

# Association Between Gene Polymorphisms of Inflammatory Cytokines and Vitamin D Receptor Gene with the Risk of Insulin Resistance and Dyslipidemia in Type 2 Diabetic Patients

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**Abstract:** The most common form of diabetes is Type 2 diabetes (T2D), and metabolic disease is the most prevalent. Inflammatory cytokines are involved in the pathogenesis of T2D and the presence of complications. The common problem is vitamin D deficiency, linked to an increased risk of obesity and metabolic dysfunction. Furthermore, vitamin D deficiency contributes to metabolic disorders; vitamin D receptor (VDR) gene polymorphisms play a role in these conditions. However, there are only a few data studies the relationships between them of small sample size and some selected polymorphisms of VDR. This opinion article investigates the association between genetic variants of inflammatory cytokines and VDR gene with the risk of insulin resistance (IR) and dyslipidemia in patients with T2D. The current project will identify the most significant risk factors for complications in T2D and clarify the causal relationship between vitamin D status and inflammatory markers with the increased risk of metabolic alterations in patients with T2D. Knowledge of these genetic variants might contribute to a better understanding of the role of inflammation and vitamin D deficiency in the etiology and progression of this disease and may lead to new strategies for prevention.

**Keywords:** vitamin D deficiency; anthropometry; VDR gene; T2D; inflammatory cytokines.

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## 1. Introduction

According to 2014 data, the World Health Organization (WHO) region with the highest diabetes prevalence, 13.7%, is the Eastern Mediterranean Region, where Egypt resides. Type 2 diabetes (T2D) is a highly prevalent metabolic disease and very widespread form of diabetes that represents a major global health problem [1,2]. According to the International Diabetes Federation (IDF), approximately 382 million people worldwide with diabetes [3]. Egypt is in the world 8th place in terms of diabetes incidence, affecting up to 9.3% of the population due to a rapidly increasing and aging population. One of the serious complications associated with T2D is Coronary artery disease (CAD) where, more than 50% of individuals with T2DM have coronary heart disease, stroke, or cardiac disease [4,5]. Microvascular and macrovascular complications are associated with T2D and lead to morbidity and mortality [6]. An association between obesity and diabetes has been previously reported. Chronic low-grade inflammation and the activation of the immune system play a role in the pathogenesis of T2D and its complications; the mechanisms are not completely clear, though [7]. Thus more studies are

required to investigate the role of inflammatory and anti-inflammatory cytokines in the onset of T2DM [8]. Increased interleukin-6 (IL-6) levels are correlated with adiposity and fat mass but not necessarily with insulin action or responsiveness [9,10]. However, another study has observed higher IL-6 levels in patients with obesity-related insulin resistance [11, 12]. It has been deduced that the constant higher systemic levels of IL-6 might lead to insulin resistance, while a temporary increase in IL-6 may help in normal glucose homeostasis. Thus, IL-6 appears to have dual functions according to the tissue and metabolic state. Therefore, during exercise, IL-6 improves glucose uptake in the skeletal muscle, causing muscle hypertrophy, myogenesis, and AMPK-mediated fatty acid oxidation, in addition to exerting an anti-inflammatory effect [12]. In adipose tissue and liver, IL-6 will have proinflammatory activities and elevate insulin resistance via upregulation of SOCS3, which is a member of the suppressor of cytokine signaling family [13]. The single nucleotide polymorphisms (SNPs) in the regulatory regions of cytokine genes modulate their expression. Although the association between tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-6 gene polymorphisms with metabolic diseases has been previously investigated [14], there is much controversy regarding their role in diabetes occurrence [15,16].

## **2. VDR polymorphisms and T2DM.**

Moreover, some studies have demonstrated an inverse relationship between 25(OH)D levels and metabolic syndrome, obesity, and insulin resistance [17-20].

Vitamin D plays several important roles in the musculoskeletal system, such as maintaining calcium homeostasis and bone metabolism. However, new functional roles linking it to several non-communicable diseases have emerged. Vitamin D deficiency causes, in addition to poor bone development, increased risk of many chronic diseases such as insulin resistance, diabetes, and cardiovascular disease. Meta-analysis of cross-sectional studies suggested that there was a statistically significant association between the vitamin D and type 2 [21,22], that are frequently linked with obesity and visceral fat obesity (VFO). The relationship between obesity and vitamin D status has been previously investigated [23, 24]. Anthropometric indices, such as body mass index BMI, were commonly used in such studies. It has been found that VFO might play a more important role in developing vitamin D deficiency than overall obesity. Thus, assessing accumulated visceral fat is important in defining individuals at high risk for vitamin D deficiency. The abdominal fat accumulation should be accurately assessed and distinguished as fat accumulation in different areas represents a different risk for metabolic disorders [25,26]. The simplest conventional method used in assessing visceral fat accumulation is measuring the waist circumference (WC) [27][28][29]. An inverse relationship has been found between 25(OH)D levels and metabolic syndrome, obesity, and insulin resistance; however, no beneficial effect of increased dose of vitamin D supplementation on insulin resistance has been found [30]. It is supposed that obese individuals accumulate vitamin D in their fatty tissue rather than converting it into 1, 25 (OH) D3. Vitamin D deficiency was associated with hyperlipidemia [31-35].

Moreover, a positive relationship between vitamin D deficiency and lipid metabolism has been observed. Previous studies have shown an inverse relationship between vitamin D serum with LDL, TCHOL, and TG [36] and a direct relationship with HDL [37]. The VDR/RXR complex can control epigenetic pathways involved in transcription process maintenance. VDR/RXR-mediated recruitment of histone acetyltransferases, which increase acetylation processes, causing chromatin decondensation and promoting gene transcription, is reported [38].

### 3. Anthropometry and T2DM

Abdominal adiposity pattern is commonly determined by waist-to-hip ratio or waist circumference (WC) and overall obesity by body mass index (BMI). Both overall obesity and unfavorable body fat distribution have been independently associated with the development of T2DM. Abdominal volume index, AVI are new parameters that showed relations with impaired glucose tolerance in T2DM patients[39]. The body adiposity index was proposed as a better indicator of body adiposity than body mass index in adults. Its association with cardio-metabolic risk factors has been suggested as a useful tool [40].

### 4. Conclusions

This review article presents a new perspective on the pathophysiologic risk factors contributing to complications in patients with T2D. Few studies have explored this issue. Moreover, the association of polymorphisms of cytokine genes with complications and comorbidities in T2D patients has been explored for a more comprehensive prevention strategy.

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### Conflicts of Interest

The author declares no conflict of interest.

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