REVIEW ARTICLE

Vitamin D and Diabetes: A New Horizon

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ABSTRACT

Diabetes mellitus is a metabolic disease which is caused by absolute or relative insulin deficiency, and the prevalence rate of Type2 diabetes mellitus (T2DM) is growing among Indians as well as through worldwide. Various risk factors play a role in the aetiopathogenesis and in the glycemic control among the type 2 diabetic patients. Therefore, identification of environmental and easily modified risk factors is urgently needed to prevent development of T2DM. One of various such risk factors, vitamin D3 level & therefore serum calcium levels are reported to alter the glycemic control. The major and most well-known function of vitamin D is to maintain calcium and phosphorus homeostasis and promote bone mineralization. However, recent evidence suggests that vitamin D and calcium homeostasis may also be important for a variety of non-skeletal diseases including T2DM. Based on basic and animal studies, vitamin D and calcium have also been suspected as modifiers of diabetes risk. The systemic review was carried out to evaluate the evidences as well as limitation in respect of vitamin D3 and serum calcium level regarding the glycemic control in T2DM. This paper seeks to examine the consistently reported relationship between glycemic control in T2DM and altered vitamin D3 & serum calcium concentrations, with reference to the possible underlying mechanisms. So the status of above two parameters is considered as an important factor in T2DM patients. Its role in present scenario should be understood both as an etiological concept & also as a therapeutic option.

Keywords: Vitamin D, Diabetes, Glycemic parameter

INTRODUCTION

Diabetes mellitus is a metabolic disease which is caused by absolute or relative insulin deficiency. Over the past 30 years International Diabetes Federation estimatesthat, the prevalence of diabetes has increased to 12-18% in urban India and 3-6% in rural India with significant regional variations, and 382 million people will have diabetes around the world. Various risk factors play a role in the aetiopathogenesis and in the glycemic control among the type 2 diabetic mellitus (T-2 DM) patients[1]. Therefore, identification of environmental and easily modified risk factors is needed to prevent development of T-2DM. There are various risk factors regarding theT-2 DMbut only few components of the pathomechanisms leading to T-2 DM are known. It remains unknown whether interventions focused on these components e.g., weight loss and increased physical activity, can prevent diabetes in prediabetics orreverse the pathology in those already diagnosed diabetics[2]. Although our current methods of treating T-2 DM and its complications have improved, prevention of the disease is highly preferable.

Recently interests have been generated in serum vitamin D_3 and serum calcium in diabetes. Serum calcium level and 1,25 dihydroxy vitamin D_3 level are reported to alter the glycemic control and there is evidence to suggest that altered vitamin D_3 and calcium homeostasis may play a role in the development of T-2 DM[3]. Although the major and most well-known function of vitamin D_3 is to maintain calcium and phosphorus homeostasis and promote bone mineralization, despite of this Vitamin D_3 also improves insulin secretion and reduces insulin resistance thus ultimately helps to poor the diabetic complications[4,5]. The role of vitamin D_3 in T-2 DM is suggested by cross-sectional studies showing that low serum concentrations of 25- hydroxyvitamin D3 [25(OH) D3] have association with impaired glucose tolerance and diabetes[(6-8)]. There are more recent accumulating evidences to suggest that altered vitamin D_3 and calcium homeostasis may also play a role in the development of T-2 DM.

Definition: *Vitamin D status by the 25(OH)D concentrations has been classified as: Deficient <10 ng/ml, insufficient; 11-20 ng/ml, optimal >20 ng/ml.*

MATERIALS AND METHODS

A literature search was conducted for longitudinal observational studies of vitamin D status and development of type 2 diabetes, and randomized controlled trials (RCTs) evaluating the vitamin D and calcium levels with or without calcium supplementation on glycemic parameters.

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PubMed and Google was searched for English-language literature through May 2014 for observational studies on the association between vitamin D/calcium status (defined by serum 25-hydroxyvitamin D (25-OHD) concentration, and vitamin D, calcium, or dairy intake) and type 2 DM (prevalence or incidence). Metabolic syndrome (prevalence or incidence) was also examined as an outcome of interest, given that insulin resistance, a feature of type 2 DM, is considered to be a central mechanism underlying the metabolic syndrome. Search terms included *diabetes, hyperglycemia, glucose, glycohemoglobin, insulin resistance, metabolic syndrome, homa, cell function, insulin secretion, vitamin D, calcium, dairy intake, lipid profile, hypertriglyceremia, hyperlipidemia* and related terms. Additional publications were identified from citations from the review articles, and personal reference lists. All theoutcomes,relatedtodiabetes included incident type 2 diabetes and, in the context of RCTs only, change in glycaemia (fasting plasma glucose, 2-h glucose level after an oral glucose tolerance test or hemoglobin A1c). Titles and abstracts of the resulting articles were examined, and full textarticles were retrieved after excluding non-eligible ones. An excluded study wasof hemodialysis, hyperparathyroidism, and other conditions or medications that affect vitamin D metabolism (e.g., epilepsy). The excluded studies was of chronic liver failure, hemodialysis, hyperparathyroidism, and other conditions or medications that affect vitamin D metabolism (e.g. epilepsy).

LITERATURE REVIEW

About the Vitamin D

It is interesting to know the correlation of vitamin D and calcium with diabetes**.** Vitamin D was discovered in 1922 by McCollum, it was termed "D" because it was the fourth known vitamin. It is, however, nowadays clear that vitamin D and its metabolites should be rather classified as (pro-) hormones than as vitamins[9].

Vitamin D is a fat soluble vitamin which has a unique metabolism and its main source is endogenous vitamin D synthesis in the skin[3]. Although the major sources of vitamin D is sun exposure, other than this it can be obtained by body through our daily diet including oily fish, milk, yogurt, orange juice & cereals, now a days multivitamin containing active form of vitamin D;25 (OH) vitamin D_3also contribute to the source[10].

In the presence of sunlight 7-dehydrocholesterol (7-DHC) in the skin is converted to pre-vitamin D_3 ($preD_3$) and thenimmediately to vitamin D3. Further exposure to sunlight degradesit into inactive photoproducts. Vitamin D (D2 or D3) made in the skin or ingested in the diet get stored in and then released from fat cells. Vitamin D in the circulation in a protein bounded form, further transported to the liver where vitamin D is converted to 25-hydroxyvitamin D[25(OH) D] by the enzyme vitamin D- 25-hydroxylase (25-OHase). This is the major circulating form of vitamin D, which is generally used to measure vitamin D status. But 25(OH)D is biologically inactive, and it needs to be convertedto its biologically active form 1,25-dihydroxyvitamin D [1,25(OH)2D] in the kidneys by the 25-hydroxyvitamin D-1α-hydroxylase (1-OHase)[11].

1,25(OH)2D feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands by negative and positive feedback mechanisms. 1,25(OH)2D enhances intestinal calcium absorption in the small intestine by stimulating the expression of the epithelial calcium channel and the calbindin 9K (calcium binding protein). 1,25(OH)2D binds to its receptor in osteoblasts and causes to increase in the expression of receptor activator of NFκB ligand (RANKL). Its receptor RANK on the preosteoclast binds RANKL and become a mature osteoclast. The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. Adequate calcium and phosphorus levels promote the mineralization of the skeleton and maintain neuromuscular function[10]. Figure 1 is depicting the entire mechanism of diabetic control through Vitamin D and calcium homeostasis.

Non Skeletal Action of Vitamin D

When a monocyte/macrophage is stimulated through its receptor by an infective agent, the signal upregulates the expression of vitamin D receptor (VDR) and the 25-hydroxyvitamin D- 1-hydroxylase (1-OHase) and 25(OH) D convert to $1,25(OH)_2D$. $1,25(OH)_2D$ returns to the nucleus where it increases the expression of cathelicidin (CD) which is a peptide capable of promoting innate immunity and inducing the destruction of infective agents[12]. It is also act locally on activated T and activated B lymphocytes which regulate cytokineand immunoglobulin synthesis respectively[13]. The local production of $1,25(OH)_2D$ does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity and the local production of $1,25(OH)_2D$ inhibits the expression and synthesis of PTH. Theproduction of 1, $25(OH)_2D$ in the kidney enters the circulation and it downregulate renin production in the kidney and also stimulate insulin secretion in the β- islet cells of the pancreas[9].

In T-2 DM there is a chronic systemic inflammation and it has been found to increase the insulin resistance. T-2 DM was found to be associated with an increase in the levels of the tumor necrosis factor-α (TNF-α) and β, the

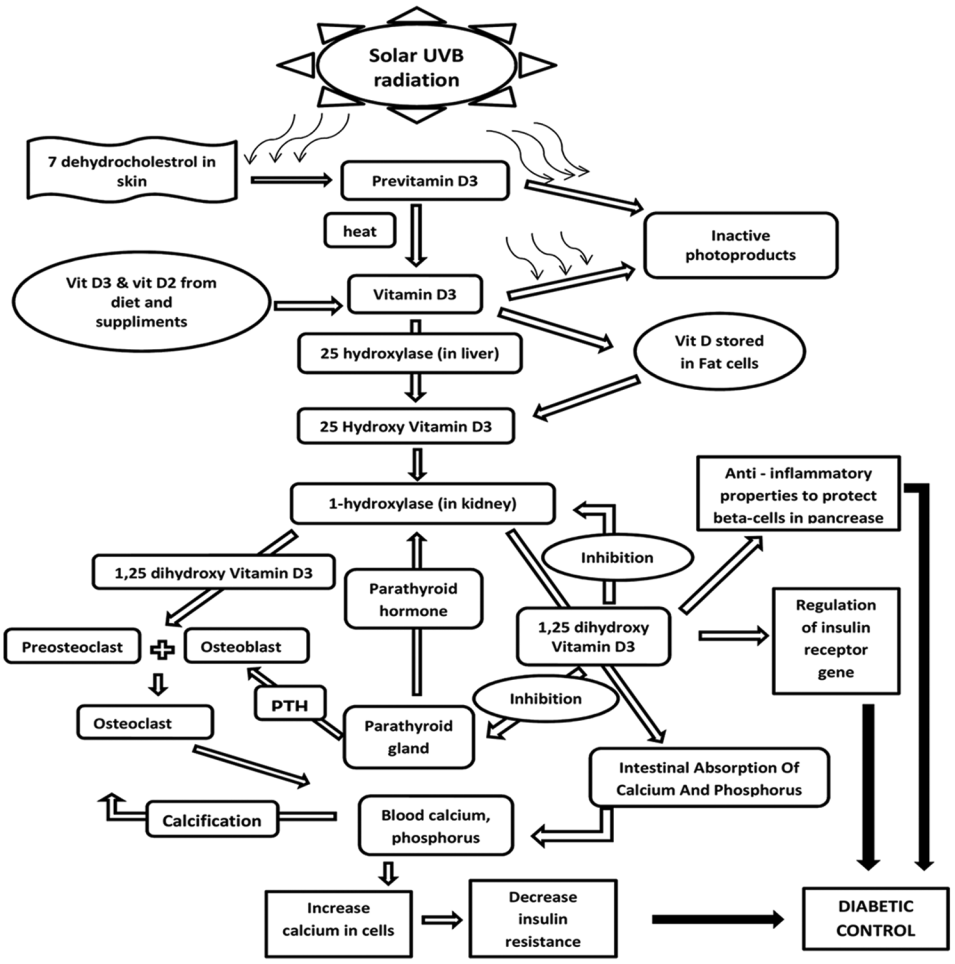

Figure 1: Schematic diagram showing complete metabolism of vitamin D with correlation to diabetic control

C reactive protein, the plasminogen activator inhibitor-1 (PAI-1), and interleukin-6 (IL-6). The increase in such kind of inflammatory mediators may precede and even predict the development of T-2 DM. In support of this concept, there is the finding that VDR has been found on almost all the cells of the immune system[1]. Furthermore,immune cells such as macrophages contain 1α-hydroxylase that can be upregulated by the inflammatory mediators and not by PTH. Vitamin D also suppresses the antigen-presenting capacity of the macrophages, it modulates the development of the CD4 lymphocytes and it inhibits the production of IFNc (interferon c) and IL-2 (interleukin 2), among other cytokines. These cytokines are known to activate the macrophages and the cytotoxic T cells, which in turn can lead to the destruction of the pancreatic islets[14].

On the other hand, cardiovascular disease is the most common cause of mortality in type 2 DM. Researchers have confirmed that vitamin D plays an important role in endothelial function, blood pressure control, and calcification of the coronary vasculature, increased vascular resistance, and prevention of cardiovascular disease (CVD)[15]. The effect of vitamin D on regulation of the lipid profile is one of the proposed mechanisms for the relationship between vitamin D deficiency and CVD[16]. So it became necessary to determine the association between serum level of vitamin D and lipid profiles, including serum concentrations of cholesterol, Triglyceride, High Density Lipoprotein, and Low Density Lipoprotein, in T-2 DM patients[17,18].

APART FROM INFLAMMATORY PROCESS ROLE OF VITAMIN D IN DIABETES

VitaminD and calcium influence the mechanisms for glucose intolerance and T-2 DM such as, defects in pancreatic beta-cell function, insulin sensitivity, and systemic inflammation[3]. And there are much evidence for above[19].

Pancreatic Beta-cell Function& Vitamin D in T-2 DM

This is known that role for vitamin D in pancreatic beta-cell function is through its direct and indirect action. Vitamin D appears to affect exclusively the insulin response to glucose stimulation, whereas it does

not influence the basal insulin secretion[20]. The direct effect of vitamin D may be mediated by binding of its biologically active circulating form, 1,25-(OH)D, to the beta-cell vitamin D receptor. Alternatively, activation of vitamin D may occur within the beta-cell by the 1-alpha-hydroxylase enzyme, which was recently shown to be expressed in beta-cells[21]. The indirect effects of vitamin D may be mediated via its important and well-recognized role in regulating extracellular calcium and calcium flux through the beta-cell. Insulin secretion is a calcium-dependent process[22]; thus, alterations in calcium flux can have adverse effects on beta -cell secretory function. Therefore it is establishedthat inadequate calcium intake or vitamin D insufficiency may alter the balance between the extracellular and intracellular cell calcium pools, which may leads to interference with normal insulin release, especially in response to a glucose load[3].

Insulin Resistance

Furthermore Vitamin D may also have a beneficial effect on insulin action either directly, by stimulating the expression of insulin receptor and thereby enhancing insulin responsiveness for glucose transport[23], or indirectly via its role in regulating extracellular calcium and ensuring normal calcium influx through cell membranes and adequate intracellular cytosolic calcium pool which in turn is essential for insulin- mediated intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue[24,25], with a very narrow range of calcium needed for optimal insulin-mediated functions.

Changes in calcium levels in primary insulin target tissues may contribute to peripheral insulin resistance via impaired insulin signal transduction, leading to decreased glucose transporter-4 activity[26]. Associations between low vitamin D level and decreased insulin sensitivity have been reported by somecross-sectional studies. A metanalysis suggested that some, but not all, observational studies have shown an inverse association between vitamin D or calcium status and insulin resistance. And clearly mentioned that there are very limited and conflicting data from human studies that have directly examined the relationship between vitamin D or calcium status and systemic inflammation in relation to T-2 DM[3].

VITAMIN D AND TYPE 1 DIABETES

There are various animal studies and clinical trials in patients with new onset of T-1 DM which showed that the improvement of vitamin D level may arrest the deterioration of pancreatic function and improve the levels of C-peptide[27].

CYP27B1 is agene which encodes the 1alpha –hydroxylase, key enzyme which facilitate the activation of vitamin D. Polymorphism in thisgene described as being associated with an increased risk of T-1 DM and it could potentially lead to the reduced expression of 1alpha-hydroxylase, less production of the active 1alpha, 25 (OH) 2 D_3, and ultimately, to the increased risk of T-1DM[28].There is strong epidemiologic data showing that the population in countries with a high prevalence of T-1 DM is commonly vitamin D deficient. Vitamin D supplementation during pregnancy decreased the risk of the development of T-1 DM for offspring[29]. Supplementation of vitamin D at an early age also decreases the risk for developing T-1 DM[30].

DISCUSSION

Vitamin D and diabetes, this relation has long been established[31]. Some studies supportsan inverse association between vitamin D status and glycosylated hemoglobin levels (HbA1C) levels[32]. Also other studies have shown that vitamin D may play a functionalrole on glucose tolerance through its effects on insulin secretion and insulin sensitivity[33].

There are some mechanisms for the effects of vitamin D such as;presence of vitamin D receptors (VDR) on pancreatic β cells[34], Vitamin D activating 1α hydroxylase is expressed in pancreatic β cells[35], presence of vitamin D responseelement in the insulin gene[36],presence of vitamin D receptor in skeletal muscle[37] and the fact that 1,25(OH)D_3 increases transcription of insulin receptor genes[38], and also suppresses the renin gene reducing hyperglycemic inducedincreases in renin levels in pancreatic β cells and blockade of renin-angiotensin activity has been proposed as a novel target for diabetes treatment[39].

Protective effects of vitamin D on diabetes, maybe due to well-known effects ofvitamin D such as its anti-inflammatory properties, its effects on calcium & phosphorusmetabolism and regulation of the insulin receptor gene[40]. It seems that vitamin D increases in calcium content of the cells, which in turns leads to increased transport of glucose into the muscle[25]. Vitamin D also regulates nuclear PPAR (Peroxisome proliferative activated receptor) that has an important role in the insulin sensitivity[41]. It was seen that vitamin D deficiency is associated with increases in inflammation. Vitamin D attenuates the expression of proinflammatorycytokines involved in insulin resistance such as interleukins, IL-1, IL-6, TNF-alpha, also down regulates NF-Kb (Nuclear factor) activity[42]. Vitamin D may affect intracellular calcium levels in pancreatic cells, which is an important stimulus for insulin secretion. In peripheral tissues, VDRs were found in skeletal muscles and adipose tissue. Vitamin D also has been shown to control insulin receptor expression and insulin responsiveness for glucose

transport[43], establishing its role in insulin secretion and sensitivity[44]. Although the data from observational studies are strong, the expected benefit from replacement of vitamin D onfasting blood glucose, glucose tolerance, or insulin sensitivity was not observed in some studies[45,46]. Apart from this vitamin D also has role in lipid profile maintenance in type 2 diabetics and some studies has reveals a novel mechanistic link between vitamin D deficiency in macrophages and foam cell formation in type 2 diabetics.

CONCLUSION

From the above discussion it appears that there is a significant relationship between reduced levels of vitamin D and calcium with type -2diabetes. The role of vitamin D and calcium homeostasis has long been established. However in the recent years in its non-skeletal action especially in pancreatic beta cell function,insulinresistance and T-1 DM. Its role in present scenario should be understood both as an etiological concept &also as a therapeutic option.

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