2). It has been estimated that 1 billion people worldwide are affected by various degrees of vitamin D deficiency (1), and the National Health and Nutrition Examination Survey (NHANES) report has shown that the prevalence of severe deficiency (<25 nmol/l) increased from 2 to 6% in the general USA population and from 9 to 29% in non-Hispanic blacks (3).

Vitamin D is generated in the skin from the nonenzymatic conversion of provitamin D3 to previtamin D during exposure to sunlight emitting ultraviolet radiation in the narrow band of 290 to 315 nm. Skin-derived synthesis of vitamin D is quite variable, depending on pigmentation, latitude, season, clothing, age, exposure to sunlight, sunscreen use, local weather conditions and dietary intake (1).

Dietary sources of vitamin D are limited, and some vitamin D comes from few food sources (between 100 and 200 IU per day), since only certain kinds of fish contain sizable amounts (Table 1).

Vitamin D is either stored in adipose tissue or converted in the liver by the enzyme 25-hydroxylase to 25-hydroxyvitamin D3 (25[OH]D3 or 25(OH)D), that is a partially water-soluble form, with a shorter half-life than vitamin D that circulates bound to vitamin D-binding protein. Serum 25(OH)D level is the best indicator of overall vitamin D status because this measurement reflects total vitamin D from dietary intake and sunlight exposure, as well as the conversion of vitamin D from adipose stores in the liver (4). In healthy whites, serum levels of 25(OH)D may vary according to environmental, hormonal, genetic, and nutritional factors (1,4).

Several conditions cause very low serum levels of 25(OH)D (i.e., below 10 ng per milliliter), including poor dietary intake of vitamin D coupled with negligible sun exposure, malabsorption due to inflammatory bowel disease, gluten enteropathy, gastric surgery, biliary disease, or intestinal overgrowth; use of antiseizure medications (e.g., phenobarbital or phenytoin), and long-term use of glucocorticoids (1,4).

25-hydroxyvitamin D is converted to the active metabolite, 1,25-dihydroxyvitamin D (1,25[OH]2D), or calcitriol, in the kidney, although other tissues have 1α-hydroxylase enzymatic activity. Calcitriol circulates in lower concentrations than 25-hydroxyvitamin D, but has much greater affinity for the vitamin D receptor and is biologically more potent.
The synthesis of calcitriol is enhanced by low levels of serum phosphate and by parathyroid hormone (PTH), which rises in response to lower levels of serum calcium and when levels of 25(OH)D fall below 30 ng per milliliter (1).

The well known role of vitamin D is in the calcium and bone metabolism, and most observational and randomized, placebo-controlled trials concerning vitamin D have focused on skeletal health outcomes and have linked low levels of 25(OH)D to fractures (1,5,6). However, vitamin D is newly recognized for potent antiproliferative, prodifferentiative, and immunomodulatory effects in many tissues (7), and a growing number of studies has reported widespread vitamin D deficiency and insufficiency in apparently healthy populations, and in patients with various pathologies (8).

Recently, attention has turned to nonskeletal effects of vitamin D insufficiency, particularly in relation to obesity (1,2,4,9), diabetes mellitus (10,11), metabolic syndrome (12,13), cardiovascular disease (14), cancer (15), and immune dysfunction (16).

**Vitamin D and obesity**

Central obesity is a major independent risk factor for type 2 diabetes (17). Interestingly, obese patients have typically plasma levels in the range of 10 to 20 ng per milliliter (1,4), and several studies in adults have demonstrated that serum 25(OH)D concentrations are inversely correlated with various measures of obesity, including weight, BMI, and waist circumference (1,2,4,18,19,20,21,22,23,24). The Framingham Heart Study has also showed that vitamin D status is strongly associated with subcutaneous and, especially, visceral adiposity (20). Cross-sectional studies in children indicated that plasma 25(OH)D concentrations are inversely associated with body mass index (BMI; in kg/m2) (25–27) and waist circumference (28,29). A study performed in healthy young women has also recently shown that vitamin D insufficiency was associated with increased fat infiltration in muscle, measured by CT scan (30). In line with all these studies, weight loss of 10%, obtained by a 20 weeks low-calorie diet, increased 25-OHD levels in obese women (31). Another study confirmed that serum vitamin D levels were higher after weight loss induced by a 2-years dietary intervention (32).

In a calcium-intervention trial in 69 pubertal children, a higher baseline vitamin D status was significantly associated with less weight gain over 24 months in univariate analyses (33). Another recent paper has shown that, after baseline adiposity and other potential confounders were controlled for, vitamin D serostatus was inversely associated with the development of adiposity in a study performed in 479 schoolchildren aged 5–12 years (34). The Women’s Health Initiative, which is a large trial that assigned women to receive either 1000 mg Ca
plus 400 IU vitamin D/d or a placebo reported that women who received the regimen of calcium and vitamin D had a small significant lower gain in BMI and waist circumference over 7 y of follow-up (35); in that study, it was impossible to separate the effects of calcium and vitamin D.

Why obese individuals are more likely to have low serum 25(OH)D concentrations? First, since 25(OH)D has a high lipid-solubility, it may well be that this vitamin is under sequestration when adipose tissue is in excess, resulting in reduced 25(OH)D bioavailability (9). An alternate explanation is that obese individuals have less exposure to ultraviolet light because of lower levels of outdoor physical activity, which would result in lower serum 25(OH)D concentrations. It is to note that lower vitamin D may induce body fat accumulation since vitamin D stimulates lypolysis (36,37) and inhibits adipogenesis (38,39) in human adipocytes, through its role in regulating intracellular calcium concentrations. In particular, in vitro studies have also shown that vitamin D can inhibit the expression of a key adipogenesis regulator, peroxisome proliferator-activated receptor-gamma (38,39).

In contrast with previous studies, a trial of overweight adults showed that supplementation with either 20,000 or 40,000 IU cholecalciferol/wk and 500 mg Ca/d did not lead to significantly greater weight loss than the calcium-only control group (40); however, none of the groups experienced significant weight changes over the 1-y study period. Evidence of beneficial effect of vitamin D supplementation on weight reduction is lacking also in other studies (41). It is possible that vitamin D may limit weight gain but does not affect long-term weight loss in individuals who are already overweight. Moreover, a prospective study performed in older subjects showed that the association between measures of body adiposity and change in 25-(OH)D completely disappeared after adjustment for leptin and diminished after adjustment for IL-6 (42). The authors suggested that obesity-related vitamin D deficiency may be mediated by leptin and, to a lesser extent, by IL-6, and that it is possible that leptin and IL-6 secreted by adipose tissue have inhibitory effects on 25-(OH)D synthesis via their receptors. Alternatively, since leptin and IL-6 are associated with insulin resistance, it may well be that hyperinsulinemia may downregulate liver 25-hydroxylase, resulting in decreased formation of 25-(OH)D.

Actually, only randomized trials or longitudinal studies that were adjusted for baseline adiposity could help to explain causation, but there is limited and inconsistent evidence of the association between vitamin D and adiposity from prospective studies.

**Vitamin D and risk of type 2 diabetes**
25(OH)D has been shown to correlate inversely with fasting serum glucose in nondiabetic postmenopausal women (21). The National Health and Nutrition Examination Survey 2001–2006 showed that low serum vitamin D levels elevate the risk for early-stage diabetes (prediabetes), adjusting for age, sex and BMI (43). Similar finding have been shown by a recent study performed in a nationally representative sample of U.S. adults, who were free of clinical cardiovascular diseases and diabetes, showing that lower serum 25(OH)D levels are associated with prediabetes, after adjusting for potential confounders, including age, sex, race/ethnicity, smoking, alcohol intake, BMI, physical activity, hypertension, systolic blood pressure, serum total cholesterol, serum C-reactive protein levels, and estimated glomerular filtration rate (44). Some evidence suggests that 25(OH)D insufficiency may be involved in the development of diabetes (10,11). Hypovitaminosis D is associated with increased diabetes prevalence and insulin resistance assessed by fasting glucose and insulin levels in non-Hispanic whites and Mexican Americans (45). A significant inverse association was observed between serum 25(OH)D concentration and type 2 diabetes incidence in a 17-year observational Finish study (44). Baseline 25(OH)D was inversely associated with 10-year risk of hyperglycemia (fasting glucose and 2 h post-OGTT) and insulin resistance (fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR) ) in a prospective population-based study of 524 middle-aged nondiabetic men and women (47). Over a 7-y average follow-up of the Framingham Offspring Study, subjects in the highest tertile of the predicted 25(OH)D score at baseline had a 40% lower incidence of type 2 diabetes in comparison with individuals in the lowest tertile, after adjustment for age, sex, waist circumference, parental history of type 2 diabetes, hypertension, low HDL cholesterol, elevated triglycerides, impaired fasting glucose, and Dietary Guidelines for Americans Adherence Index score (48). Although these and some other epidemiologic studies (49) have reported an association between low serum 25(OH)D levels (below 30 ng/ml) and diabetes, others did not find an independent association after multivariable adjustment for confounding variables (50,51), or in subgroup analyses in women (52).

A recent meta-analysis suggested that there is insufficient evidence to conclude that an inverse association exists between 25(OH)D levels and diabetes (53). Since reduced kidney function is responsible for lower renal 1-a hydroxylase activity, a deficit in kidney function in diabetes may be a potential confounder in the association between 25(OH)D levels and this metabolic disease (54,55). Markers of inflammation have been shown to be associated with both diabetes (56) and low 25(OH)D levels (57), thus resulting as further possible confounding variables in the relationship between vitamin D and diabetes.
Pharmacologic doses of 1,25-dihydroxyvitamin D3 have been shown to delay the onset of diabetes in animal models of diabetes (58). Unfortunately, only few intervention studies evaluated the effects of vitamin D supplementation on glucose metabolism. High-dose calcitriol (1.5mg daily for 7 days) did not increase insulin sensitivity measured by euglycemic clamp compared with placebo in healthy volunteers who were not vitamin D deficient at baseline (59). However, 1-month treatment with cholecalciferol (1332 IU daily) improved insulin sensitivity and first-phase insulin secretion in 10 women with T2DM (of whom seven were vitamin D deficient at baseline), albeit with no effect on second-phase insulin secretion (60). Interestingly, daily intake of a vitamin D–fortified yogurt drink, either with or without added calcium, improved glycemic status in patients affected by type 2 diabetes (T2D) (61). Actually, clinical studies designed specifically to assess the effect of vitamin D supplementation on glucose metabolism are currently underway at N.I.H. (National Institute of Health). These studies are evaluating the effect of vitamin D supplementation in high-risk populations with both vitamin D deficiency and impaired glucose metabolism. Larger doses of vitamin D (2000–7000 IU daily) are currently used, and the results of these studies will be informative.

Cohort studies have documented a reduced risk of diabetes when higher dietary calcium and vitamin D intake are associated (52,62). Calcium may have a confounding effect on the influence of vitamin D on risk to develop diabetes in these studies, and it is to note that calcium intake could indirectly lead to an improvement in vitamin D status because there would be less need for conversion of 25(OH)D to 1,25-dihydroxyvitamin D (63).

It is noteworthy that the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, a large population-based prospective study, showed that higher serum 25OHD levels, but not higher dietary calcium, were associated with a significantly reduced risk of diabetes in Australian adult men and women, after adjusting for traditional risk factors (64). The use of OGTT to diagnose diabetes ensured that all incident cases were included in this study (64).

In contrast with the previous findings, other studies do not support a positive effect of vitamin D on glucose tolerance. For example, a 1-year study performed in a total of 330 overweight or obese subjects (21-70 years old) showed that subjects randomized to cholecalciferol (20,000 or 40,000 IU per week) and calcium (500 mg daily) did not obtain an improvement of glucose tolerance (65). Moreover, the Women’s Health Initiative trial, involving postmenopausal women, showed that treatment with calcium and 25(OH)D3 (at lower doses than in other studies) did not reduce the risk of developing diabetes, defined by self-report (66).
Vitamin D, insulin secretion and insulin effect

Which are the mechanisms linking vitamin D to glucose metabolism, insulin and risk of diabetes? An inverse associations between vitamin D and fasting insulin concentrations or HOMA-IR index have been reported in most of the studies performed in adults (45,48,67,68,69,70), even independently of BMI or obesity (70). Only one epidemiological study could not find this relationship (71). Concerning adolescent subjects, the National Health and Nutrition Examination Survey, performed between 2001 and 2006, confirmed an inverse association between vitamin D and insulin serum levels in adolescent male subjects (72). As far as insulin secretion is concerned, it is now accepted that vitamin D increases insulin secretion either in animal models (58,73,74,75) or in humans (60,76,77). Concerning insulin effect, two randomized controlled trials of high-dose vitamin D supplementation showed a significant increase in insulin sensitivity in insulin-resistant Indian men or South-Asian women, either after 6 weeks or 6 months of treatment, respectively (78,79). Most of studies have confirmed that vitamin D increases insulin sensitivity, independently of other mechanisms influencing insulin effect (BMI, body fat distribution, etc) (77,80,81). Moreover, treatment with 25(OH)D3 and calcium attenuated a rise in fasting glucose and progression of insulin resistance in a placebo controlled trial of nondiabetic subjects with impaired fasting glucose (82). Interestingly, the Australian Diabetes Obesity and Lifestyle (AusDiab) study showed that serum 25OHD was positively and independently associated with HOMA-S, a marker of insulin sensitivity, whereas dietary calcium intake was not associated with either HOMA-S or type 2 diabetes risk (66). The conclusions of these studies are reinforced by the finding that weight loss of 10%, obtained after 20 weeks of low-calorie diet, increased 25-OHD levels in obese women, and this increase was mainly associated with improvement of insulin resistance (30).

The expression of vitamin D receptors in both pancreatic β-cells and skeletal muscle cells, which, upon activation by vitamin D supplementation, result in increased insulin release and responsiveness to insulin for glucose transport (60), may serve as an underlying mechanism to explain correlation between vitamin D and risk of diabetes. Interestingly, evidence from in vitro studies suggests that vitamin D may alter insulin sensitivity via a direct stimulatory effect on insulin receptor expression (83), modulation of inflammation (84), and adiponectin levels (85).

Only some studies do not confirm the protective effect of vitamin D on the risk of diabetes. For example, a recent study performed in middle-aged Italian men and women reported that 25(OH)D concentrations were associated with euglycemic clamp-derived
insulin sensitivity, but not after adjustment for BMI (86). Seemingly, the association of 
25(OH)D with the measures of insulin resistance were not significant after 
adjustment for VAT in the Framingham Heart Study (20). Alvarez et al have 
suggested that 25(OH)D may be more clinically relevant to insulin sensitivity in vitamin D– 
insufficient subjects (80).

**PTH, vitamin D and risk of diabetes**

Even though PTH is positively associated with insulin sensitivity (87), and PTH levels 
are often elevated in vitamin D-deficient states (1), 25(OH)D and PTH concentrations have 
been shown to be independently associated with whole-body insulin sensitivity in a cohort of 
healthy women (80). These results suggest that 25(OH)D and PTH may influence insulin 
sensitivity through independent mechanisms (80).

**Vitamin D in patients with type 2 diabetes**

Concerning patients affected by type 2 diabetes, serum 25(OH)D have been shown to be 
inversely associated with hemoglobin A1c (HbA1C), especially in participants with higher 
BMI, and at concentrations less than 65 nmol/l (88). Hypovitaminosis D is more prevalent in 
patients with type 2 diabetes than in those without diabetes (89). Lastly, 1-month treatment 
with daily cholecalciferol improved insulin sensitivity and first-phase insulin secretion in 
women affected by type 2 diabetes (60).
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<th>Food</th>
<th>Serving size description</th>
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<td>Cod liver oil</td>
<td>1 Tablespoon</td>
<td>1360</td>
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<tr>
<td>Salmon, cooked</td>
<td>100 g (3.5 oz)</td>
<td>934</td>
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<tr>
<td>Mackerel, cooked</td>
<td>100 g (3.5 oz)</td>
<td>457</td>
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<tr>
<td>Sardines, canned in oil</td>
<td>50 g (1.75 oz) (drained)</td>
<td>98</td>
</tr>
<tr>
<td>Tuna fish, canned in oil</td>
<td>86 g (3 oz)</td>
<td>80</td>
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<tr>
<td>Milk, nonfat, reduced fat, and whole, vitamin D fortified</td>
<td>1 Cup</td>
<td>98</td>
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<tr>
<td>Margarine, fortified</td>
<td>1 Tablespoon</td>
<td>60</td>
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<tr>
<td>Pudding, prepared from mix and made with vitamin D fortified milk</td>
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