

Role of vitamin D receptor (VDR) genetic polymorphism in onset of type 2 diabetes mellitus: A Review

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ABSTRACT: Numerous studies disclosed the independent role of VDR genetic polymorphisms involved in pathogenesises of various metabolic disorders like type 2 diabetes mellitus in different populations, however no any conclusive or even key study conducted on South Asian population especially Pakistani population except on Indian population. Worldwide, vitamin D deficiency and type 2 diabetes mellitus (T2DM) are two interrelated and most common health problems. Such interrelationship is involved complex inheritance pattern. The polymorphisms of various genes including vitamin D receptor (VDR) might affect genetic susceptibility of T2DM by developing malfunctioning of beta pancreatic cells or insulin resistance. Genetic architecture of T2DM is different among various ethnic populations. The present review will focus on concept that polymorphism of VDR gene may has role in susceptibility of onset of T2DM and its pathogenesises.

Keywords: Pathogenesis, T2DM, VDR polymorphism.

INTRODUCTION

Diabetes mellitus is endocrinological health issue which is reaching epidemic extents globally. Such increase in T2DM prevalence is endorsed by various environmental and genetic factors. Financial impact of T2DM is incalculably arduous as approximate anticipated cost of Pakistan's health centers will be up to \$490 billion in coming ten years (Hussain et al., 2014). Common pathophysiological complications of T2DM are micro- and macro-vascular diseases, nephropathy and neuropathy. Such complications may develop due to sustained hyperglycemia, insulin resistance and dysfunction of beta cells (Ishaq et al., 2013; Sohial, 2014; Orozco et al., 2008). Insulin resistance established in early development lead to type 2 diabetes mellitus. With passage of time the compensatory reaction of pancreatic beta cells becomes weakened and leads to sustained hyperglycemia (van de

Bunt et al., 2014; Maedler, 2008; Zanuso et al., 2010).

T2DM patients have significantly higher risk for a variety of vascular complications; retinopathy, neuropathy, atherosclerosis, cardiovascular diseases, hypertension leading to infections (Sreelatha et al., 2015). Perhaps there are a number of different causes of T2DM, though exact etiologies are still not known. Combination of genetic and environmental factors that contribute to T2DM onset are life style, dietary habit, BMI, hypovitaminosis D and family history (Sreelatha et al., 2015; Konstantinos et al., 2017; Zheng et al., 2018).

Physical inactivity and obesity are consequences of overweight which contribute to prone T2DM through insulin resistance. Obesity is prevalent in developed and developing countries even in urban part of the world. Predominant distribution of fat in non-obese people is

accountable of T2DM. Although a few etiological hazards for the development of insulin resistance and dysfunction of beta cell have been recognized, gaps remain in understanding etiology of such disorders. In addition, factors associated with the longitudinal evolution of these diseases have received very limited studies (American Diabetes Association, 2015).

Both acquired and genetic factors are measured to have imperative roles in onset T2DM. First degree relatives and monozygotic twins affected 50% to T2DM due to heritability (Pierce et al., 1995; Herder and Roden, 2011). More than 50 various genes are related to T2DM (Imamura and Maeda, 2011; Wheeler and Barroso, 2011). Obesity and low socioeconomic are considered major risk factor for T2DM after genetic menaces (Fagard and PNilsson, 2009; Meigs, 2010).

BETA CELL DYSFUNCTION AND INSULIN SENSITIVITY

In normal physiological reaction to increased level of glucose in blood, insulin synthesized from beta cells binds to the insulin receptors present on plasma membrane of insulin target tissues, which consequently persuades a cascade of signaling transduction to permit for the transportation of glucose in the cell for glucose consumption. Although, in reduced insulin sensitivity state, there can be defects at insulin receptor location or in signaling the pathway, which results in diminished insulin action and thus lower amounts of glucose being transported into the cell (Bloomgarden, 1998; Kadowaki et al., 2007; Shoelson and Donath, 2011) and typical lifestyle features; stress, smoking, less use of dietary fibers and magnesium (Reaven and Tsao, 2003). Lack of insulin sensitivity is also causing polycystic ovary syndrome and fatty liver (Lima et al., 2009; Bethea and Nestler, 2008).

In case of dysfunction of beta cells, the concentration of insulin synthesized cannot overwhelm the lack of insulin sensitivity in multiple organs, subsequently resulting in hyperglycemia (Maedler, 2008). Therefore, though both dysfunction of pancreatic beta cells and lack of insulin sensitivity take part in the development of T2DM, it is certainly dysfunction of beta cells that is serious to the progression of the diseases diabetes mellitus cannot arise deprived of impairment of the insulin production (Maedler, 2008; Gastaldelli, 2011). Limited knowledge exists about the etiology of dysfunction of pancreatic beta cells, however; both environmental and genetic factors are considered to play a role. Few plausible menaces which have currently been recognized involve glucotoxicity to the beta cell which would be the outcome of prolonged enduring hyperglycemia, lipotoxicity caused by elevated levels of free fatty acid that often coexist in people with higher adiposity and lack of insulin (Bonora, 2008), oxidative stress and long-lasting subclinical inflammation (Greenberg and McDaniel, 2002), additional visceral

adipose tissue (Hanley et al., 2003; Utzschneider et al., 2004), lack of insulin sensitivity of pancreatic beta cells (Bonora, 2008) and low adiponectin (Kharroubi et al., 2003; Bacha et al., 2004). Family histories as well as genetics are also considered to take part in defining risk of dysfunction of pancreatic beta cells (Marchetti et al., 2002; Marchetti et al., 2006).

VITAMIN D

Vitamin D (Figure 1) is necessary for the homeostasis of calcium to prevent rickets and osteomalacia (Norman, 1998). In teenagers, hypovitaminosis D predisposes to rickets, a disorder of bones characterized by poor mineralization of skeletal tissues causing retardation of growth and deformities of skeletal comprising bony projections with rib cage and deformed legs or collided knees. In old age people, hypovitaminosis D develops osteomalacia, a defect in mineralization producing tender bone pain and weakness of muscles (Holick, 2003; Holick, 2011).

Sources of Vitamin D

Mostly the cutaneous production of vitamin D after the exposure to sunlight is considered to be main source in which mainly ultraviolet B (UVB) radiation of sunlight (290 to 315 nm) commence the photochemical reaction (Holick et al., 2007). Furthermore, other than this endogenous synthesis, humans can also get vitamin D through food supply. Almost all food sources are initiated from ultra violet radiation of plant ergosterol and sterol, present in plasma membranes of both fungus and yeast and synthesizing vitamin D₂ or ergocalciferol and vitamin D₃ or cholecalciferol by animal sources (Calvo et al., 2004; Calvo et al., 2005).

However, vitamin D₂ is less effective as compared to vitamin D₃ in raising serum concentrations of vitamin D (Tripkovic et al., 2012) and suggested that vitamin D₃ can be employed for clinical as well as nutritional demands (Vieth, 2009).

Metabolism of Vitamin D

Cholecalciferol enters blood stream through binding to protein known as vitamin D binding protein (DBP) and undergoes hydroxylation through cytochrome P450 enzyme hydroxylase (CYP2R1) to 25-hydroxyvitamin D also known as calcidiol in liver. Calcidiol is the chief circulating type of this vitamin in body (DeLuca, 2004; Strushkevich et al., 2008). Subsequently, 25-hydroxyvitamin D is then transported to kidneys where 1-alpha-hydroxylase converts 25-hydroxyvitamin D into active metabolite of vitamin D that is 1,25-dihydroxyvitamin

D or calcitriol (Sakaki et al., 2005).

Circulating 25-hydroxyvitamin D may be transported to tissues by two different processes; it may move directly across the cell membrane or bound to binding protein in the circulation to reach target tissues, predominantly to kidneys through megalin of the endocytic receptor (Nykjaer et al., 1999). The process of hydroxylation of the vitamin D in liver is not firmly regulated, while renal production of 1,25-hydroxyvitamin D is strongly regulated through calcium, phosphorous, parathyroid hormone and 1, 25-hydroxyvitamin D itself (Breslau, 2008). When levels of calcium in blood are not sufficient, parathyroid hormone levels are elevated which stimulate calcitriol production consequently enhancing the absorption of calcium in the intestine (Segersten et al., 2002). Maintenance of non-renal dihydroxyvitamin D production is mostly unknown, however, alpha hydroxylase mRNA is maximum in renal tissues (Omdahl et al., 2002).

About 2 to 3% of the human genome is indirectly or directly regulated through vitamin D coordination (Bouillon et al., 2008). Furthermore, it has been established that locally produced dihydroxyvitamin D may control more than 2000 genes which take part in various processes comprising immunity, cell growth, inflammation and cell proliferation (Nagpal et al., 2005; Norman, 2006). The genomic function of vitamin D requires the joining of calcitriol to strong affinity receptor, vitamin D receptor (VDR). It is a member of superfamily of the nuclear hormone receptors which acts as a ligand activated transcription factor (Ogunkolade et al., 2002). However, the VDR can be present in organs involve in metabolism of calcium and homeostasis constituting the bone, intestine, parathyroid glands and kidney. VDRs have also been recognized in many other tissues: breast, heart, colon, pancreas and prostate (Anderson et al., 2003; Clemens et al., 2009).

Moreover, besides genomic function, vitamin D also facilitates a rapid non-genomic function that is found through the attachment of vitamin D to a cell membrane VDR. Such non-genomic functions of vitamin D are vital in nuclear transcription activity, and the membrane associated actions, such as elevating calcium uptake, secretion of calcium from its intracellular stores and excitement of protein kinase C action (Norman, 2006; Fleet, 2004).

Factors affecting vitamin D levels

A number of factors may affect the production of vitamin D *in vivo*. Solar zenith angle (SZA), that is the role of time of day, latitude and time of year significantly affects the relationship of vitamin D synthesis and sunlight exposure (Kimlin, 2008).

Dark skin coloration is also important influential factor for dermal vitamin D production, due to less absorption of ultraviolet radiations with higher melanin component.

People with intensive skin pigmentation contain high melanin component that absorbs ultraviolet photons and therefore contends along 7-dehydrocholesterol (Clemens et al., 2009). Prevention of sunlight exposure, wrapping of body by clothing as well as sunscreen routine also decreases dermal synthesis of vitamin D (Holick et al., 2007; Fleet, 2004).

The composition of body is another significant indicative factor for vitamin D level, as different studies have constantly revealed that people with higher adiposity have poor levels of vitamin D (Liel et al., 1999; Arunabh et al., 2003) due to repossession of fat soluble vitamins in adipocytes (Wortsman et al., 2003; Blum et al., 2008). Furthermore, people with disorders of malabsorption; fibrosis, cystic, celiac and Chron's diseases have reduced bioavailability of vitamin D because of a diminished capability to absorb this vitamin (Lo et al., 2005). People with kidney and liver disorders also suffer from deficiency of vitamin D because of impairments in metabolism of vitamin D (Masuda et al., 1999; Ishimura et al., 2000).

Genetic influences are another important determinant of levels of vitamin D and take part in inter-individual deviation in vitamin D considerably influencing both quantities and variation in synthesis (Arguelles et al., 2009; Karohl et al., 2010). The VDR gene and other genes polymorphisms, as all genes exhibit inclusively variable contributions in production, function and metabolism of vitamin D.

Vitamin D and type 2 diabetes mellitus

The actions of vitamin D upon skeletal health are indicating its significant action in many other disorders and health conditions including; cardiovascular diseases, cancer, autoimmune disorders, and T2DM (Holick, 2011; Boyd et al., 1986). Deficiency of vitamin D is related with reduced insulin secretion, and supplementation of vitamin D reestablished normal insulin secretion (Norman et al., 2004; Clark et al., 2010). Moreover, seasonal changes in insulin and glucose concentrations (Behall et al., 2004; de Souza and Meier, 2007), as well as seasonal changes in diagnosis and management of T2DM have been noted. There are more diagnosis and lesser glycemic control during winter as compared to summer (Doro et al., 2006). Furthermore, most case control research outcomes have also documented that T2DM patients or those with impaired tolerance of glucose are expected to have a poor concentration of vitamin D than to those without T2DM (Pittas et al., 2006; Scragg et al., 2004).

Only two randomized control trials suggesting the effects of this vitamin supplementation on incidence of T2DM are available in literature (de Boer et al., 2008; Avenell et al., 2009), as most of these trials stated the effects of vitamin D on insulin resistance, glycemic control and insulin secretion in preliminary inferences and determined no statistically significant action of vitamin D supplementation

[400 IU/day] (de Boer et al., 2008); 800 IU/day (Avenell et al., 2009) on occurrence of diabetes mellitus after three to seven years of follow-up.

Association of vitamin D and insulin resistance

A number of researches have examined the function of vitamin D in initial pathophysiological conditions underlying T2DM, especially lack of insulin sensitivity and pancreatic beta cell dysfunction. A significant role of this vitamin with lack of insulin and pancreatic beta cell function has been derived. Uneven outcomes have also been stated in cross sectional analyses considering the relationship of vitamin D with function of the beta cell, indicating a positive association (Boucher et al., 1995; Baynes et al., 1997; Wu et al., 2009) or no significant relationship (Orwoll et al., 1994; Chiu et al., 2004; Scragg et al., 2004; Gulseth et al., 2010; Del Gobbo et al., 2011; Rhee et al., 2012).

Mechanism

Numerous prospective processes have been recommended to describe the relationship of vitamin D to T2DM and its associated manifestations. Vitamin D can directly increase action of insulin for the transportation of glucose via exciting the expression of insulin receptors (Maestro et al., 2000), as (vitamin D response element) VDRE is located in promoter region of insulin receptor gene (Maestro et al., 2003). Vitamin D cannot directly affect lack of insulin sensitivity by maintaining intracellular processing of insulin mediated by the regulation of calcium pool (Draznin et al., 1987; Draznin, 1988). Elevated intracellular calcium may stop insulin target cells to sense sharp intracellular fluctuations in calcium which is necessary for insulin action involving glucose transport (Norman et al., 2004; Worrall and Olefsky, 2002). This is also significant to note that initial determinants of peripheral sensitivity of insulin, skeletal muscle and adipocytes, express the VDR (Norman, 2006; Bischoff et al., 2001) and like sensitivity of insulin, the expression of VDR decline in skeletal muscle with age (Bischoff-Ferrari et al., 2004). In addition, the expression of vitamin D α -hydroxylase observed in various tissues of wistar rats (Li et al., 2008), initiating the local synthesis of vitamin D. With respect to pancreatic beta cell function, calcitriol can apply direct effects by binding of its active form in circulation to the beta cell VDR (Johnson et al., 1994; Zeitz et al., 2003). Instead, activation of this vitamin could happen within the pancreatic beta cell by vitamin D 1- α -hydroxylase that has been designated to express in pancreatic beta cells (Bland et al., 2006). Furthermore, assuming the occurrence of VDRE in insulin gene promoter region, this may interpret the transcriptional activation of insulin gene through vitamin D (Maestro et al., 2003). Vitamin D can also employ indirect effect on beta cell function by maintaining

extracellular calcium and its flux through the beta cell (Sergeev and Rhoten, 1995) as secretion of insulin is a calcium dependent phenomenon (Holick, 2011). Based on the relationship between T2DM and systemic inflammation (Donath and Shoelson, 2011) vitamin D may also improve the sensitivity of insulin and promote the function of the beta cell by regulating the generation and actions of cytokines (Pittas et al., 2007). However, limited data have described the association between vitamin D and T2DM (Pittas et al., 2007; Cigolini et al., 2006).

Role of genetics

Genetic variations can explain discrepancies in the literature with respect to the relationship of vitamin D to T2DM. Much research has been focused on various genotypes associated to the VDR, vitamin D binding protein (DBP) and vitamin D-1- α -hydroxylase. Polymorphisms that have been recognized in VDR gene, specifically *Apal*, *TaqI*, *FokI* and *BsmI* may be related with T2DM, lack of insulin sensitivity and dysfunction of the pancreatic beta cell. However, recent evidences are limited and their outcomes have been inconsistent. Studies have found imperative relationships of specific VDR polymorphisms with higher lack of insulin sensitivity (Chiu et al., 2001; Oh et al., 2002; Ortlepp et al., 2002; Filus et al., 2003; Tworowska-Bardzinska et al., 2008) and insulin secretion (Hitman et al., 1998; Speer et al., 2001; Ogunkolade et al., 2002). Though, most of these researches have focused on Caucasian populations and have employed surrogate measures of beta cells functions and lack of insulin based during fasting. With regard to T2DM specifically, Ortlepp et al. (2001) observed a greater prevalence of T2DM among those with a certain *BsmI* genotype for VDR gene as compared to those deprived of this genotype. Some case-control studies described no significant variations in frequencies of the genotype for different VDR genes in T2DM versus controls (Ortlepp et al., 2001; Boullu-Sanchis et al., 1999; Ye et al., 2001; Malecki et al., 2003; Bid et al., 2009; Dilmec et al., 2010; Vural et al., 2012). Therefore, further investigation into association between VDR polymorphisms and risk of T2DM is warranted predominantly in various ethnic populations. Genetic polymorphisms of the vitamin binding protein have been recognized suggesting an association of these polymorphisms and enhanced risk of T2DM (Hirai et al., 1998) and lack of insulin sensitivity as calculated through fasting glucose or levels of insulin (Baier, 1996; Szathmary 2007). However, another gene related to vitamin D studied for a possible association with T2DM is vitamin D-1- α -hydroxylase (CYP1 α), it is accountable for the change of hydroxyvitamin D to dihydroxyvitamin D (calcitriol). So far, single study has been done to date (Malecki et al., 2003), which suggested no significant polymorphism in CYP1 α gene in T2DM patients versus controls in the Polish population. Hence, significant

association of specific genotype of CYP1 α gene with T2DM was observed in obese subgroup. However, precise mechanism of this finding was not clear. Earlier, Jorde et al. (2012) suggested that no significant relationship of T2DM exist with many single nucleotide polymorphisms (SNP) linked with serum vitamin D level.

Vitamin D receptor polymorphisms

Four allelic variants of vitamin D receptor gene have been recognized: *Apal*, *FokI*, *Bsml* and *TaqI* (Pittas et al., 2006). The functions of these vitamin D receptor polymorphisms have been comprehensively studied in T2DM patients (Ogunkolade et al., 2002). Polymorphism genotype *Apal* of VDR gene showed relationship to the insulin secretion in Bangladeshi population, which are at high risk of T2DM with higher prevalence of hypovitaminosis D. A correlation of *Apal* polymorphism with fasting blood glucose level and intolerance of glucose was evident among those people who had diabetes symptoms at pre-diagnosis stage. Ogunkolade et al. (2002) illustrated a positive relationship between the *Bsml* (genotype bb) and *TaqI* (genotype TT) polymorphisms with decreased insulin secretory potential. Speer et al. (2001) proposed that obese T2DM patients have greater levels of C- peptide and VDR polymorphism of *Bsml* allele (BB-genotype) indicative of their probable role in pathogenesis of T2DM. Insufficiency of vitamin D was measured in these subjects and polymorphism of *TaqI* was an element related to insulin secretion. Though, there is strong evidence of link between T2DM and VDR polymorphism; conflicting results among different populations are reported (Malecki et al., 2003).

In T2DM, the vitamin D receptor gene polymorphism of allele *Apal* (aa genotype) was related with impaired secretion of insulin in Caucasian population, thus this population had a higher risk of developing T2DM (Oh et al., 2002). Contrary to that, VDR gene polymorphisms of alleles *FokI*, *TaqI*, *Apal* and *Bsml* had no noteworthy association with T2DM in a case control research within Bangladeshi population by Islam et al. (2014). Insulin sensitivity was significantly decreased in T2DM cases of Bangladeshi origin.

It was concluded by Sung et al. (2012) that distributions of VDR gene alleles of the four SNPs (*Bsml*, *TaqI*, *Tru9I* and *Apal*) were same in T2DM patients and controls. These evidences supporting or opposing a relationship of vitamin D receptor genotypes with menace of T2DM are conflicting.

Polymorphisms present in intron 8 (*Bsml*) and exon 9 (*TaqI*) of vitamin D receptor gene had substantial linkage with type 2 diabetes mellitus, while distribution as well as frequency of genotype *FokI* (exon 2) and *Apal* (exon 8) of the VDR were significantly similar in T2DM patients and healthy people. These results confirmed the previous inferences that VDR gene genotypes *Bsml* as well as *TaqI* polymorphisms are related with onset of type 2 diabetes mellitus (Speer et al., 2001; Nosratabadi et al., 2010).

Furthermore, Al-Daghri et al. (2012) explained that *Bsml* and *TaqI* single nucleotide polymorphisms that are significantly more common in T2DM patients were allied with elevated levels of cholesterol and lower levels of high density lipoprotein (HDL) cholesterol. However, such results are yet not unambiguous as other researchers failed to demonstrate the analogous relationship between *FokI*, *Apal*, *Bsml* and *TaqI* polymorphisms and onset of type 2 diabetes mellitus in Indians (Ortlepp et al., 2002), Turkish (Dilmec et al., 2010), Polish (Malecki et al., 2003) and American populations (Oh et al., 2002). The reasons of these discrepancies might be elucidated by the differences in the genetic background among ethnic groups. An overview of VDR gene of the significant allelic variations associated to T2DM.

Although the summary depicted below is scarce and not compatible, nonetheless it portrays a possible association between VDR gene, metabolism of vitamin D and T2DM etiology/traits.

CONCLUSION

The prevalence of T2DM is intensely increasing, both in Pakistan and worldwide. Furthermore, assuming the lack of correct diagnosis of vitamin D deficiency and multi-system implications in most populations are at greater risk of having inadequate levels of serum vitamin D, with over 75% people having vitamin D deficiency while 18% reported insufficient vitamin D levels (Masood et al., 2010). Evolving evidence proposes a prospective role for this vitamin in risk of T2DM as well as its underlying pathophysiological complications, specifically lack of insulin sensitivity and dysfunction of beta cell. However, many epidemiological, interventional and biological researches have suggested a probable relationship of vitamin D to lack of insulin sensitivity and function of beta cell, although these evidences have been inconsistent. In recent years, a number of polymorphisms, such as *Bsml* and *FokI* have been observed in the vitamin D receptor genes which are able to change the function of the VDR protein, while other polymorphisms in VDR gene found through variation of alleles in sites of restriction enzyme are *TaqI* and *Apal*. The genetic background of T2DM remains unclear. However, it is suggested that the vitamin D receptor gene is an innovative candidate gene responsible to the susceptibility to T2DM.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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