REVIEW ARTICLE

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# The Role of Vitamin D Receptor Gene Polymorphisms in Type 2 Diabetes Mellitus Susceptibility and Pathogenesis

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## Abstract

Type 2 Diabetes Mellitus (T2DM) is a multifactorial disease influenced by both genetic and environmental factors. Among the genetic factors, vitamin D receptor (VDR) gene polymorphisms have been studied for their potential role in T2DM susceptibility. Vitamin D, through its receptor (VDR), plays a crucial role in various biological processes, including glucose metabolism, insulin secretion, and inflammation regulation. Vitamin D deficiency is associated with diabetes mellitus. In addition, genetic variations in the VDR gene could influence an individual's risk of developing T2DM through calcium metabolism alteration and modulation of insulin secretion. Three single nucleotide polymorphisms BsmI, ApaI and TaqI of the VDR gene were located in key untranslated regions that influence gene expression. Moreover, FokI is a T > C substitution occurring in exon 2. These four VDR gene polymorphisms have been shown to impact insulin production and secretion, suggesting their potential involvement in the development of T2DM.

**Keywords:** T2DM; VDR gene polymorphisms; BsmI; ApaI; TaqI; FokI.

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and β-cell dysfunction. The incidence and prevalence of diabetes mellitus are rapidly increasing, making it one of the most widespread and expensive chronic diseases globally. It is characterized by insulin resistance and dysfunction of the pancreatic islets of beta cells. Hyperglycemia, oxidative stress, metabolic disturbances, and an increased risk of vascular complications are the principal pathological features associated with the disease **(Ssekamatte et al., 2023)**.

Type 2 diabetes mellitus is the predominant form of diabetes and accounts for at least 90% of all cases of DM. It has become globally epidemic and is expected to be the seventh leading cause of mortality by 2030 **(Wang et al., 2020; Mehta et al., 2022)**. T2DM pathogenesis is driven by both environmental and genetic factors, with elevated hepatic glucose production, impaired insulin secretion, and insulin resistance acting as key drivers in the development of disease **(Jensen and Dabelea, 2018)**.

Vitamin D has been reported to exert a key role in the pathogenesis of diabetes. It elicits its actions on target tissues through its binding to the cytosolic /

nuclear vitamin D receptor (VDR), which is a member of the steroid/thyroid hormone receptor family that acts as a transcriptional activator of several genes (Li et al., 2013). Several polymorphisms in the VDR gene were reported to affect an individual's susceptibility to T2DM. Studies have investigated the relationship between specific VDR polymorphisms and insulin resistance, β-cell function, and inflammation, all of which are key components in T2DM pathophysiology (Küchler et al., 2022).

# 2. Diabetes Mellitus

## 2.1. Classification of Diabetes Mellitus

Diabetes can be classified into the following general categories:

### 2.1.1. Type 1 Diabetes Mellitus

Type 1 diabetes mellitus is an autoimmune disease resulting from inflammatory infiltration of the islets of Langerhans and the selective destruction of β-cells in the pancreas that leads to absolute insulin deficiency. It is associated with the presence of alleles of the Human leukocyte antigen (HLA) class II genes within the major histocompatibility complex (MHC) **(Maiese et al., 2007)**.

### 2.1.2. Type 2 Diabetes Mellitus

Type 2 diabetes mellitus, previously referred to as non-insulin dependent diabetes mellitus or adult-onset diabetes mellitus, accounts for 90-95% of all diabetes mellitus cases. This form encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency **(American Diabetes Association, 2009)**.

The pathogenesis of T2DM arises from the interplay of genetic, environmental and lifestyle factors, which lead to a decrease in insulin sensitivity in the liver, adipose tissue and skeletal muscles, followed by chronic pancreatic β cell dysfunction and insulin resistance which leads to inability to maintain blood glucose homeostasis **(Gardner et al., 2012)**.

There are various causes of T2DM with the majority of T2DM patients being overweight or obese. Excess weight itself causes some degree of insulin resistance **(Marathe et al., 2017)**. The risk of developing T2DM increases with age, obesity and lack of physical activity. It occurs more frequently in women with prior gestational diabetes mellitus (GDM), in those with hypertension or dyslipidemia, and in certain racial / ethnic subgroups (African American, American Indian, Hispanic / Latino, and Asian American **(Araneta et al., 2015)**. It is often associated with strong genetic predisposition, more than type I diabetes mellitus **(American Diabetes Association, 2009)**.

### 2.1.3. Gestational Diabetes Mellitus

Gestational diabetes is carbohydrate intolerance resulting in hyperglycemia of variable severity with the onset or first recognition being during pregnancy. It is usually diagnosed in the second or third trimester of pregnancy. Individuals at high risk for GDM include older women, those with previous history of glucose intolerance, women from certain high-risk ethnic groups. Considering that the high blood glucose is distributed from placenta to fetus, it must be controlled for proper growth and development of fetus. This type of diabetes usually resolves after pregnancy by itself **(McIntyre et al., 2019)**.

### 2.1.4. Other specific types of diabetes mellitus

This class includes monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use in the treatment of HIV/AIDS, or after organ transplantation) **(American Diabetes Association, 2019)**.

## 2.2. Diagnostic Tests for Diabetes Mellitus

Diabetes may be diagnosed based on HbA1c criteria or plasma glucose criteria, either by the fasting plasma glucose (FPG) or the 2h post prandial blood glucose (2h PPBG) value after a 75-g oral glucose tolerance test (OGTT) **(American Diabetes Association, 2019)**.

FPG, 2-h PPBG after 75-g OGTT, and HbA1c are equally appropriate for diagnostic testing. The HbA1c test had several advantages to the FPG and OGTT, including greater convenience (fasting not required) and less day-to-day perturbations during

stress and illness. These advantages must be balanced by greater cost, the limited availability of HbA1c testing in certain regions of the developing world, and the incomplete correlations between HbA1c and average glucose in certain individuals **(American Diabetes Association, 2019)**.

It has been reported that HbA1c cut point of ≥6.5% (48mmol/mol) identifies one third fewer cases of undiagnosed diabetes mellitus than a fasting glucose cut point of ≥126mg/dl (7.0mmol/L). HbA1c is an indirect measure of average blood glucose levels whose levels can be influenced by numerous factors that may impact hemoglobin glycation other than glycaemia including age, race/ethnicity, and anemia /haemoglobinopathies **(American Diabetes Association, 2019)**.

## 2.3. Risk Factors for Type 2 Diabetes Mellitus

T2DM risk factors include a complex combination of genetic, metabolic and environmental factors that interact with one another contributing to its prevalence. Although individual predisposition to T2DM due to non-modifiable risk factors (ethnicity and family history/genetic predisposition) has a strong genetic basis, evidence from epidemiological studies suggests that many cases of T2DM can be prevented by improving the main modifiable risk factors (obesity, low physical activity and an unhealthy diet) **(Hu et al., 2001; Schellenberg et al., 2013)**.

### 2.3.1. Ethnicity and Family History/Genetic Predisposition

Globally, the incidence and prevalence of T2DM are found to vary widely depending on ethnicity and geographical region. Whilst no clear reasons have been found, contributing factors such as modern lifestyle factors (which promote obesity), socioeconomic and direct genetic propensity or gene environmental interactions have been postulated. Genetic predisposition plays an important part in the risk of developing T2DM. Over the past decade, several T2DM genome-wide association studies have shown the complex polygenic nature of T2DM in which most of these loci increase T2DM risk through primary effects on insulin secretion, and a minority act through reducing insulin action. Interactions between susceptibility loci and environmental factors could underlie the missing heritability of T2DM thus the impact of a given genetic variant can be modulated by the environmental factors **(Galicia et al., 2020)**.

Modern research is meticulously working to discover a genetic variant that contributes to disease and increases the risk of T2DM. Genetic variations might add to the outcome of the possibility of T2DM, and modifications in these gene traits could also increase the chances of diabetes and obesity **(Himanshu et al., 2020)**.

### 2.3.2. Obesity, Low Physical Activity and Unhealthy Diet

Obesity (body-mass index [BMI] ≥30 kg/m2) is the strongest risk factor for T2DM and is associated with metabolic abnormalities resulting in insulin resistance. There is a negative correlation between BMI and the age at which T2DM is diagnosed. The exact mechanisms by which obesity induces T2DM and insulin resistance remain to be elucidated; however, numerous factors have shown a significant role in the development of this pathological process, which involves both cell-autonomous mechanisms and inter-organ communications **(Galicia et al., 2020)**.

A sedentary lifestyle is another risk factor for T2DM. There are three primary benefits of physical activity on the delay of T2DM onset. First, the contraction of skeletal muscle cells induces an increase in blood flow into the muscle, enhancing glucose uptake from plasma. Second, physical activity reduces the notorious intra-abdominal fat, which is a known risk factor that promotes IR. Finally, moderate-intensity exercise has been shown to improve glucose uptake by 40%. Physical activity improves glucose uptake and insulin sensitivity, but it can also improve or even reverse inflammation and oxidative stress, which are T2DM predisposing factors **(Galicia et al., 2020)**.

## 2.4. Pathogenesis of Type 2 Diabetes Mellitus

Regarding the pathophysiology of the disease, a malfunctioning of the feedback loops between insulin action and insulin secretion results in abnormally high glucose levels in blood. Fasting hyperglycemia is caused by unrestrained basal hepatic glucose output, primarily a consequence of hepatic resistance to insulin action. Post-prandial hyperglycemia, on the other hand, results from abnormal insulin secretion by β-cells in response to

a meal, impaired hepatic glucose production, and defective glucose uptake by peripheral insulin-sensitive tissues, particularly the skeletal muscle **(Giorgino et al., 2005)**.

Chronic hyperglycemia further impairs β-cell secretory kinetics and tissue sensitivity to insulin, a phenomenon known as glucotoxicity. Thus, both impaired insulin action (insulin resistance) and dysfunctional insulin secretion (insulin deficiency) represent core elements in the pathogenesis of type 2 diabetes. In addition to the insulin resistance in the muscle and liver, and impaired insulin secretion in the β-cell, the fat cell+ (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), α-cell (hyperglucagonaemia), kidney (increased glucose reabsorption) and brain (insulin resistance) all play important roles in the development of glucose intolerance in type 2 diabetic individuals **(Defronzo, 2009) (Figure 1)**.

## 2.5. Micro and Macro Vascular Complications of Diabetes Mellitus

Hyperglycemia is the principal cause of micro vasculopathy but also appears to play an important role in causation of macro vasculopathy. There is thought to be an intersection between micro and macro vascular complications, but the two disorders seem to be strongly interconnected, with micro vascular diseases promoting atherosclerosis through processes such as hypoxia and changes in vasa vasorum **(Chawla et al., 2016)**.

### 2.5.1. Diabetic Macrovascular Complications

The macrovascular disorders associated with prediabetes include CVD, stroke, and peripheral vascular disease. These disorders are established in patients with T2DM, but their initiation and progression are well recognized to occur during the prediabetes stage. In fact, the traditional CVD risk factors (dyslipidemia, obesity, hypertension) are quite prevalent among individuals with prediabetes **(Brannick and Dagogo, 2018)**.

#### 2.5.1.1. Cardiovascular Disease

Myocardial infarction and congestive heart failure as well as coronary artery disease and atherosclerosis have all been reported in individuals with prediabetes. It has been reported that the increase in HbA1c % was associated with increased cardiovascular mortality **(Brannick and Dagogo, 2018)**.

#### 2.5.1.2. Stroke

Individuals with prediabetes have an increased risk of cerebrovascular diseases, including transient ischemic attack, stroke, and recurrent stroke **(Brannick and Dagogo, 2018)**.

#### 2.5.1.3. Peripheral Vascular Disease

Prediabetes is common in patients with peripheral vascular disease. The development of diabetes is independently associated with mortality in peripheral vascular disease patients **(Brannick and Dagogo, 2018)**.

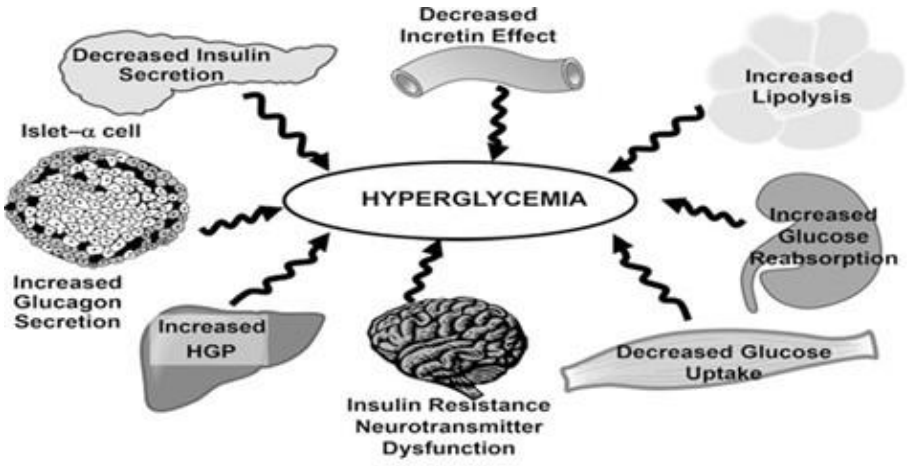


**Figure 1.** The Ominous Octet describing the major pathophysiologic effects which involve multiple organs in type 2 diabetes **(Defronzo, 2009)**.

### 2.5.2. Diabetic Microvascular Complications

Pathological changes in the diabetic microvasculature alter organ perfusion, including organs heavily dependent on their microvasculature supply, namely the retina, kidneys, and peripheral nervous system. The clinical problems associated with these changes–retinopathy, nephropathy, and neuropathy–drive a large burden of T2DM morbidity. Microvascular disease also contributes to peripheral vascular disease, reduced myocardium vascularization, and poor wound healing **(Orasanu and Plutzky, 2009)**.

#### 2.5.2.1. Diabetic Retinopathy

The risk of development of diabetic retinopathy in T2DM patients has been found to be related to both severity of hyperglycemia and presence of hypertension. Several studies have explored the association between diabetic retinopathy and macrovascular complications **(Chawla et al., 2016)**.

#### 2.5.2.2. Diabetic Nephropathy

The pathogenic mechanisms underlying diabetic nephropathy involve generation of reactive oxygen species (ROS), accumulation of advanced glycation end product (AGE), and activation of intracellular signaling molecules such as protein kinase C. The direct association between the presence of microalbuminuria and macrovascular complications has also been well established in many studies **(Chawla et al., 2016)**.

#### 2.5.2.3. Diabetic Neuropathy

Diabetic neuropathy is a life-threatening complication that involves both peripheral and autonomic nerves, affecting almost half of the diabetic population. The risk of development of diabetic neuropathy is directly proportional to both the duration and magnitude of hyperglycemia. In addition, some individuals may also possess genetic facets that influence their predisposition in developing such complications **(Chawla et al., 2016)**.

## 2.6. Treatment of Type 2 Diabetes Mellitus

Effective treatments include lifestyle interventions (such as dietary modification, physical activity, and behavioral therapies), pharmacotherapy, medical devices, and bariatric surgery **(Ruze et al., 2023)**.

### 2.6.1. Lifestyle Interventions

Given their inexpensiveness and minimal side effects, lifestyle interventions are always the first option, or more precisely, the cornerstones for the management of obesity and T2DM. These lifestyle interventions include self-monitoring of body weight, blood glucose, diet, and physical activity that contribute to weight loss and glycemic control **(Ruze et al., 2023)**.

Dietary modification (medical nutrition therapy) and physical activity are two primary and significant lifestyle interventions. Although there is no optimal diet or physical activity regimen for every patient, optional and professional guidelines have recommended various appropriate dietary patterns and multiple types of physical activities that facilitate energy restriction, induce weight loss and improve glycemic status **(Ruze et al., 2023)**.

### 2.6.2. Pharmacotherapy

Considering the limited efficacy of lifestyle interventions, other therapeutic approaches are needed to maintain or strengthen obesity and T2DM management effectively. Technically, both weight-loss and glucose-lowering medications must be taken for a long time unless they are intolerable, or cessation is highly indicated due to the safety concerns related to any possible side-effect **(Ruze et al., 2023)**.

#### 2.6.2.1. Oral Medications

In addition to lifestyle intervention, many pediatric patients require glucose lowering medication to achieve normalization of blood glucose and A1C levels. Although many oral glucose lowering medications have been approved for adults with T2DM, only metformin has been approved by the FDA for use in pediatric patients aged 10 years and older. Patients taking metformin are advised to take daily multivitamins due to a possible poor absorption of vitamin B12 and/or folic acid **(George and Copeland, 2013)**.

#### 2.6.2.2. Insulin Therapy

Many care providers prefer insulin at the time of diagnosis for all patients with type 2 diabetes, and its use is essential for those with significant hyperglycemia or ketosis. For patients treated with

oral medications, insulin is often the first step toward intensification of therapy, once oral medications and lifestyle interventions are insufficient for achieving optimal glycemic control **(George and Copeland, 2013)**.

## 3. Role of Vitamin D and Its Receptor in Type 2 Diabetes Mellitus

Vitamin D prohormone (calciferol; sunshine vitamin) is a collective term for vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is mainly synthesized in the skin through the photochemical action of solar ultraviolet type B radiation on 7-dehydrocholesterol (7-DHC). In contrast, the body is unable to produce vitamin D2 and can only be consumed through the consumption of plants in the diet **(Schmitz et al., 2021)**.

The structural difference between vitamin D2 and vitamin D3 affects metabolic activity with the latter exhibiting a better affinity for vitamin D binding protein (VDBP) and VDR. Vitamin D is biologically inert and requires two hydroxylation steps for its activation. Initially, it is hydroxylated in the liver by cytochrome P450 enzyme (CYP2R1; 25-Hydroxylase) to calcifediol (25-hydroxy vitamin D3; [25(OH)D3]) and further metabolized to calcitriol (1,25-dihydroxy vitamin D3; 1,25(OH)2D3) by CYP27B1 (1α-Hydroxylase) in the kidneys and other tissues/organs, including the brain **(Jeong et al., 2024)**.

Vitamin D has been linked to calcium homeostasis and bone remodeling. However, calcium homeostasis represents only one aspect of the pleiotropic functional profile of the molecule. Vitamin D is also involved in multiple biological processes such as detoxification, energy metabolism and the mechanisms of regulating the immune system. Moreover, it has been increasingly recognized for its impact on glucose metabolism, regulation of insulin secretion and attenuation of systemic inflammation (Dominguez et al., 2021; Carlberg, 2022). Several studies found an inverse correlation between insulin level and 25-(OH) vitamin D level in T2DM patients **(Al-Hazmi, 2019)**. An overview of vitamin D metabolism and its physiological action is presented in **Figure 2 (Battault et al., 2012)**.

### 3.1. Role of Vitamin D receptor gene polymorphisms in Type 2 Diabetes Mellitus

The VDR gene is located on chromosome 12 (12q13.11) and contains nine exons. Several common allelic variants have been identified, and some variants appear to influence the receptor's function and, therefore, an individual's risk of T2DM. Four polymorphisms in the VDR gene—FokI, BsmI, TaqI, and ApaI—have been the most extensively studied for their association with T2DM. These polymorphisms affect the binding affinity of vitamin D to its receptor, the receptor's gene expression, and downstream signaling pathways. There is sample evidence suggesting a role for vitamin D in insulin secretion, which includes the presence of the VDR in β cells and the vitamin D–dependent calcium-binding proteins (DBP) in pancreatic tissue. It has been shown in both *in vitro* and *in vivo* models that vitamin D itself is essential for normal insulin release in response to glucose and for maintenance of glucose tolerance **(Palomer et al., 2008)**.

#### 3.1.1. FokI Polymorphism

The FokI polymorphism (rs2228570) involves a single nucleotide change that results in an altered translation start site, producing a protein with a longer or shorter form. The "f" allele (short form) has been linked with lower VDR activity, whereas the "F" allele (long form) produces a more active receptor. Studies have shown mixed results regarding the association between FokI polymorphisms and T2DM. Some suggest that the "ff" genotype is associated with an increased risk of T2DM, while others report no significant association **(Mahjoubi et al., 2000; Bo et al., 2002)**.

#### 3.1.2. BsmI Polymorphism

The BsmI polymorphism (rs1544410) is a G-to-A substitution in the 3' untranslated region of the VDR gene. This polymorphism has been associated with altered VDR expression and vitamin D metabolism. Some studies indicate that the "b" allele is linked with a higher risk of T2DM, particularly in populations with low vitamin D levels **(Cyganek et al., 2006)**. However, the findings have been inconsistent across different ethnic groups.

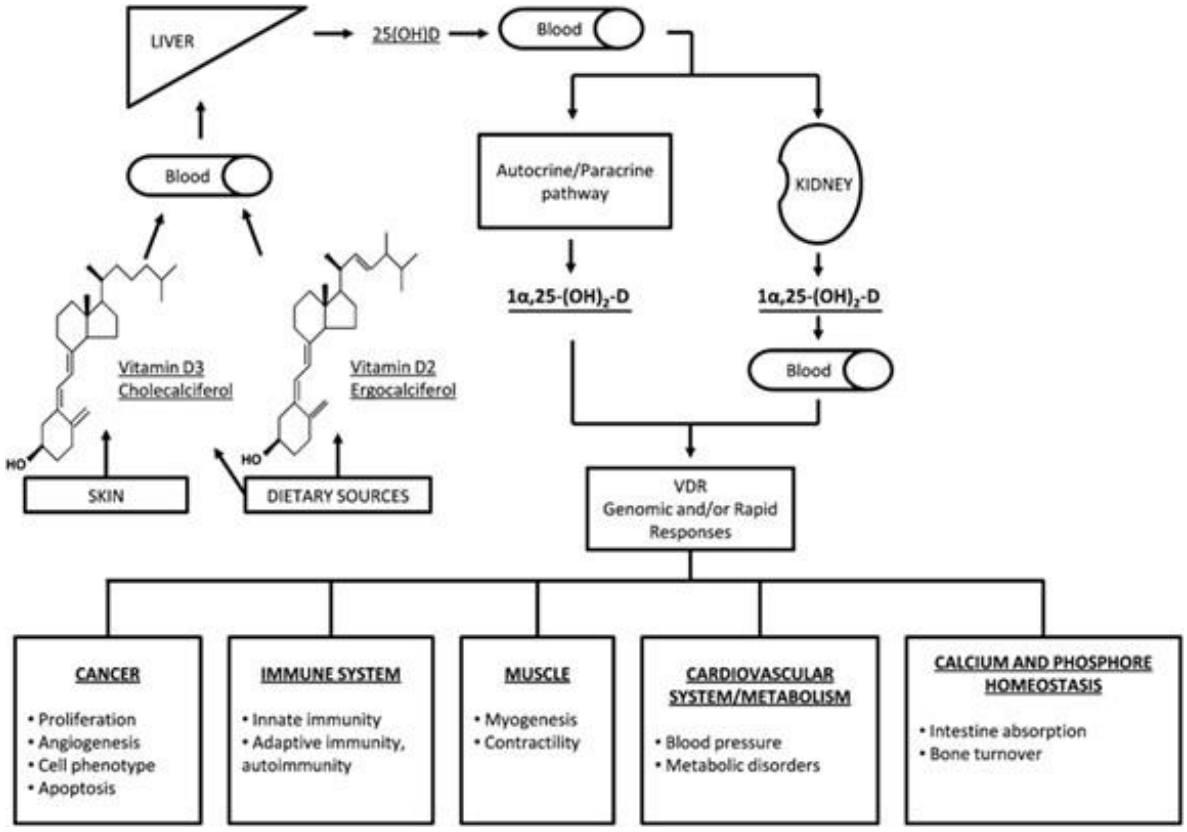


**Figure 2.** Schematic of vitamin D metabolism and physiological actions **(Battault et al., 2012)**.

### 3.1.3. TaqI Polymorphism

The TaqI polymorphism (rs731236) is a synonymous single nucleotide polymorphism in the coding region of the VDR gene. It does not alter the amino acid sequence of the VDR protein but may affect its transcriptional regulation. Several studies have suggested that the TaqI "T" allele is associated with a higher susceptibility to T2DM **(Klashami et al., 2022)**, while others report no significant association **(Su et al., 2015)**.

### 3.1.4. ApaI Polymorphism

The ApaI polymorphism (rs7975232) is another variant in the 3' untranslated region of the VDR gene. Studies investigating its role in T2DM have shown mixed results, with some suggesting an association between the "A" allele and an increased risk of developing the disease **(Zhang et al., 2012)**, while others do not find significant associations **(Dilmec et al., 2010)**.

## 3.2. Mechanisms Linking VDR Polymorphisms and T2DM

The impact of VDR gene polymorphisms on T2DM is thought to occur through several mechanisms **(Sung et al., 2012)**:

**1. Insulin Secretion:** VDRs are expressed in pancreatic β-cells, where they play a role in insulin secretion. Vitamin D deficiency or polymorphisms leading to decreased VDR activity may impair insulin secretion, increasing the risk of T2DM **(Sung et al., 2012)**.

**2. Insulin Sensitivity:** Vitamin D affects the expression of insulin receptors in peripheral tissues such as muscle and adipose tissue. VDR polymorphisms that reduce receptor activity may decrease insulin sensitivity, contributing to insulin resistance in T2DM **(Sung et al., 2012)**.

**3. Inflammation:** Chronic low-grade inflammation is a hallmark of T2DM, and vitamin D's anti-inflammatory effects may mitigate this process. VDR polymorphisms may modulate vitamin D's ability to reduce inflammatory cytokines, such as TNF-α, IL-6, and CRP, thus influencing T2DM risk **(Sung et al., 2012)**.

**4. Gene Expression and Epigenetics:** VDR polymorphisms may alter the transcriptional

regulation of key genes involved in glucose metabolism, insulin resistance, and inflammation. Additionally, vitamin D may modulate epigenetic factors that influence gene expression, providing a potential link to T2DM susceptibility **(Sung et al., 2012)**.

### 3.3. Clinical Implications and Future Research

Understanding the role of VDR gene polymorphisms in T2DM could have significant clinical implications. Personalized medicine approaches could be developed, where individuals are screened for specific VDR polymorphisms, and vitamin D supplementation is tailored accordingly. Further studies are needed to clarify the inconsistent findings across different populations and ethnic groups **(Sung et al., 2012)**.

Additionally, the potential for genetic-environmental interactions (e.g., dietary vitamin D intake, sunlight exposure) should be explored in larger cohort studies to better understand how VDR polymorphisms and vitamin D status interact in the pathogenesis of T2DM **(Sung et al., 2012)**.

## 4. Conclusion

The association between VDR gene polymorphisms and T2DM is an area of growing interest, with several studies suggesting a potential link. However, the findings are often inconsistent, and further research is needed to better understand the mechanisms underlying these associations. Exploring the role of vitamin D and its receptor in T2DM may provide insights into novel therapeutic approaches and improve the management of this complex disease.

### Conflict of Interest

The authors report no declaration of conflict of interest.

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