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The $Rs_{2241766}$, Rs_{266729} and $Rs_{1501299}$ Polymorphisms in *ADIPOQ* Gene Play Substantial Role in Predisposition to Diabetes

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ABSTRACT

One of the most frequent non-communicable diseases in the world is Diabetes Mellitus (DM). Diabetes mellitus affects one out of every eleven persons worldwide (90 percent having type 2 diabetes mellitus). Adiponectin is the most common peptide secreted by adipocytes, and its decline is linked to obesity-related disorders such as insulin resistance, diabetes mellitus, and heart disease. Single Nucleotide Polymorphisms (SNPs) in the adiponectin gene (*ADIPOQ*) have been linked to diabetes in several meta-analysis studies. The *ADIPOQ* gene's rs2241766, rs266729 and rs1501299 polymorphisms have been identified as the most prevalent SNPs linked to the development of DM across the formats. Despite the fact that all three SNPs are heavily correlated to DM, two common SNPs rs2241766 and rs266729 are linked to Type 1 Diabetes Mellitus (T_1DM), Type 2 Diabetes Mellitus (T_2DM) and Gestational Diabetes Mellitus (GDM), whereas rs1501299 is associated with T_1 DM and T_2 DM but not with GDM.

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Keywords: Adiponectin, *ADIPOQ* gene, Diabetes mellitus, Single nucleotide polymorphism.

INTRODUCTION

The Metabolic Syndrome (MS) is a new wave of diseases that has afflicted the human population in recent decades. It has spread globally, with obesity and Diabetes Mellitus (DM) being lumped together under the MS banner, affecting millions of individuals all over the world [1]. DM is a severe public health problem that affects over 400 million individuals around the world. Diabetes mellitus is one of humanity's oldest disorders. It was first recorded over 3000 years ago in an Egyptian manuscript [2]. Diabetes is caused by a lack of insulin secretion, pancreatic cell damage, or insulin resistance due to a lack of insulin use. The continued rise in the number of diabetic patients worldwide,

Which is anticipated to reach 366 million in 2030 in the older population (>65 years), may be due to an inclination to unhealthy lifestyles [3]. Nephropathy, neuropathy, cardiovascular and renal problems, retinopathy, and food-related diseases are among the many consequences linked with DM [4,5]. Type 1 diabetes mellitus (T_1DM) and Type 2 Diabetes Mellitus (T_2DM) have been classified for decades based on the presence (T_1DM) or lack (T_2DM) of autoantibodies against pancreatic islet-cell antigens and age at diagnosis [6]. T_1DM is an autoimmune disease that affects pancreatic cells, causing insulin production to be reduced or impaired [7]. T_2DM, also termed as non-insulin dependent diabetes mellitus, is the most prevalent type of diabetes mellitus, characterized by hyperglycaemia, insulin resistance, and insulin insufficiency [8]. Prevalence of diabetes in pregnancy has been rising in lockstep with the global obesity pandemic. Not only is the prevalence of type 1 and type 2 diabetes rising among women of reproductive age, but also the reported rates of Gestational Diabetes Mellitus (GDM) are skyrocketing [9]. GDM affects roughly 5% of pregnancies however the percentage varies significantly depending on the demographic parameters of the community [10].

LITERATURE REVIEW

Adipokines (both pro-inflammatory and anti-inflammatory) secreted by adipose tissue are essential regulators of metabolic homeostasis [11]. The metabolism community has shown a lot of interest in adiponectin over the last 20 years since its discovery, and a lot of effort has gone into dissecting the molecular mechanisms of its action [12]. Adiponectin is a type of adipokine that is well known for its anti-diabetic, anti-inflammatory, anti-atherogenic, and cardio protective effects [13]. Adiponectin is a 244 amino acid protein hormone that circulates in high concentrations (5-30 μg/mL) in the blood and accounts for 0.01 percent of total serum proteins. Adiponectin is generated as a 28–30 kDa monomer that is assembled into homooligomers with different molecular weights [14]. Adiponectin is found in the liver, heart, pancreatic cells, kidney, and maybe muscle cells, among other tissues. Adiponectin inhibits genes involved in glucose synthesis, thus suppressing hepatic gluconeogenesis. Adiponectin enhances insulin sensitivity and so improves whole-body energy homeostasis by acting locally in critical metabolic regions. By regulating cell death, decreasing inflammation, and boosting cell survival, adiponectin provides substantial protection against a variety of pathogenic events in diverse cells [12].

The protein adiponectin is encoded by the APM_1/ADIPOQ gene, which has three exons and two introns and is found on chromosome 3q27 [15] which have been linked to a susceptibility locus for metabolic syndrome, diabetes mellitus and cardiovascular disease. As a result, APM_1/*ADIPOQ* is a candidate gene for metabolic syndrome and diabetes study [16]. The rs2241766, rs266729 and rs1501299 are essential loci in the *ADIPOQ* gene. The polymorphism rs2241766 is found in exon 2 of the gene, and it may affect the shearing or stability of precursor mRNA, as well as the protein level. The rs1501299 is found in the *ADIPOQ* gene's second intron, and its polymorphism may alter the function of the neighbouring exon, while rs266729 is found in the promoter. *ADIPOQ* polymorphisms rs17366743, rs10937273, rs17300539, rs182052, rs822396, rs266729, rs17846866, rs822393 and rs3774261 have also been linked to DM [17]. Although a number of SNPs have been identified to be involved in the pathogenesis of DM, this study, however, aimed to sort out the prime SNPs involved in the development of all three forms of diabetes namely T_1DM, T_2DM and GDM.

Association of adiponectin gene polymorphisms in Diabetes Mellitus (DM)

Obesity, insulin resistance, and diabetes all have low plasma adiponectin levels, according to population-based human studies. Individuals with low adiponectin levels had a 9.3-fold higher chance of developing DM than patients with high adiponectin levels, according to a follow-up research [18]. These findings suggest that adiponectin plays a key role in the pathophysiology of DM and that low adiponectin levels are a predictor of insulin resistance and DM. Quite a lot of cross-sectional and genetic studies conducted worldwide suggest the association of polymorphisms in adiponectin gene (*ADIPOQ*) with the pathogenesis of different types of diabetes including type 1, type 2 and gestational diabetes in pregnant women. According to the literatures, a number of ADIPOQ SNPs such as rs2241766, rs1501299, rs17300539 and rs266729 have been shown to be linked to T_1DM

[17, 19]. T_2DM, the predominant form of the disease, is also evidenced to be inclined to a number of including rs1501299, rs2241766, rs266729, rs17366743, rs17300539, rs182052, rs822396, rs17846866, rs3774261, rs10937273 and rs822393 [17, 20]. Moreover, experimental studies imply that rs2241766 and rs266729 SNPs are comprehensively allied to GDM [17,21]. On the basis of these background studies, our observation suggests that three SNPs rs1501299, rs2241766 and rs266729 in adiponectin gene are extensively associated with the pathogenesis of diabetes across the formats. While all three SNPs are significantly linked to DM, two common SNPs rs2241766 and rs266729 are linked to all forms of diabetes, whereas rs1501299 is associated with T_1DM and T_2DM but not with GDM.

Role of ADIPOQ rs2241766 single nucleotide polymorphisms in Diabetes Mellitus (DM)

T_1DM is substantially associated with *ADIPOQ* rs2241766 (+45 G 15 G (T/G)) among Swedish Caucasians [22]. This SNP creates a block of haplotypes that can be found all over the world, and the SNP was found to be significantly linked with T_1DM in both single marker and haplotype analysis. A number of studies have identified a link between rs2241766 and 45 T/G and T_2DM [23]. Polymorphism of the adiponectin gene at position 45 has been linked to an increased incidence of T_2DM in the Japanese population. As a result, people with the genotype G/T or G/G at position 45 have a much higher risk of T_2DM [24].

Both genotypes may predispose to low adiponectin concentrations of the TNF-α and SNP 45 G allele of the adiponectin gene, thereby favouring the development of impaired glucose tolerance or T_2DM in Spanish individuals [25]. T_2DM prevalence is closely associated with the adiponectin rs2241766 (SNP 45 T>G) polymorphism in the South Indian population [26] and Singaporean Chinese adults [27]. In the Iraqi population, the rs2241766 SNP (SNP 45 T/G) of the adiponectin gene is a risk factor for the development of T_2DM [28]. Individuals with impaired glucose tolerance who have the G-allele of SNP >45 are more likely to develop T_2DM [29]. In Asians and whites, however, a recent meta-analysis found no significant links between the SNPs+45 T>G (rs2241766) with T_2DM. One possibility is that distinct populations may have been exposed to a wide range of environmental influences during their existence. Furthermore, differences in lifestyle as well as study sample size may have contributed to this disparity. Low, et al. [30] reported that a significant association was found between rs2241766 and 45 T/G and GDM, In Iranian GDM population the rs2241766 (+45 T/G) polymorphism of the adiponectin gene has been linked to circulating adiponectin levels [31].

Malaysian gestational diabetes patients with the TG/GG genotype in adiponectin gene polymorphism rs2241766 (SNP45) exhibited lower plasma adiponectin levels than other groups, showing that adiponectin SNP rs2241766 has a role in circulating plasma adiponectin levels and subsequent risk of GDM [30]. In patients with GDM, the genotype GT/GG and G-allele of SNP rs2241766 (+45 T>G) in the adiponectin gene were more prevalent than in non-GDM patients [31]. The adiponectin SNP rs2241766 may be linked to the epidemic of GDM in women in the Nantong area of China. Pregnant women with the adiponectin SNP rs2241766 genotype TG+GG have lower plasma adiponectin levels and are more likely to suffer microsomal and neonatal hypoglycaemia. Reduced plasma adiponectin levels and the worst pregnancy outcomes could be linked to the adiponectin gene allele +45 G [32]. Patients with GDM who have the rs2241766 G allele or TG/GG genotype have a significantly higher proportion of adiponectin than healthy people who have the T allele or TT genotype [33]. During the first trimester, gestational diabetes patients have somewhat lower plasma adiponectin levels than healthy people.

Role of ADIPOQ rs266729 single nucleotide polymorphisms in Diabetes Mellitus (DM)

The adiponectin promoter polymorphism rs266729 (-11377 C/G) has been linked to Diabetic Nephropathy (DN) in female T_1DM patients [34]. However, the study found no evidence of a genetic link between *ADIPOQ* gene variants and DN in male T_1DM patients. The trend of decreasing creatinine and cystatin levels in DN patients with the GG genotype relative to TT and TG carriers was a critical element in both

male and female patients [35]. According to evidence, genetic variation in the promoter region of this gene may play a role in the risk of DN, in part *via* affecting *ADIPOQ* plasma levels. Furthermore, investigations have shown that the 11377 C>G polymorphism can change the sequence of one of four SP_1 binding sites in the *ADIPOQ* promoter region, lowering *ADIPOQ* promoter transcription activity [36].

The polymorphism of the adiponectin promoter rs266729 (–11377 C>G) is also linked to T_2DM [37]. The G allele of adiponectin-11377 has been linked to a greater risk of T_2DM in the Chinese population; hence the G allele is being regarded as a potential SNP for T_2DM [37,38]. At this position, the G allele contributes to the development of T_2DM. T_2DM is more common in those who have the G allele than in people who don't [37]. In French Caucasians, two SNPs in the promoter region of the adiponectin gene, rs17300539 (SNP-11391) and rs266729 (SNP-11377), were found to be strongly linked to the development of hypoadiponectinemia and T_2DM [39]. In population-based case–control studies, significantly elevated risks for dominant model and G versus C allele of 11377 C>G (rs266729) were observed this could be due to the ethnicity of the study populations, which were mostly white other causes could be different sample size [40]. Beltcheva, et al. [41] reported that the polymorphism of the adiponectin promoter rs266729 (–11377 C>G) is linked to GDM.

In pregnant and non-pregnant women's adipocytes, the sequence changed by rs266729 could play a different role. As a result, it's plausible that the G allele, which many people have to lower *ADIPOQ* expression in non-pregnant people, makes the promoter less susceptible to inhibition when combined with gestation [41]. The *ADIPOQ* rs266729 gene polymorphism and GDM had a statistically significant connection [42]. Among women with GDM, the G allele (genotypes GG and CG) was shown to be more prevalent. AG allele in rs266729 (–11377 C>G) is an independent risk factor for GDM, according to a multivariate logistic regression analysis that took into account age, pregnancy BMI, previous pregnancies, and the gene polymorphism *ADIPOQ* rs266729. Variation of ADIPOQ rs266729 may raise the risk of GDM in Asian and European countries, according to a meta-analysis of SNPs in the adiponectin gene [43].

Role of ADIPOQ rs1501299 single nucleotide polymorphisms in Diabetes Mellitus (DM)

The rs1501299 (+276 G/T) adiponectin gene polymorphism in the ACDC gene is linked to T_1DM in Swedish Caucasians, but not to nephropathy in T_1DM [22]. While comparing to a healthy individual, the relative risk of the prevalence of SNP +276 G/T for T_1DM patients is found higher. The adiponectin gene's rs1501299 (SNP+276) polymorphism is linked to insulin resistance and T_2DM etiology [44]. In a Japanese population, +276 G>T (rs1501299) was shown to be strongly linked to T_2DM susceptibility [24]. However, this is not the case in French or Swedish. In Chinese populations, 276 GG is linked to a higher risk of T_2DM [45].

In Asians and whites however a recent meta-analysis found no significant links between the +276 G>T (rs1501299) and T_2DM. When compared to those with the T/T genotype, those with the G/G genotype at position 276 had lower plasma adiponectin levels, a higher insulin resistance index, and a higher chance of developing T_2DM [24]. In various ethnic groups, the rs1501299 in the adiponectin gene has been linked to insulin resistance and susceptibility to T_2DM [23, 39,46]. In German and American Caucasians, the exon 2 variant rs1501299, alone or in combination with rs2241766 as a haplotype, has been associated to obesity and insulin resistance [23,46,47]. Individuals with impaired glucose tolerance who had the T-allele of SNP rs1501299 are also more likely to develop T_2DM.

CONCLUSION

Adiponectin is a fat-derived hormone that has attracted a lot of research in recent years because of its many protective benefits against insulin resistance/diabetes and atherosclerosis. It's been examined extensively in both human and animal models. Reduced adiponectin levels in humans are thought to play a key role in the development of diabetes, obesity, and cardiovascular disease. The importance of adiponectin as a physiological regulator of insulin sensitivity, glucose, and lipid metabolism, as well as cardiovascular homeostasis has been reliably proven in human and rodent model. Polymorphisms in the adiponectin gene were found to be associated with all types of diabetes,

including T_1DM, T_2DM, and GDM. A significant number of SNPs in the adiponectin gene, such as rs2241766, rs266729, rs1501299, rs17366743, rs17300539, rs182052, rs822396, rs17846866, rs10937273, rs3774261 and rs822393, have been linked to the etiology of DM. All three types of diabetes have been linked to the two most common SNPs, rs2241766 and rs266729. On the other hand, rs1501299 is linked to T_1 DM and T_2 DM but not with GDM. However, the occurrence of a given SNP can differ amongst populations, and it may even be absent in a group of people with DM. The genetics, environmental variables, and patients' lifestyles may all play a role in this difference. Thus, the existence of a number of SNPs in the adiponectin gene, in addition to other known causes, could be regarded a risk factor for developing DM among patients worldwide. Because obesity and related pathologies impede endogenous adiponectin production a viable therapeutic approach is to use pharmacological or dietary interventions to restore adipose tissue's ability to secrete adiponectin. This unique concept has the potential to be a fresh and revolutionary therapeutic approach for the treatment of metabolic diseases in the future.

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