REVIEW ARTICLE

DIABETICO-PROTECTIVE ROLE OF VITAMIN D

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ABSTRACT

Studies worldwide have observed a link between VDR polymorphism and Diabetes Mellitus. Diabetes is a complex disease characterized by insulin deficiency caused by the alterations in the function of pancreatic β-cells, insulin sensitivity and systemic inflammation. Vitamin D deficiency has been identified as a contributing factor to Diabetes. Vitamin D acting via the nuclear vitamin D receptor (VDR) gene, located on human chromosome 12q12–q14, also acts as a transcription factor and regulates the beta cell secretion of Insulin. Studies have shown that vitamin D deficiency is widespread in those with diabetes but only few have studied the link between the two. Better understanding of the exact biochemical significance of vitamin d receptor polymorphisms and its association with metabolic disorders such as diabetes mellitus is required. To find out the association at the genetic level to combat the rampant prevalence of diabetes linked with VDR polymorphisms research engines employed were PubMed, Medline, etc. and articles selected were up to 2018.

The objective of this review is to provide an overview regarding the Diabetico-protective role of vitamin D and its receptors and to discuss the polymorphism of VDR and the possible mechanism involved in the development of the disease.

KEYWORDS: Hyperglycemia, Receptors, Calcitriol, Polymorphism, Restriction Fragment Length.

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INTRODUCTION

Diabetes, with a prevalence of 2.8% in 2000, is estimated to rise to 4.4% in 2030 with a gigantic increase in diabetic's population worldwide to 366 million[1]. Vitamin D3 remains the solitary nutritional base amongst the many factors leading to diabetes. Vitamin D3, a multifunctional hormone, plays a diverse biological role in a number of physiological processes and is involved in the control of blood pressure, insulin secretion immunoregulation, antiangiogenesis and lipid metabolism [2]. Active vitamin D3 brings about its effects by binding to the vitamin D receptor (VDR) found in target cells[3] which act as a transcriptional activator of many genes[4]. Better understanding of role of vitamin D came with the discovery of its binding proteins, receptors and final activation by hydroxylation of vitamin D3, in various tissues (e.g. pancreatic beta cells and cells of the immune system)[3,5].

Diabetes is a metabolic disorder of multiple etiologies caused by defects in insulin secretion and insulin action. It has been recognized as the fastest growing disease and according to the World Health Organization, it is estimated that the total number of people with diabetes will double from 171 million in 2000 to 366 million by 2030[6,7]. The current prevalence of type 2 diabetes mellitus in Pakistan is 11.77% [8]. Epidemiological studies indicate that vitamin D deficiency is commonly seen in individuals suffering from diabetes [9]. Vitamin D supplements early in life lowers the risk of developing Type 2 Diabetes Mellitus (T2DM)[10]. Vitamin D exerts its effects directly via the binding of the activated form of vitamin D, (1, 25(OH)2D3), to the intracellular vitamin D receptor (VDR) in β-cells[11] thereby improving pancreatic β-cell function, enhancing insulin receptor sensitivity, and diminishing insulin resistance. Hence, in the absence of expression of the VDR gene all these actions are compromised and this might lead to progression of T2DM[10]. Association between Vitamin D deficiency and diabetes in humans came through conformational studies in

animal models, which demonstrated that vitamin D deficiency can lead to inhibition in insulin secretion[12]. The beta cells of Pancreas are richly provided with receptors for 1, 25(OH)2D3[13].

It has also been reported that specific vitamin D receptor polymorphisms interact with the HLA DRB1 allele and poor expression of DRB1*0301 predisposes to type 1 diabetes[14]. The identification of receptors for 1, 25(OH)2D3 in cells of the immune system led to experiments in animal models of type 1 diabetes in which the administration of high doses of 1, 25(OH)2D3 was shown to prevent type 1 diabetes[15], mainly through immune regulation. It has been demonstrated that 1, 25(OH)2D3 is one of the most powerful blockers of dendritic cell differentiation and that it directly blocks IL-12 secretion, Lymphocyte proliferation is inhibited and regulator cell development is enhanced[16].

From the many VDR polymorphisms identified, four single-nucleotide polymorphisms (SNPs) of this gene have been studied the most and include BsmI (rs1544410), ApaI (rs7975232), TaqI (T>C; rs731236), and FokI (C>T; rs2228570)6. To find out the association at the genetic level to combat the rampant prevalence of diabetes linked with VDR polymorphism search engines employed were PubMed ------ and articles selected were upto 2018.

The aim of the present review was to analyze the association between the VDR polymorphism of the VDR gene in diabetic patients to better our understanding and course of treatment for the growing diabetes epidemic.

DISCUSSION

The VDR gene is thought to be involved in the pathogenesis and progression of DM. Vitamin D deficiency is common in even in those populations that live in sufficient sunshine belts like Lahore where 87.5% of adults had Vitamin D levels less than 15 ng/ml.[17]. In recent years, several studies have examined the links between VDR gene polymorphisms and type 1 and type 2 diabetes mellitus (T1DM and T2DM) in different ethnicities and regions and the results have been inconsistent[18, 19, 20].

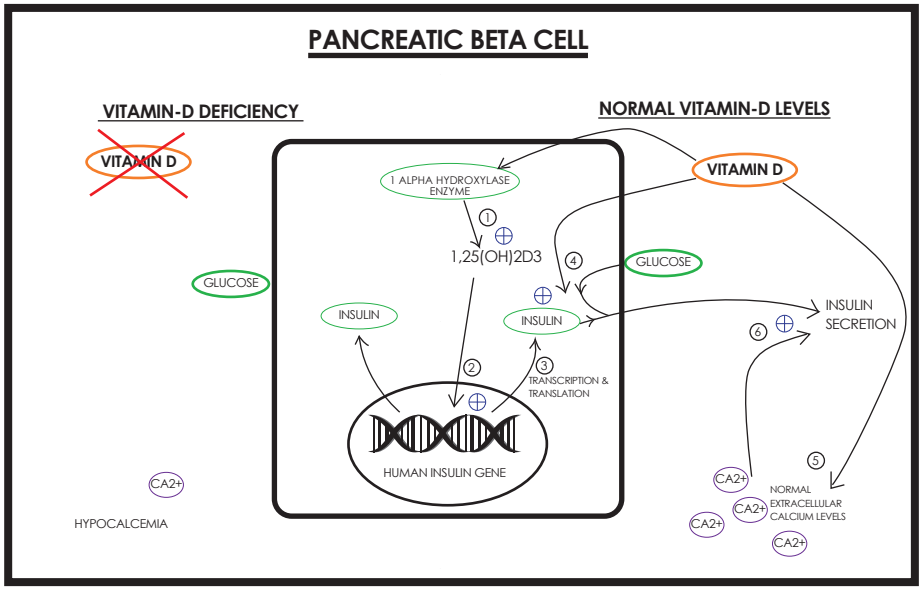

FIGURE1: mechanism of vitamin D action on pancreas
(1) Alpha hydroxylase enzyme converts Vitamin D[25(OH) D3] to active Vitamin D [1, 25(OH)2 D3] inside the pancreatic Beta cell.
(2)Vitamin D increases the transcriptional activation of the human insulin gene1.(3) Increased levels of insulin inside the beta cell.
(4)Vitamin D promotes glucose mediated insulin secretion from the beta cell.2(5)Vitamin D ensures normal levels of extracellular calcium.3(6)Normal levels of extracellular levels of calcium ensures normal secretion of the insulin from the beta cells4.

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Damage and destruction of β-cell through mediators involved in β-cell apoptosis results in diabetes type 1. 1, 25(OH)2D3, counteracts cytokine induced expression β-cell of pancreatic islets both at the mRNA and protein levels and has a positive impact on insulin sensitivity[21]. There is a negative impact of 1, 25(OH)2D3 deficiency on beta cell function[22].

The VDR protein is at the core of the endocrine system of vitamin D and is widely expressed in pancreatic β-cells like many other different cell types such as vascular smooth muscle cells, osteoblasts and chondrocytes, liver, adipose tissue, muscle, dendritic cells and lymphocytes [23-27]. Once activated, 1, 25(OH)2D3 first binds to the VDR, which simultaneously heterodimerizes with the retinoid X receptor alpha (RXRa) [28]. The VDR-RXRa complex translocate into the nucleus and positively or negatively regulates gene transcription by binding to vitamin D responsive elements (VDREs), located in the promoter region of target genes on DNA[14].

Since vitamin D decreases the proliferation of type 1 helper (Th-1) cells and inhibits the production of cytokines such as IL-2, TNF-a and interferon-γ[28]. VDR gene polymorphisms are associated with multiple autoimmune pathologies[29].

The association of VDR gene with Diabetes

The vitamin D receptor gene (VDR) is a nuclear receptor located on chromosome 12q13.1[30]. Several single nucleotide polymorphisms (SNPs) are present for this human VDR gene and four of them have been studied in relation to type 1 and type 2 diabetes mellitus susceptibility, namely FokI, BsmI, ApaI and TaqI polymorphisms. The ApaI, BsmI and TaqI polymorphisms are located near the 3' end of the VDR gene. However, BsmI and ApaI SNPs are also positioned in intron 8 and the TaqI is a silent SNP in exon 9[31,32,33]. The FokI polymorphism is placed within the 5' end of the VDR gene. FokI alters the start codon (ATG) and is the only locus that leads to a different sized protein[23,34].

Type 1 Diabetes

Type 1 diabetes, the insulin dependent diabetes, is caused by a complex autoimmune destruction of insulin producing pancreatic islet β-cells. This was recognized by the detection of autoantibodies against islet β-cells and discovery of infiltrating autoimmune cells such as macrophages T cells, B cells. Different factors, including genetics and some viruses, may contribute to type 1 diabetes[35]. One potential cause is Vitamin D receptor Polymorphisms discussed as under:

BsmI gene, BB genotype odds against type 1 diabetes in Asians.

BsmI gene polymorphism, the B allele and BB genotype, increases the likelihood of developing type 1 diabetes in Asians, whereas, bb genotype was found with the Latino and African adult subjects studied in the overall population[36]. Other studies conducted in Egypt[37], Chile[38] and Asia [39], have also found a positive association between BsmI gene polymorphism and type 1 diabetes in their respective populations. Researchers have also found children with BsmI-bb and TaqI-TT polymorphisms have a lower chance of developing type 1 diabetes compared to those children with BsmI-BB, BsmI-Bb, and TaqI-tt polymorphism[40]. In southern European population which has low incidence of type 1 DM and association of T1DM and FokI, BsmI, ApaI and TaqI polymorphisms in the group of Caucasian children was found. This study also discovered less frequency of FokI-FF genotype and F allele along with BsmI-BB genotype and B allele in the subjects with T1DM. Whereas ApaI-AA genotype and A allele, TaqI-TT genotype and T allele were more frequent in individuals with type 1 diabetes[41].

The FokI polymorphism, has been suggested to increase the likelihood of developing type 1 diabetes[31,32]. The genotype and allele distribution, including the risk allele (F or f), of the FokI vitamin D receptor polymorphism differs between patients and controls in many studies. An increased risk of developing type 1 diabetes is associated with the FF genotype and/or F allele in the Japanese, Rumanian, Uruguayan, Turkish and Iranian populations[29,42;43,46]. In contrast, studies from Egypt, Italy and Croatia observed an association with the ff genotype increased the risk of developing type 1 diabetes[47, 48, 37]. However, a study from Australia found no significant difference in distribution of vitamin D receptor polymorphisms TaqI, FokI, ApaI in children with type 1 diabetes[49]. A study from Pakistan also found no association between the risk of developing type 1 diabetes and FokI and ApaI polymorphisms[50].

Type 2 Diabetes

Type 2 diabetes, also known as non-insulin-dependent diabetes, is a chronic condition that affects the way body metabolizes glucose, either by resisting the effects of insulin, or by not producing enough insulin to maintain a normal glucose level[51]. PTH, associated with insulin synthesis and secretion in the pancreas, has its concentration regulated by vitamin D. During Hypovitaminosis D, there is an increase in PTH which can be a cause of beta-cell dysfunction, leading to insulin resistance and eventually hyperglycemia[52]. The association between VDR polymorphisms and risk of type 2 diabetes has also been investigated by various researchers as under:

FokI polymorphism, according to results of 2 separate studies, in the vitamin D receptor gene increases the likelihood of developing type 2 diabetes, and the allele f and variant homozygote ff of FokI may be the risk factors for type 2 diabetes[53, 54]. An Egyp-

tian study found association of FokI polymorphism with increased risk of type 2 diabetes in patients with metabolic syndrome [55]. A meta-analysis consisting of 10 studies also found a positive association between the FokI polymorphism and type 2 diabetes, particularly in East Asian populations[53, 54]. Despite all of these findings, a study on a Tunisian population found no association between the FokI polymorphism and type 2 diabetes hinting to the possibility that the risk is specific to some particular ethnic populations[56].

BsmI polymorphism, according to a meta-analysis, was found slightly significantly associated to the risk of type 2 diabetes for Bb vs. bb and BB+Bb vs. bb. This implied that the allele B and the variant homozygote BB of BsmI were the risk factors for type 2 diabetes. The FokI polymorphism was significantly associated with the risk of developing type 2 diabetes in only Chinese people, but not in Caucasians[18]. Another study based in Saudi Arabia found an association between the TaqI and BsmI polymorphisms and type 2 diabetes[57], along with a similar study on the Emirati population finding a similar association but with the FokI polymorphism instead[58]. At the same time, a study found no association between BsmI and FokI polymorphisms and type 2 diabetes[59], which was similar to the other large sample size studies [60, 61, 62].

Complications Associated with Diabetes

Diabetes affects many major organs, including your heart, blood vessels, nerves, eyes and kidneys. Although long-term complications of diabetes develop gradually, they can eventually be disabling or even life-threatening[54]. Studies show that TaqI polymorphism may have interactive effects with FokI in the progression of diabetes and its complications[58]. Association of FokI polymorphism with type 1 diabetes, has been found to affect insulin secretion and sensitivity and is a causative factor for the development of diabetic retinopathy and Diabetic Nephropathy. However, association of these complications with BsmI polymorphism was not found.

CONCLUSION

In conclusion, this review shows the evidence of significant association between Fok 1 polymorphism and both types of diabetes mellitus. There is an increased risk of developing type 1 diabetes associated with FF genotype and F allele in Japanese, Rumanian and Uruguayan population. The studies from Egypt, Italy and Croatia show an association with ff genotype with increased risk of type 1 diabetes. Regarding type 2 diabetes, an increased association was found with f allele and variant homozygote ff of Fok 1 gene. A very weak association has been found between Bsm 1 polymorphism and T2DM. It is also observed that the allele B and the variant homozygote BB of Bsm 1 were may be the risk factors of type 2 diabetes mellitus.

Sample size was the main source of heterogeneity. Future larger sample sizes are needed to investigate the association between VDR gene polymorphism and both type of diabetes mellitus. Also there is a need to review the gene-environment interactions of VDR polymorphism with T2DM.

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