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Review

The complex interplay between vitamin D deficiency and diabetes

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Summary. It has been recently highlighted the link between vitamin D and metabolic and immunological processes, which established its role as an essential component of human health preservation. Vitamin D has been defined as natural immune modulators, and through the activation of its receptors (VDRs), it regulates calcium metabolism, cellular growth, proliferation and apoptosis, and other immunological functions. In this setting, vitamin D has also been reported to influence glucose regulation via effects on insulin secretion and action. Vitamin D deficiency is strongly associated with obesity mostly due to the storage of vitamin D in adipose tissue because of its lipophilic properties. The decrease in vitamin 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. On the other hand, retrospective analysis and observational studies demonstrated high prevalence of vitamin D deficiency in patients with type 1 diabetes and suggested a contributory role in the pathogenesis of type 1 diabetes, specially with certain allelic variations of the VDR. Vitamin D supplementation during pregnancy and early childhood decreased the risk of autoimmune diabetes and perhaps, even after the onset of diabetes, it may improve glycemic control. In addition, in subjects that are affected by a high risk of developing diabetes (impaired fasting glucose and/or glucose tolerance, possibly without obesity) vitamin D supplementation could be helpful on the prevention of type 2 diabetes.

Key words: Type 1 diabetes, type 2 diabetes, vitamin D

«Le complesse interazioni tra deficit di vitamina D e diabete»

Riassunto. È stata recentemente messa in evidenza la relazione tra vitamina D e processi immunologici e metabolici, che ha permesso di stabilire il ruolo di tale vitamina come componente essenziale del mantenimento dell'omeostasi dell'organismo umano. La vitamina D è stata definita come immunomodulatore naturale, e attraverso l'attivazione dei suoi recettori (VDR), regolatore del metabolismo del calcio, della crescita cellulare, della proliferazione e dell'apoptosi, nonchè di altre funzioni immunologiche. In questa contesto, la vitamina D è risultata in grado di influenzare la regolazione del metabolismo del glucosio tramite effetti sulla secrezione e sull'azione dell'insulina. La carenza di vitamina D è fortemente associata con l'obesità, soprattutto a causa del deposito di vitamina D nel

tessuto adiposo grazie alle sue proprietà lipofile. La diminuzione nei livelli di vitamina D può verificarsi attraverso diversi meccanismi, quali una diminuzione della concentrazione di calcio, un aumento di PTH o un effetto diretto della vitamina D sul peggioramento dell'insulino-resistenza e della secrezione insulinica, aumentando così il rischio di insorgenza di diabete di tipo 2. D'altra parte, studi retrospettivi e osservazionali hanno dimostrato un'alta prevalenza della carenza di vitamina D in pazienti con diabete di tipo 1 ed hanno suggerito un ruolo contributivo nella patogenesi del diabete di tipo 1, specialmente in associazione ad alcune variazioni alleliche della VDR. La supplementazione di vitamina D durante la gravidanza e la prima infanzia è risultata in grado di ridurre il rischio di diabete autoimmune e forse, anche dopo l'insorgenza del diabete, in grado di migliorare il controllo glicemico. Inoltre, nei soggetti che sono caratterizzati da un alto rischio di sviluppare il diabete (alterata glicemia a digiuno e/o tolleranza al glucosio, possibilmente senza obesità) la supplementazione di vitamina D potrebbe essere utile alla prevenzione del diabete di tipo 2.

Parole chiave: Diabete mellito tipo 1, diabete mellito tipo 2, vitamina D

Introduction

It has been recently highlighted the link between vitamin D and metabolic and immunological processes, which established its role as an essential component of human health preservation. Vitamin D has been defined as natural immune modulators, and through the activation of its receptors (VDRs), it regulates calcium metabolism, cellular growth, proliferation and apoptosis, and other immunological functions (1).

In this setting, vitamin D has also been reported to influence glucose regulation via effects on insulin secretion and action (2). Vitamin D insufficiency, typically assessed by circulating blood levels of 25-hydroxy vitamin D (25(OH)D), has long been suspected as a risk factor for Type 1 diabetes (T1D)(3). This finding was explained by the higher rates of metabolic disorders including diabetes and hypertension (4,5) with increasing distance from the equator, suggesting possible associations of vitamin D insufficiency in areas with less sunlight. More recently, there is accumulating evidence to suggest that altered vitamin D and Calcium homoeostasis may play a role in the development of Type 2 diabetes (T2D)(6–9).

The aim of our literature review is to analyze the current knowledge about:

a) the metabolism of vitamin D
b) the prevalence of vitamin D insufficiency/deficiency in patients with T1D and T2D
c) the relationship between vitamin D and insulin incretion
d) the therapeutic effects of vitamin D supplementation on disease severity and progression.

The metabolism of vitamin D

Vitamin D is the derivative of a steroid, 7-dehydrocholesterol, which is derived from cholesterol and it is found in the sebaceous glands of the skin of animals. Upon exposure to sunlight, 7-dehydrocholesterol will absorb UVB light (280 to 315 nm) and convert to precalciferol in the skin. Much of the precalciferol eventually is isomerized into cholecalciferol (also called vitamin D3) through thermal conversion (10).

Both vitamin D3 formed in the skin and vitamin D3 absorbed from the digestive tract, travel to the liver, where they are hydroxylated at carbon 25 to form calcidiol (also called 25-hydroxy vitamin D3, abbreviated as 25(OH)D) by liver 25-hydroxylase, CYP2R1 and CYP27A1. 25(OH)D is the major circulating vitamin D metabolite and a reliable indicator of vitamin D status. Following the hydroxylation in liver, calcidiol is further hydroxylated by 1-α-hydroxylase, CYP27B1, in the proximal convoluted tubule cells of kidney, forming calcitriol (also called 1,25-dihydroxy vitamin D3, abbreviated as 1,25(OH)2D) which is considered the active form of vitamin D (11).

At the cellular level, 1,25(OH)2D interacts with nuclear vitamin D3 receptor (VDR), which belongs to the superfamily of nuclear hormone receptors, to modulate gene transcription.

Ligand binding initiates a conformational change that increases the receptor's affinity to the retinoid X receptor (RXR). Once the VDR-1,25(OH)2D complex is heterodimerized with RXR, this complex will bind to vitamin D3 response elements (VDREs) and recruit a number of nuclear coactivator or corepressor proteins. The transcription of genes for specific mRNA may be ultimately either enhanced or inhibited by this ligand-activated transcription factor (12, 13).

Prevalence of vitamin D insufficiency/deficiency in patients with Type 1 diabetes and Type 2 diabetes

Several studies have examined the prevalence of vitamin D deficiency among individuals with T1D, both in childhood and adulthood and in a variety of geographic locations (14).

A case-control survey of 170 Qatari youth with T1D and 170 age-, gender- and ethnicity-matched controls demonstrated a significant increase in the prevalence of vitamin D deficiency (25OHD/30 ng/ml) in the T1D subjects (90.6%), in a country in which vitamin D deficiency in non-diabetic children was also high (85.3%), likely due to culturally limited sunlight exposure (15). In this analysis, the incidence of fractures and a family history of vitamin D deficiency were also significantly higher in diabetic children.

Another prospective study of 129 Swiss children and adolescents with T1D also reported a high prevalence of vitamin D deficiency (25OHD/50 nmol/L) in these patients (60.5%), possibly attributed to the absence of vitamin D supplementation in many Swiss foods (16).

In this study a control group comparison was not available.

An older, but larger study of young adults in Sweden demonstrated lower levels of vitamin D in participants with T1D compared with age and sex-matched controls, both at the time of diagnosis and when assessed 8 years later, particularly in diabetic men (17) Interestingly, they noted a positive correlation between 25OHD concentrations at diagnosis and at 8-year follow-up, but no correlation with HbA1c, suggesting perhaps an individual propensity toward deficiency.

Consistent with the data from the northern hemisphere, an australian study of 47 adolescents with T1D, compared with gender- and age-matched historical control data, also reported a significantly lower mean 25OHD level in T1D participants (54.7 nmol/L vs. 64.6 nmol/L) (18); furthermore, adolescents with T1D were three times more likely to have vitamin D deficiency (B50 nmol/L).

Vitamin D insufficiency was also reported as common in a study of pediatric patients with T1D in the northeastern United States; 25OHD levels <30 ng/ml were present in 76% of subjects, and 25OHD concentration correlated negatively with age (19) And, in our own investigation of T1D subjects (14–40 years of age) in a southern US location, we found that 25OHD concentrations were lower in participants with T1D (n = 115) and 53% of T1D participants were vitamin D insufficient (B30 ng/ml) while only 38% of age-matched healthy control participants (n = 55) were vitamin D insufficient (20).

Finally, a recent comparison of 25OHD concentrations measured in 720 T1D plasma samples and 2,610 control plasma samples in the United Kingdom also confirmed that both male and female T1D subjects had lower circulating levels of 25OHD compared with the general population (21).

In contrast to these studies, Bierschenk and coworkers (22) demonstrated that median 25OHD levels were comparable between established T1D subjects, new-onset T1D subjects and control subjects (including first-degree relatives of T1D subjects), when studied in individuals residing in a solar rich environment in the United States. Interestingly, however, in this study, vitamin D levels in all groups were suboptimal, with 76.1% of new-onset T1D, 68.5% of established T1D and 70.1% of control subjects having 25OHD levels below 30 ng/ml (22). By comparison, in a recent study of 57 adolescent subjects with T1D recruited from the Diabetes Center at Vanderbilt Medical Center, the authors report that serum 25OHD levels were comparable to a general adolescent population, as reported by the National Health and Nutrition Examination Survey (NHANES 2001–2004) (23); furthermore, when comparing the T1D subjects with HbA1c values C9% (n = 27) to those with HbA1c values <9% (n = 30), they found no difference in 25OHD status or bone mineral density (BMD) between groups (24). In this study, however, only 43% of T1D women and 40% of T1D men had 25OHD levels >30 ng/ml.

Lower vitamin D levels are present in both obese adolescents and obese adults (25, 26); also, an inverse correlation between vitamin D and body mass index (BMI) has been established (27, 28), attributable in part to increased vitamin D storage in adipose tissue (29). Because obesity is a primary risk factor for T2D, lower vitamin D levels in T2D would be anticipated. In addition, some studies have demonstrated an association between lower vitamin D levels and either metabolic syndrome or carbohydrate intolerance. Despite this, studies examining vitamin D levels in patients with established T2D provide inconsistent results (14).

Cross-sectional studies in adults comparing T2D with geographic controls have demonstrated: (1) a higher prevalence of vitamin D deficiency (<50 nmol/L) in South Asians with T2D living in the United Kingdom (30) (2) a lower prevalence of severe vitamin D deficiency (<12.5 nmol/L) in Saudi Arabians with T2D (31) and yet (3) a similar prevalence of deficiency in elderly patients with T2D in Indonesia (<50 nmol/L) (32).

In African Americans, a concurrent racial disparity characterized by both lower serum 25OHD levels (25, 26) and a higher prevalence of T2D, compared with European Americans, would predict an overlap of vitamin D deficiency and T2D in this group. Studies directly examining the prevalence of vitamin D deficiency among African Americans with T2D are limited; however, an analysis of serum 25OHD concentrations, diabetes and ethnicity from the National Health and Nutrition Examination Survey, years 1988–1994 (NHANES III), failed to confirm an association between serum 25OHD quartile and diabetes relative risk in non-Hispanic blacks, though the expected inverse correlation was seen in non-Hispanic whites and in Mexican Americans (26). In contrast, a study of 133 adults with diabetes (116 with T2D, 17 with T1D) evaluated at a US academic medical center confirmed a high combined prevalence of vitamin D deficiency (51.1%; B20 ng/mL) in this cohort and reported relatively lower 25OHD levels in African Americans.

Studies directly comparing vitamin D deficiency in T1D and T2D are also imperfect. A study by Di Cesar and coworkers (33) reported that 63.5% of adult type 2 diabetics (n = 50) were vitamin D deficient (<20 ng/ml) compared with only 36% of type 1 diabetics (n = 63), though their T1D cohort was significantly younger (49 vs. 61 years) and had a lower BMI (26 vs. 34 kg/m).

These studies suggest that the relationship between T2D and vitamin D is multifactorial and concurrently influenced, at minimum, by ethnicity, geography, BMI and age. Studies have also examined vitamin D levels as they relate to the relative risk of T2D, though this type of analysis does not directly address the prevalence of vitamin D deficiency in individuals with T2D. Nevertheless, a meta-analysis of 28 studies, including 99,745 adult participants demonstrated that higher levels of vitamin D in middle-aged and elderly individuals were associated with a 55% reduction in relative risk of T2D (34). Another meta-analysis reviewing all MEDLINE observational studies reported through January 2007 combined data from those studies that reported an association between 25OHD level and prevalent T2D (34). When data from non-Hispanic blacks were excluded, they found a significant inverse association between 25OHD concentration and T2D (OR = 0.36; 95% CI: 0.16, 0.80). These authors also examined case-control studies from the same time period and noted that of 13 studies published from 1979 to 2006, 10 studies reported lower serum 25OHD levels in patients with T2D or glucose intolerance, compared with nondiabetic controls (35). An examination of 3,983 adults participating in the NHANES Survey for years 2001-2002 and 2003–2004 also suggested that 25OHD levels were negatively associated with the prevalence of diabetes (36).

In contrast, a population-based longitudinal assessment over 11 years of follow-up in Norway demonstrated that while individuals in the lowest quartile for serum 25OHD concentration had an increased hazard ratio for T2D (RR = 1.89), adjustment for BMI eliminated this as a significant risk association (37).

Studies have also examined prospectively, whether low serum 25OHD levels impact, prospectively, the development of T2D at some time in the future. A recent population-based prospective study of 5,200 Australian men and women in which serum 25OHD levels were assessed at baseline demonstrated that during a 5-year follow-up period, each 25-nmol/L increment in serum 25OHD was associated with a 24% reduced risk of subsequently being diagnosed with T2D (38).

Similarly, a retrospective analysis of pooled data available from two nested case–control studies collected between 1973 and 1980 in Finland, demonstrated that during a 22-year follow-up period, men (free of diabetes at baseline) with baseline serum 25OHD levels in the highest quartile had a significantly reduced risk of incident diabetes (39, 40). One of these two studies, however, demonstrated that participants in the highest serum 25OHD quartile also had lower BMIs (41), reinforcing the hypothesis that obesity is a common risk factor for both vitamin D deficiency and future T2D. A study examining 524 non-diabetic European-origin adults found that baseline 25OHD levels were significantly inversely associated with 10-year risk of hyperglycemia and insulin resistance, even after adjusting for BMI (42). Finally, in a very recent study of 489 Canadian adults considered at risk for T2D, a higher baseline 25OHD level independently predicted better b-cell function and glucose homeostasis 3 years later (43).

Vitamin D deficiency and risk of diabetic complications

Vitamin D deficiency is associated with increased inflammatory markers in diabetics including CRP, monocyte toll-like receptor (TLR) 2, TLR4, and nuclear factor-kappa B (NFKB) expression; this might predict increased microvascular complications.

However, no statistically significant difference was found in 25-OH D levels in diabetics with microvascular complications compared to those without (44) On the other hand, another study showed that persistent microalbuminuria is associated with lower 25-OH D levels in T1DM compared to controls (45) Cardiovascular diseases increased with low 25-OH D levels in the general population (46) but these results have not been specifically studied in diabetics.

25-OH D deficiency has been prevalent upon the initial presentation of T1DM patients who presented with DKA, making it a contributing factor. However, given that levels improved spontaneously after correction of acidosis, the direct contribution of 25-OH D deficiency in the acute presentation of DKA remains controversial (47).

Role of Vitamin D deficiency in the pathogenesis of diabetes

Association between Vitamin D and insulin resistance.

25-OH D plays an important role in glucose homeostasis via different mechanisms. It not only improves insulin sensitivity of the target cells (liver, skeletal muscle, and adipose tissue) but also enhances and improves β-cell function. In addition, 1,25-dihydroxyvitamin D protects β- cells from detrimental immune attacks, directly by its action on β-cells, but also indirectly by acting on different immune cells, including inflammatory macrophages, dendritic cells, and a variety of T cells. Macrophages, dendritic cells, T lymphocytes, and B lymphocytes can synthesize 25-OH D, all contributing to the regulation of local immune responses (48, 49)

Vitamin D associated gene polymorphisms and insulin resistance

Gene polymorphisms of the DBP, VDR, or vitamin D 1alpha-hydroxylase (CYP1alpha) genes may affect insulin release and result in insulin resistant. In addition, these gene polymorphisms may disturb vitamin D production, transport, and action (48).

Electrophoretic variants of DBP have been associated not only with diabetes, but also with prediabetic traits. Two frequent missense polymorphisms at codons 416 GAT → GAG (Asp → Glu) and 420 ACG → AAG (Thr → Lys) in exon 11 of the DBP gene are the genetic basis for the three common electrophoretic variants of DBP (Gc1F, Gc1S, and Gc2) and the resulting circulating phenotypes (Gc1F/Gc1F, Gc1F/Gc1S, Gc1S/Gc1S, Gc1F/Gc2, Gc1S/Gc2, and Gc2/Gc2) (44). These variants of DBP are the serum carriers of vitamin D metabolites and have been associated with a higher risk of type 2 DM or prediabetic phenotypes in several studies (50-54). However, some studies have shown that the genetic variants of the DBP gene are not associated with diabetes (55, 56).

VDR functions as a transcription factor when bound to 25-OH D. VDRs are present in pancreatic β-cells and vitamin D is essential for normal insulin secretion (57). Several VDR polymorphisms have

been found since the early 1990s, including Apa1 (58), EcoRV, Bsm1 (59), Taq1 (60), Tru91 (61), Fok1 (62), and Cdx2 (63). To date, three adjacent restriction fragment length polymorphisms for Bsm1, Apa1, and Taq1at the 3' end of the VDR gene have been the most frequently studied (64) VDR polymorphisms have been reported to be related to type 1 DM (65-67).

The Bsm1 polymorphism has been shown to be associated with type 1 DM in Indians living in the south of the country (65), and combinations of Bsm1/Apa1/Taq1 have been shown to influence susceptibility to type 1 DM in Germans (66). In a Taiwanese population, the AA genotype of the Apa1 polymorphism was found to be associated with type 1 DM (67). In type 1 DM, four well-known polymorphisms (Fok1, Apa1, Bsm1, and Taq1) in the VDR gene have been implicated in the susceptibility to type 1 DM, however the results to date have been inconclusive. A metaanalysis (57 case-control studies in 26 published studies) indicated that the Bsm1 polymorphism is associated with an increased risk of type 1 DM (BB + Bb versus bb: OR = 1.30, 95% CI = 1.03–1.63), while the Fok1, Apa1, and Taq1 polymorphisms were not, especially in Asians (68). The VDR genotype may affect insulin resistance, both with regards to insulin secretion (the Apa1 VDR polymorphism) and insulin resistance (the Bsm1 VDR polymorphism) (69). In type 2 DM, the VDR gene polymorphism aa genotype was found to be associated with defective insulin secretion in Bangladeshi Asians, a population at increased risk of type 2 DM (70). The associations of the Fok1, Apal, Bsm1 and Taq1 polymorphisms of the VDR gene with type 2 DM were also explored in a case-control study (308 type 2 DM patients and 240 control cases). In this study, no associations were found between the four polymorphisms examined and type 2 DM (71). In another study, the distributions of alleles and genotypes of the four single-nucleotide polymorphisms in intron 8 (Bsm1, Tru91, Apal) and exon 9 (Taq1) of the VDR gene were similar in patients with type 2 DM (n = 309) and controls (n = 143) (72). Therefore, the evidence supporting an association of VDR genotypes with the risk of diabetes is conflicting (48).

Polymorphisms of the CYP1alpha gene involved in the metabolism of vitamin D may influence the susceptibility to type 2 DM. A study on the association of two markers, one in intron 6 and the other located upstream from the 5' end of the CYP1alpha gene, with type 2 DM in a Polish population found no differences in the distributions of genotypes, haplotypes, and haplotype combinations between the groups. However, the T-C/T-T heterozygous haplotype combination was more prevalent in the subgroup of obese type 2 DM patients (BMI ≥ 30) than in the controls (41.5% versus 28.6%, P = 0.01), suggesting an association with the risk factors for diabetes and obesity (73, 48).

Effects of Vitamin D on the immune system and insulin resistance

Basic science and epidemiological studies indicate that vitamin D has importance not only for cardiovascular health, but also for the immune response. Vitamin D has been shown to have a role in the development and function of the immune system. In fact, inadequate vitamin D and other nutrients during the development of the immune system may play a critical role in the development of autoimmune diseases. Evidence from animal models and prospective studies of rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, and type 1 DM suggests that vitamin D has an important role as a modifiable environmental factor in autoimmune diseases (74-76).

The immune system plays a central role in the destruction of β-cells (77). The detection of VDR in almost all cells of the immune system, especially antigen-presenting cells (macrophages and dendritic cells) and activated T cells (78-80), led to the investigation of a potential role for vitamin D as an immunomodulator. In addition, activation of nuclear VDR is also known to modify transcription via several intracellular pathways and influence proliferation and differentiation of immune cells (81,82). The importance of vitamin D in immune regulation is highlighted by the facts that VDR is expressed in activated inflammatory cells, that T-cell proliferation is inhibited by 25 OH D, and that activated macrophages produce 25 OH D (78,83). Vitamin D signaling pathways regulate both innate and adaptive immunity, maintaining the associated inflammatory response within physiological limits. The innate immune response involves the activation of Toll-like receptors (TLRs) on polymorphonuclear cells,

monocytes, macrophages, and a number of epithelial cells (84). 1,25-dihydroxyvitamin D primarily influences dendritic cell maturation and macrophage differentiation, and also reduces the release of cytokines (85). The adaptive immune response is initiated by cells specializing in antigen presentation, including dendritic cells and macrophages, which are responsible for presenting antigens for specific recognition by T lymphocytes and B lymphocytes (86). 25 OH D exerts an inhibitory effect on the adaptive immune system by modifying the capacity of antigen-presenting cells (APCs) to induce T lymphocyte activation, proliferation and cytokine secretion (87). 25 OH D decreases the maturation of dendritic cells and also inhibits the release of interleukin-12 (IL-12) (stimulating T-helper 1 cell development), IL-2, interferon-γ (INF-γ), and tumor necrosis factor α (TNFα) (stimulators of inflammation), which involves the destruction of β-cells resulting in insulin resistance. Overall, 25-OH D directly modulates T-cell proliferation and cytokine production, decreases the development of T helper 1 (TH1) cells, inhibits TH17 cell development, and increases the production of Thelper 2 (TH2) cells and T regulatory cells (88). These immunomodulatory effects of 1,25-dihydroxyvitamin D can lead to the protection of target tissues, such as β-cells (48).

Inflammation, Vitamin D, and insulin resistance

Chronic inflammation is involved in the development of insulin resistance, which increases the risk of type 2 DM. VDR is known to be expressed bymacrophages and dendritic cells, suggesting that vitamin D plays an important role in the modulation of inflammatory responses (89). Both cell types express the enzymes vitamin D-25-hydroxylase and 1α-hydroxylase and can produce 1,25-dihydroxyvitamin D (90) Several studies have supported the role of vitamin D and 1,25-dihydroxyvitamin D as an anti-inflammatory agent. Macrophages are cells with a large capacity for cytokine production, in particular TNFα, which is one of the most important products released from these cells. The transcriptional activation of the TNFα gene in macrophages is largely dependent on nuclear factor κB (NF-κB) dependent transcriptional activation (91). In lipopolysaccharide-(LPS-) stimulated murine macrophages, 25-OH D upregulates IκB-α (the inhibitor of NF-κB) by increasing mRNA stability and decreasing IκB-α phosphorylation. Furthermore, increased IκB-α levels can reduce the nuclear translocation of NF-κB (92). In addition, 25-OH D suppresses the expressions of TLR2 and TLR4 proteins and mRNA in human monocytes in a time- and dose-dependent fashion (93). Recently, it has also been suggested that inflammation and activation of the innate immune system could be downregulated by hydroxyvitamin D by increased levels of inflammatory markers (TNFα, IL-6, IL-1, IL-8, cyclooxygenase-2, intercellular adhesion molecule-1, and B7-1) in monocytes from type 2 DM compared with monocytes from healthy controls (94). In summary, 1,25-dihydroxyvitamin D inhibits the release of the pro-inflammatory cytokine TNFα and regulates the activity of NF-κB, (95) and suppresses the expressions of TLR2 and TLR4 proteins and mRNA in human monocytes, reducing the release of cytokines. Therefore, vitamin D may also function to reduce insulin resistance and the risk of diabetes by decreasing inflammatory responses.

Other molecular actions of Vitamin D to alter glucose homeostasis

Several mechanisms have been proposed to explain the impact of vitamin D on insulin resistance including gene polymorphisms and the immunoregulatory function of vitamin D and inflammation as mentioned previously. The regulation of serum calcium via PTH and 1,25-dihydroxyvitamin D following changes in dietary calcium and obesity has been proposed to mediate the effects of vitamin D on insulin resistance (48).

Vitamin D and PTH have also been associated with a variety of other actions beyond their classical functions, including cell growth, differentiation and apoptosis. Both hormones have been shown to increase levels of intracellular calcium and other rapid signaling pathways in a variety of tissues including adipocytes and muscle cells. Vitamin D may reduce adiposity, thereby improving insulin sensitivity indirectly through improving muscle mass and the reduction in vitamin D status with increased adiposity (96). In addition, obesity, increasing sequestration of vitamin D

in adipose tissue, is also known to be associated with reduced vitamin D status.

Effects of vitamin D supplementation on diabetes severity and progression

Given that vitamin D deficiency increases the risk of diabetes development and supplementation showed protective effects, many studies looked at the protective effect of vitamin D on diabetes progression and control (97). One randomized controlled study aimed to assess the effect calcitriol (given as 0.25 mcg every other day) compared to nicotinamide, within 4 weeks of diabetes diagnosis, on the preservation of beta-cell function; it showed no improvement in C-peptide and HbA1c levels but significantly lower insulin doses in the calcitriol-treated group (98) Even when the dose of calcitriol was increased to 0.25 mcg daily and after a followup of 2 years, there was no protective effect of such supplementation on C-peptide levels (99). Conversely, in LADA patients, when calcitriol (0.5 mcg daily) was added to insulin, it showed stabilization or improvement in fasting and 2 h after 75-g glucose load C-peptide level at 1 year, especially in those whose diabetes duration was less than 1 year (100). Similarly, in a study in Saudi Arabia, vitamin D3 supplementation to T1DMpatients who were deficient showed improvement in glucose control (with significantly lower HbA1c) when 25OHD level reached >75 nmol/L at 12 weeks (101).

Guidelines of Vitamin D supplementation in children

The American Academy of Pediatrics and the Canadian Pediatric Association recommended vitamin D supplementation of 400 IU daily, starting the first few days of life (102). The Institute of Medicine (IOM) recommended that the adequate intake and RDA for children below 1 year of age is 400 IU/d and for all individuals of 1 year to 70 years should be 600 IU/d (103). It seems prudent to ensure that all infants in the United States and other areas with comparable sunlight exposure receive enough vitamin D, especially in winter (104)Whether these recommended doses are enough to allow extraskeletal benefits of vitamin D is still unknown. Until now, no specific recommendations regarding vitamin D supplementation in patients with T1DM or at risk of developing autoimmune diabetes (105) but intakes between 5 mcg daily and the 25 mcg daily, tolerable upper intake level, may be desirable (97, 104).

Conclusions and recommendations

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. On the other hand, retrospective analysis and observational studies demonstrated high prevalence of 25-OH D deficiency in patients with T1DM and suggested a contributory role in the pathogenesis of T1DM, specially with certain allelic variations of the VDR.

Vitamin D supplementation during pregnancy and early childhood decreased the risk of autoimmune diabetes and perhaps, even after the onset of diabetes, it may improve glycemic control.

Despite all these data, the best dose to be used and the target population in order to decrease the incidence of T1DM have not been yet defined. In addition, 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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