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New insights on the role of vitamin D in type 2 diabetes mellitus: Review Article

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Abstract: Background: Type 2 diabetes mellitus (T2DM) and vitamin D deficiency are both disorders of high prevalence in the world. Evidence supports an association between low vitamin D levels and risk for T2DM, and its complications. There remains insufficient evidence to suggest whether treatment of low vitamin D can prevent or improve T2DM. **Aim**: this review will focus on the current understanding of the role of vitamin D in the pathogenesis of T2DM, and questioning if vitamin D supplementation can improve the pancreatic function, thus providing a better glycemic control or slow down its complications. **Conclusion and recommendation**: deficient vitamin D levels increases the risk of developing T2DM. This finding highlights the need for conducting large-scale health screening to identify those at risk of DM using vitamin D blood level assessment. However, more studies are required to ascertain the effect of vitamin D supplementation in T2DM patients.

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INTRODUCTION

T2DM and vitamin D deficiency are two endemic disorders, showing high prevalence's in the world. T2DM prevalence is in a rise, around 285 million people have diabetes and this number is expected to reach 438 million by the year 2030; due to the obesity epidemic, ageing of populations, and sedentary lifestyle (Hu, 2011). Despite the advances in the diagnosis and management of diabetes, achieving optimal glycemic control is still considered challenging. This is because care of T2DM warrants intense life-style adaptations, polypharmacy and insulin centered regimens. In addition, progressive β-cell dysfunction and insulin resistance can make antidiabetic agents less effective (Faria et al., 2014; Garland et al., 2014; Montane et al., 2014).

Hypovitaminosis D has become endemic with a global prevalence of 30-87%, due to the use of sunscreen, protective clothing and hats; increase of obesity, inappropriate ingestion of foods rich in vitamin D, and ageing (Hilger et al., 2013). Also, sun exposure is often inadequate due to the sociocultural and religious practices prevalent in the some societies and there is a lack of a nationwide food fortification program for vitamin D (Souza et al., 2016).

Over the past decade, the relationship of vitamin D deficiency to the risk of developing DM and its complications has been of great interest to scientists (Huang et al., 2012; Haroon et al., 2015). Hypovitaminosis D has been independently associated with increased rates of T2DM, and metabolic syndrome, meanwhile, its higher plasma level has been related with a lower risk for the development of DM in high risk patients (Pittas et al., 2012; Lim et al., 2013; Kayaniyil et al., 2014). It has also been associated with markers of endothelial dysfunction and insulin resistance (O'Hartaigh et al., 2013; Bhadra et al., 2016).

T2DM and vitamin D deficiency have risk factors in common such as American-African race, obesity, aging and low physical activity. The presence of vitamin D receptors (VDR) and vitamin D-binding proteins (DBP) or Calbindin-D 28K in pancreatic tissue and the relationship between certain allelic variations in the their genes with glucose tolerance and insulin secretion have further supported this hypothesis (Gandhi et al., 2015). The major source of vitamin D is the sunshine; hence role of vitamin D in T2DM has been linked with seasonal variations in glycemic control which is worst in winters (Li and Zhou, 2015).

Kostoglou-Athanassiou et al., (2013) observed statistically significant more T2DM patients had vitamin D insufficiency/deficiency than their studied controls and an inverse relationship was found between HbA1c levels and 25(OH)D3 levels

in the patient group, implying that vitamin D levels may affect glucose control in T2DM.

Vitamin D replenishment improves glycemia and insulin secretion in T2DM patients with hypovitaminosis D. The results of vitamin D supplementation trials in preventing T2DM are rather conflicting however; it has been shown to be useful in improving impaired glucose tolerance in a pre-diabetic state (Kostoglou-Athanassiou et al., 2013; Song et al., 2013; Mahajan and Sharma, 2015).

This review will focus on the role of vitamin D as a genetic and environmental factor in T2DM, and its suggested protective role as a supplementation.

1. Biological pleotrophic effects of vitamin D on β-cells insulin secretion

There is ample evidence suggesting a role for vitamin D in insulin secretion, which includes the presence of 1α-hydroxylase, and DBP in pancreatic tissue (Mahajan and Sharma, 2015), and VDR in β-cells and skeletal muscle (Anagnostis et al., 2010).

Vitamin D may play a functional role on glucose tolerance through its effects on insulin secretion and insulin sensitivity (Palomer et al., 2008). It directly induces β-cell insulin secretion by increasing intracellular calcium concentration via non-selective voltage dependent calcium channels and by activation of β-cell calcium dependent endopeptidase which facilitates the conversion of proinsulin to insulin. It increases the responsiveness of cells to insulin by stimulating the expression of insulin receptors (Zittermann, 2006). Manna and Jain, (2012) showed that vitamin D upregulates GLUT-4 translocation to the cell surface leading to glucose uptake and utilization in adipocytes and myocytes having treated with high glucose. Variations in ionic calcium contribute to peripheral insulin resistance via impaired insulin signal transduction leading to reduced GLUT-4 activity. Moreover, calcium is not only necessary for insulin exocytosis but also for β-cell glycolysis, which plays a role in signaling circulating glucose concentration (Ojuka, 2004). Vitamin D also directly improves insulin sensitivity by upregulating PPAR, which has been associated with the regulation of fatty acid metabolism in skeletal muscle and adipose tissue by increasing the expression of carnitine palmitoyltransferase I, promoting β-oxidation, thus reducing lipid deposition and inhibits free fatty acid induced insulin resistance (Zittermann, 2006; Ning et al., 2015). 1,25(OH)D suppresses the renin gene reducing hyperglycemic induced increases in renin levels in pancreatic β-cells, and blockade of renin-angiotensin activity has been proposed as a novel target for diabetes treatment (Cheng et al., 2011). At the molecular level, vitamin D activates the transcription/ expression of the human insulin gene and vitamin D response element is also present in human insulin gene promoter region. The direct action of vitamin D on the β-cells through direct modulation of its growth has also been suggested to be responsible for increased insulin secretion (Zittermann, 2006).

T2DM has been traditionally regarded as a purely metabolic disorder. However, recent investigation has revealed the role of chronic inflammation in the T2DM pathogenesis. Palmitic acid acts on immune receptors such as TLR4, induces chronic low-grade tissue inflammation (Lee, 2014). Vitamin D behaves like an immunomodulator as it stimulates phagocytosis and suppresses the antigen presenting capacity and activation of IL-12. It attenuates the expression of proinflammatory cytokines involved in insulin resistance and β-cell apoptosis such as IL-1, IL-6, and TNF-α. It also down regulates the activation of NF-κB which is an important regulator of genes encoding pro-inflammatory cytokines implicated in insulin resistance (Palomer et al., 2008). Macrophages and dendtritic cells express 25- and -α hydroxylase enzymes and can synthesize active molecule of vitamin D which can suppress the expression of TLR2 and TLR4 molecules (Cohen-Lahav et al., 2007). It has been reported that $1,25(OH)_2D3$ preserve the insulin content of human islets and prevent MHCI expression, and NO release. These data clearly support the role of vitamin D in lowering the inflammatory responses in the body thereby protect the vital tissues such as β-cells from free radical mediated injury (Mahajan and Sharma, 2015). The beneficial effects of vitamin D in T2DM are also attributed to an increase in GSH levels (Jain et al., 2014; Mahajan and Sharma, 2015). The expression of DBP has been shown to protect β-cells from the destructive action of cytokines (Chun, 2012).

2. Role of vitamin D in the pathogenesis of T2DM

As vitamin D modulates insulin receptor gene expression and insulin secretion, it is an interesting environmental candidate for T2DM pathogenesis. The association of life style factors has also been explored. A lot of physical exercise is normally done outdoors and thus allows photosynthesis of vitamin D. Furthermore, vitamin D is a lipophilic vitamin and stored in body fat cells which makes it more difficult for obese people to take advantage of this vitamin (Thuesen et al., 2012).

2.1. Vitamin D deficiency and glycemic control in T2DM patients of different races

Hypovitaminosis D, owing to depletion or relative VDR resistance, has long been suspected to be a risk factor for glucose intolerance without altering glucagon secretion. The German LURIC study found that higher vitamin D levels were significantly associated with better glycemic status in 3,316 elderly patients scheduled for coronary

angiography (O'Hartaigh et al., 2013). Similar results were described by a Korean study group exploring 12,263 subjects of the Korea National Health and Nutrition Examination Survey older than 19 years (Rhee et al., 2012). A significant inverse relationship between vitamin D status and insulin resistance was also observed, independent of adiposity, in Korean adolescents (Chung et al., 2014). Additionally a meta-analysis with 3,612 diabetes cases (mean age 61.6 years) demonstrated an inverse association between circulating vitamin D and incident T2DM (Forouhi et al., 2012). A study on Indian Punjabi population showed insufficient as well as deficient vitamin D levels in type 2 diabetics as compared to healthy controls (Khanna et al., 2014). Another meta-analysis with 4,996 cases showed that each 10nmol/L increment in vitamin D levels was significantly associated with a 4% lower risk of T2DM (Song et al., 2013; Bachhel et al., 2015). In a cross-sectional analysis of a general population sample in eastern Finland, an inverse association was observed between 25(OH)D3 levels and fasting insulin, fasting glucose and 2 h glucose tolerance test, implying that low serum 25(OH)D3 may be associated with impaired glucose metabolism (Hurskainen et al., 2012). An inverse association of insulin resistance with 25(OH)D3 levels was observed which was profoundly found at 25(OH)D3 levels between 16-36ng/ml (Heaney et al., 2013). In a nested case-control study conducted among 608 women with newly diagnosed T2DM, higher plasma 25(OH)D3 concentration was associated with lower risk of T2DM (Pittas et al., 2010). In a prospective observational study with a mean follow up of 2.7 years, higher plasma 25(OH)D3 assessed repeat-edly was associated with a lower risk of incident diabetes in high-risk patients (Pittas et al., 2012). In a longitudinal study of the determinants of insulin resistance and the metabolic syndrome, a significant inverse association of baseline 25(OH)D3 with fasting glucose at follow up was observed (Kayaniyil et al., 2014). Significant negative correlation between 25(OH)D and HbA1c was also observed when compared between diabetic and nondiabetic patients (Laway et al., 2014; Papandreou and Hamid, 2015). A meta-analysis study by Forouhi et al., (2012) found a strong inverse association between baseline 25(OH)D and incidence of T2DM. Mauss et al., (2015) found a significant association of both FPG and HbA1c with severe 25(OH)D deficiency, in a large sample of healthy German working older adults. Apparently healthy people can suffer from vitamin D deficiency as well as from T2DM. One third (33%) of all diabetes cases in theirs apparently healthy study sample were newly detected reflecting the presence of a high proportion of undiagnosed diabetes cases in the population (Mauss et al., 2015). It has been reported that vitamin D deficiency makes a person 91% prone to insulin resistance and pre-diabetic state even in the presence of normal blood sugar levels, as well as increase the risk of microvascular complications in T2DM (Bajaj et al., 2014; Mahajan and Sharma, 2015). Vitamin D replenishment improves glycemia and insulin secretion in patients with T2DM with established hypovitaminosis D, thereby suggesting a role for vitamin D in the pathogenesis of T2DM (Alam et al., 2014). Maintaining vitamin D at adequate levels can be a useful preventive technique, since vitamin D status in healthy adults was inversely associated with future risk of T2DM (Khan et al., 2013). Vitamin D dose in initial years of life is shown to reduce risk of future development of disease modulated by immune protective effects (Harinarayan, 2014). Therefore vitamin D deficiency may be related to impaired insulin secretion /insulin resistance in T2DM (Talaei et al., 2013).

However, in a large cohort study of older adults involving 7791 subjects, initially diabetes-free, serum 25(OH)D levels were inversely associated with incident diabetes in women but not in men (Schöttker et al., 2013). Many studies have explored the association of T2DM and vitamin D levels in older and chronically ill participants, but not in healthy working adults populations (Mattke et al., 2013). Meanwhile, others reported no association between T2DM and vitamin D levels (Talaei et al., 2013). Another meta-analysis reported a small improvement on fasting glucose and insulin resistance but no beneficial effect was seen on HbA1c (Husemoen et al., 2012). Also, an inverse association of 25(OH)D with HbA1c was not detected in younger Americans (Ford et al., 2011).

2.2. Vitamin D deficiency and diabetic complications

Vitamin D involvement in diabetic complications was also reported in some studies. Wang et al., (2008) studied 1739 Framingham participants without prior cardiovascular disease, and found that low 25(OH)D levels <15ng/ml have been shown to correlate with the presence of cardiovascular disease in diabetics. An inverse independent relationship was shown between circulating 25(OH)D levels and the prevalence of microvascular complications in T2DM patients (Sadiya et al., 2016). Vitamin D deficiency was associated with the presence of diabetic retinopathy, and those with more advanced stages (grades 2-4) had lower concentrations of 25(OH)D. Also, Low vitamin D status is characteristically associated with advanced diabetic nephropathy (Alcubierre et al., 2015). Good status of vitamin D could delay diabetic nephropathy (Mao et al., 2014) through protection of podocyte or by reducing the

renal fibrosis as shown in mice experiment (Zhang et al., 2014; Papandreou and Hamid, 2015). In addition, vitamin D administered to T2DM with nephropathy was found to ameliorate albuminuria (Huang et al., 2012). At a molecular level, vitamin D appears to reduce oxidative stress (Salum et al., 2013).

2.3. Role of gene polymorphism in vitamin D related molecules in T2DM

Polymorphisms in the candidate genes: VDR, DBP and 1α-hydroxylase were positively linked to T2DM (Ogunkolade et al., 2002), but not in all population studies (Reis et al., 2005). Genetic alterations might contribute to the pathogenesis of T2DM by at least four different mechanisms: alteration in calcium metabolism, modulation of adipocyte function, modulation of insulin secretion and modification of cytokine expression (Palomer et al., 2008).

2.3.1. VDR gene polymorphism

VDR is a member of nuclear receptor superfamily of ligand activated transcription factors when bound to 1,25(OH)2D3. More than 25 different polymorphisms in the VDR locus, such as Apa1, Taq1, Bsm1 and Fok1 have been linked with insulin secretion and sensitivity in few but not in all T2DM population studies (Tuorkey and Abdul-Aziz, 2010). Apa1 was associated with lower insulin secretion in healthy Bangladeshi Asian population (residing in London) with vitamin D deficiency (Hitman et al., 1998). Taq1 has been reported to be an independent predictor of insulin secretion. While Bsm1 and Apa1 were associated with fasting glucose, HOMA-IR, postprandial C-peptide levels "has a possible role in the T2DM pathogenesis"; on the other hand, Fok1 was linked with insulin resistance (Angel et al., 2004). BsmI predisposes to altered calcium absorption, elevated parathyroid hormone (PTH) and T2DM, and is associated with elevated fasting glucose in healthy young men long before the onset of T2DM (Ortlepp et al., 2003). FokI can further influence the severity of metabolic syndrome in T2DM Egyptian patients (Mackawy and Badawi, 2014). Inhibition of vitamin D binding to its receptor and subsequent signaling might alter the cytokine secretion profile (Chun, 2012). Thus, altered transcription of the VDR gene in pancreatic β-cells can modify insulin secretion and might lead to a higher degree of insulin resistance on adipocytes (Palomer et al., 2008). These data provide evidence for VDR as a candidate gene contributing to the susceptibility to T2DM (Papandreou and Hamid, 2015).

On the contrary, in Polish, Chile and Finnish Caucasians populations, no positive association of VDR polymorphism with T2DM has been reported (Reis et al., 2005). Ye et al., (2001) concluded that VDR polymorphisms were not a major predisposing gene for T2DM in Caucasians, despite being associated with susceptibility to obesity. They suggested that this effect could be related to a direct action of vitamin D on adipocyte differentiation and metabolism or to an indirect modulation of insulin secretion (Ye et al., 2001).

Therefore, the evidence supporting the association of VDR polymorphism with T2DM is still conflicting and requires more studies (Palomer et al., 2008; Mahajan and Sharma, 2015). Shab-Bidar et al., (2011) elucidated the discrepancies in the results of different vitamin D-diabetes studies pertaining to the genetic variations of the population.

2.3.2. Gene polymorphism in DBP "Calbindin-D 28k gene"

Polymorphism in this gene has been associated with increased risk of prediabetic phenotype and T2DM in many (Mahajan and Sharma, 2015) but not in all studies (Ye et al., 2001). Alterations in serum DBP concentration usually coincide with parallel changes in the total concentration of vitamin D. DBP was found to be linked to fasting insulin in a genome scan in Pima Indians with T2DM. Further, studies in subarctic Amerindians, Polynesian and Japanese T2DM subjects indicated an association of the Gc1allele with fasting insulin and plasma glucose (Palomer et al., 2008).

By contrast, Iyengar et al., (1989) found no relationship between the Gc genotype and fasting insulin levels in a Hispanic population of the San Luis Valley. It has been postulated that nutritional differences might account for the lack of relationship between the Gc genotype and glucose in the latter study (Palomer et al., 2008). However, other studies in American, French and Polish Caucasian populations found no evidence of an association between DBP polymorphisms and T2DM. These discordant findings may be related to dissimilar genetic backgrounds of the populations' studied (Malecki et al., 2002). Thus, the effect of DBP variants on the development of T2DM may be characteristic of non-Caucasian populations (Palomer et al., 2008).

T2DM is polygenic, therefore, many different combinations of alleles may exist among patients. As a consequence, abnormalities in insulin secretion associated with DBP polymorphisms might play an important role only in certain environmental or genetic backgrounds. It has been suggested that the different DBP variants bind the diverse vitamin D metabolites with variable affinity, thereby affecting the intracellular amount of vitamin D in the β-cell. Alternatively, if DBP binds to other ligands such as fatty acids, it may exert its action by means of an increase in the concentration of islet fatty acids, which may finally induce β-cell abnormalities (Palomer et al., 2008).

2.3.3 Gene polymorphism in 1α-hydroxylase (CYP1 α) gene

Polymorphism in this gene may influence the risk of T2DM due to deficient vitamin D production. However, Malecki et al., (2003) observed that CYP1**α** was not a major gene for T2DM in Polish Caucasian subjects. Some in vitro studies suggest a direct effect of this gene on vitamin D action in adipocyte metabolism (Malecki et al., 2003).

The accumulated evidence indicates that although gene polymorphism in VDR and in other candidate genes influences the risk of developing T2DM, the conclusions are relatively variable in different cohorts. The reasons may be variable because of ethnic variations, study design, gene environment interactions, dietary and life style factors. This strongly suggests the need to conduct more studies in different populations in order to draw any definite conclusions.

3. Intervention trials using vitamin D supplementation for T2DM patients of different races

Effects of vitamin D supplementation on glucose homeostasis have been shown in numerous studies. Insufficient vitamin D and calcium hinders the glycemic control and supplementation of both nutrients is essential to optimize glucose metabolism (Pittas et al., 2006). In addition, in peo-ple with a tendency to develop T2DM, optimal blood levels of vitamin D may retard the clinical development of T2DM (Kostoglou-Athanassiou et al., 2013).

For example, Inzucchi et al., (1998) showed a 60% improvement in insulin sensitivity by increased serum 25 (OH)D concentration from 10-30 ng/ml. Von Hurst et al., (2010) showed that vitamin D supplementation significantly improved insulin sensitivity. Talaei et al., (2013) showed that mean FPG was significantly reduced after increased vitamin D intake. Monthly supplementation with 120,000 units of vitamin D also improved insulin sensitivity (Pittas et al., 2006). One study on 5,677 subjects with impaired glucose tolerance showed that vitamin D supplementation increased insulin sensitivity by 54% (Inzucchi et al., 1998). One follow-up study, through 20 years on 4,843 patients with T2DM, showed that vitamin D intake was associated with reduced prevalence of the T2DM (Zehra and Tahseen, 2010; Mitri et al., 2011). In a randomized controlled trial, the administration of 2000IU cholecalciferol daily for 16 weeks was found to improve β-cell function in adults at high risk for diabetes (Boucher et al., 1995). A meta-analysis of 21 prospective studies revealed that higher $1,25(OH)_2D_3$ levels were associated with lower risk of T2DM and this association was not affected by age, sex, duration of follow-up, sample size, diabetic diagnostic criteria and assay procedure. They further stated that each 10nmol/l increase in $1,25(OH)_2D_3$levels were associated with a 4% lower risk of T2DM (Song et al., 2013). Nurses Health Study reported an increased risk of T2DM in 8,3779 females in the age group of >20 years who had deficient vitamin D levels. The study advocated the combined daily intake of >800IU of vitamin D and >1200mg of calcium to lower the risk of diabetes by 33% (Pittas et al., 2006; Mitri et al., 2011). Prolonged treatment of osteomalacia with vitamin D increases insulin secretion and improves glucose tolerance (Palomer et al., 2008). Many studies showed significant improvements in serum FPG, insulin and in HOMA-IR after treatment with vitamin D, suggested that vitamin D supplementation could reduce insulin resistance in T2DM (Mahajan and Sharma, 2015).

3.1. Inconsistent/conflicting results regarding vitamin D supplementation for T2DM

Studies on associations between insulin secretion and serum 25(OH)D have been inconsistent. Vitamin D supplementation improves stimulated insulin secretion in response to an oral glucose load in patients with impaired glucose tolerance, in non-diabetic healthy subjects, but not in patients with established T2DM and is accompanied by a significant increase in serum calcium levels and a reduction in serum free fatty acid levels (Zittermann, 2006). Short-term vitamin D replenishment in Bangladeshi Asian population increased insulin secretion without altering glycemia, while longer vitamin D treatment also improved glucose levels (Boucher et al., 1995). It has been reported that vitamin D treatment in a T2DM Bulgarian female patients with a high prevalence of hypovitaminosis D, partially normalized insulin secretion and action (Borissova et al., 2003). Results of the various short-term meta-analysis studies (follow up ≤ 3 months) suggested that vitamin D supplementation had a positive impact on glycemic control and metabolic parameters such as insulin resistance and β-cell dysfunction. However, there was no such effect in the long-term studies (follow up > 3 months). Haroon et al., (2015) concluded from the assessment of 17 randomized control trials and 7 longitudinal studies that vitamin D supplementation did not improve hyperglycemia, β-cell secretion, or insulin sensitivity. Moreover, serum 25(OH)D3 levels were not related to glucose status in an English population (Palomer et al., 2008). In a meta-analysis involving 328 patients and 6 randomized controlled trials (RCTs), vitamin D supplementation was shown to improve HbA1c but failed to show any improvement in other parameters such as fasting blood glucose, HOMA-B, and HOMA-IR (Gao et al., 2013). Some Iranian studies also showed that calcitriol, and vitamin D injection couldn't have effect on diabetes and

insulin resistance, although some of them reported significant effects (Bonakdaran and Afkhami Zadeh, 2011).

However, conflicting results have also been obtained (Witham et al., 2010; Al-Daghri et al., 2012; Heshmat et al., 2012; Breslavsky et al., 2013). It has been reported that vitamin D replacement in Asian population with vitamin D deficiency and T2DM resulted in an increase in insulin resistance and worsening of glycemic control (Forouhi et al., 2012). Also, RCTs demonstrated a lack of significant effect on glycemic parameters (Khanna et al., 2014). A meta-analysis reported that vitamin D supplementation did not reduce the risk of developing diabetes over 7 years of follow-up. They further concluded that probably higher levels of vitamin D affect the risk of T2DM (Mahajan and Sharma, 2015). Witham et al., (2010) found out that vitamin D intake (at different dosage) had no effects on insulin resistance or on HbA1c as did Lind et al., (1989). Nagpal et al., (2009) reported that vitamin D supplementation had no effect on mean of insulin sensitivity but two years treatment with vitamin D did improve HOMA-IR. Haroon et al., (2015) concluded that vitamin D3 supplementation might not decrease insulin resistance and hyperglycemia in patients with established T2DM. Similarly, another meta-analysis concluded that there was insufficient evidence to support a beneficial role of vitamin D on hyperglycemia or insulin resistance (George et al., 2012). However, this analysis was conducted by pooling data from patients with normal glucose tolerance, impaired glucose tolerance and T2DM (Heaney et al., 2013), and the literature search was restricted to March 2011 and hence they captured very limited number of studies. Vitamin D may affect adipogenesis thus modulating energy expenditure in adipose tissue; this may explain why the administration of vitamin D to patients with DM and the metabolic syndrome appears to have contradictory results (Landrier et al., 2012; Kostoglou-Athanassiou et al., 2013). Current evidence based on randomized controlled trials and longitudinal studies do not support that vitamin D supplementation can improve hyperglycemia, β-cell secretion or insulin sensitivity in patients with established T2DM. This showed that the pathogenetic and therapeutic role of vitamin D in glucose metabolism is still unclear. Large-scale trials with proper study design, optimal vitamin D supplementation and longer follow up need to be conducted (Haroon et al., 2015).

3.2. Interpretation and limitations of research studies in consideration

Nevertheless, while some publications report associations of vitamin D levels and T2DM (Schöttker et al., 2013); there are others stating the opposite (Mauss et al., 2015); indicating a lack of reliable evidence. Furthermore, inconclusive results whether vitamin D supplements are beneficial for otherwise healthy adults in preventing diseases beyond bone disorders Schöttker et al., 2013; Mahajan and Sharma, 2015). An explanation for the lack of association could be the existence of a variable threshold among the different ethnic groups. It has been reported that non-Hispanic black people had decreased sensitivity to vitamin D or PTH (Scragg et al., 2004; Palomer et al., 2008; Jorde et al., 2013; O'Hartaigh et al., 2013). The positive effect of vitamin D on β-cell function and glucose tolerance is partly being due to correction of hypocalcemia and secondary hyperparathyroidism (Haroon et al., 2015). Individual variability may also be partly explained by VDR polymorphisms. In addition, 25(OH)D3 was chosen as a marker of vitamin D deficiency, as currently recommended, however, vitamin D circulates in several forms in the blood (Kostoglou-Athanassiou et al., 2013). Almost all studies assessed insulin secretion or sensitivity and resistance based on HOMA related parameters that are not as accurate as the glucose clamp techniques (Haroon et al., 2015). Kampmann et al., (2014) used the gold-standard method of hyperglycemic clamp however; no significant association was also noted. Limitation of some studies in that they did not evaluate the effects of placebo on FPG, insulin or HOMA-IR, however, they evaluated the effects of vitamin D at different doses on glucose homeostasis (Pittas et al., 2006).

Also, the generalizability of the findings is somewhat limited as some samples consisted predominantly of: male industrial workers in certain country, females, healthy subjects; those with impaired fasting glucose or T2DM (Schöttker et al., 2013). Also a lot of heterogeneity in the ethnicity, methodology of the studies (short term trials versus long term), small sample size, supplementation of vitamin D (oral dose versus intramuscular; ergocalciferol versus calcitriol or cholecalciferol); the appropriate dose of vitamin D that can achieve non-skeletal benefits which still remains unclear (Palomer et al., 2008; Haroon et al., 2015). As observed in some studies, supraphysiological dosing of vitamin D may have been harmful (Jorde et al., 2013). Moreover, many studies did not analyze the effect of all possible confounders e.g. baseline vitamin D status, HbA1C "a better marker of glycemic status" and anti-diabetic medication of participants. This information's should be included in the medical history assessment of further studies (Mauss et al., 2015).

Diabetes related reasons likely responsible for not finding a beneficial effect with vitamin D treatment include degree of hyperglycemia and duration of diabetes. Selective inclusion of patients with higher baseline glucose or HbA1c values may have been

associated with greater improvements with vitamin D supplementation. In addition, the included subjects in some studies were treated with metformin and/or insulin, which might have masked the positive effects of vitamin D (Shab-Bidar et al., 2011; Jorde et al., 2013).

3.3. Does vitamin D deficiency and T2DM relationship is vice versa cause and effect?

Some studies are of observational type, therefore no conclusion can be made as far as the cause and effect relationship between vitamin D deficiency and T2DM is concerned. In streptozotocin-induced diabetic rats, plasma calcium levels, DBP, circulating vitamin D and bone mass are reduced as compared with control. Insulin deficiency causes hypocalcemia, hypophosphatemia, increased enzymatic activity of alkaline phosphatase and its isoenzymes in serum and impairments of vitamin D3 25- and 1α-hydroxylase isoforms expression (Palomer et al., 2008). A decrease in bone resorption processes was established after vitamin D3 administration as it is evident from normalization of bone morphometrical parameters and mineral metabolism (Labudzynskyi et al., 2014). However, hyperinsulinemia has also been associated with increased bone mineral density in subjects with and without diabetes (Palomer et al., 2008). Administration of a single high dose of vitamin D increases blood glucose in patients with diabetes (Labudzynskyi et al., 2014). Further, no benefits in glucose tolerance have been found with vitamin D supplementation in subjects without vitamin D deficiency (Zittermann, 2006).

The coexistence of insulin resistance and vitamin D deficiency has generated several hypotheses. Vitamin D deficiency is usually detected in obesity in which insulin resistance is also a common finding. 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, leaving open the possibility that vitamin D and diabetes are not related at all (Manna and Jain, 2012). Vitamin D is efficiently deposited in body fat stores where it is no longer bioavailable, which explains why a significant proportion of persons with obesity are chronically vitamin D deficient with functional alterations such as elevated PTH levels (Zittermann, 2006; Palomer et al., 2008). This secondary hyperparathyroidism may contribute to the production of glucose intolerance which, in turn, is also associated with obesity. As stated above, vitamin D stimulates insulin secretion but inhibits PTH synthesis. PTH and insulin increase vitamin D production, and thus, acute insulin deficiency in DM may decrease vitamin D production. In support of this, patients with hyperparathyroidism have an increased prevalence of diabetes and insulin resistance (Scragg et al., 2004). Moreover, after parathyroidectomy, there is a correction of abnormal insulin resistance and glucose intolerance. Thus, the relationship between hypovitaminosis D, altered insulin secretion and T2DM may be the result of several related metabolic effects (Palomer et al., 2008).

Further longitudinal studies should seek to establish clearly the temporal sequence of the association between vitamin D deficiency and T2DM. Ultimately, randomized controlled trials with long-term follow-up are needed to examine whether vitamin supplementation is a useful intervention in preventing or delaying the onset of T2DM. Vitamin D screenings of people at risk for T2DM could possibly be benefit. The workplace seems to be a promising setting for that (Mauss et al., 2015).

Also, the lack of experience and professional skills of nursing care staff, in addition to overload work and the huge number of diabetic patients, increase the need for intensive training for nurses, and the involvement of the patient in treatment plan (Hroub and Brair 2015).

CONCLUSION

In this review I underscore the need for future studies given that both vitamin D deficiency and T2DM are conditions with huge public health concern worldwide. Evidence is accumulating on the possible role of vitamin D in the pathogenesis of T2DM; alterations in its status and/or action may affect insulin sensitivity, β-cell function or both. More research in this field will bring awareness about the importance of assessment of vitamin D level among the routine laboratory tests for T2DM patients. It seems that vitamin D supplementation might improve diabetic state. Experimental studies as well as large scale RCTs with good study design, optimal vitamin D supplementation and long-term follow up are warrants.

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