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Review article

Adiponectin gene polymorphisms associated with diabetes mellitus: A descriptive review

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ABSTRACT

Diabetes is currently a growing concern of the age. Prevention and treatment of diabetes is a global health priority. Adiponectin is an adipocyte derived protein hormone that enhances insulin sensitivity and ameliorates diabetes by enhancing fatty acid oxidation and glucose uptake in skeletal muscle and reducing glucose production in the liver. Low serum adiponectin concentrations are associated with diabetes, central obesity, insulin resistance and metabolic syndrome. Adiponectin gene is located on chromosome 3q27, where a locus of susceptibility to diabetes was mapped. Several cross-sectional studies showed that single nucleotide polymorphisms (SNPs) in adiponectin gene (ADIPOQ) were associated with diabetes. SNPs in ADIPOQ help in assessing the association of common variants with levels of adiponectin and the risk of diabetes. Two common SNPs, rs2241766 and rs1501299, have been linked significantly to type 1 diabetes mellitus which endow the world with a block of haplotypes. Experimental evidences also suggest that rs1501299, rs2241766, rs266729, rs17366743, rs17300539, rs182052, rs822396, rs17846866, rs3774261 and rs822393 are significantly associated with type 2 diabetes mellitus which is the predominant form of the disease. In addition, rs2241766 and rs266729 are extensively associated with gestational diabetes, a condition that develops in women during pregnancy. Therefore not a particular single mutation but a number of SNPs in adiponectin gene could be a risk factor for developing diabetes among the individuals worldwide. This study firmly suggests that adiponectin plays a crucial role in the pathogenesis of type 1, type 2 and gestational diabetes mellitus.

1. Introduction

Diabetes mellitus, also known as simply diabetes, is the most prevalent disease in Westernized, developed countries, and the prevalence of this disease increases with age, accounting for 8.4% of all deaths worldwide [1]. Diabetes is a well-recognized multifactorial endocrine metabolic disorder characterized by hyperglycemia (high blood sugar levels over a prolonged period) triggered by insulin secretion deficiencies, insulin action or both [2]. The chronic hyperglycemia of diabetes is associated with dysfunction, long-term damage and failure of different organs, particularly the kidneys, heart, blood vessels, nerves and eyes. The development of diabetes involves various pathogenic processes including autoimmune destruction of the pancreatic β-cells with subsequent insulin insufficiency which causes insulin resistance [3]. The reason for the carbohydrate, fat and protein metabolism disorders in diabetes is insulin deficient activity on target tissues. Insulin deficient action results from insufficient insulin secretion and/or diminished tissue response [4]. The great majority of diabetes cases fall into two broad categories of etiopathogenetics. Type 1 diabetes (T1D), falls in one category, is caused due to an absolute deficiency in insulin secretion from pancreatic beta cells. Genetic marker tests and serological evidences of an autoimmune pathological process in pancreatic islets can often be utilized for identification of individuals with increased risk of developing T1D [5]. The more prevalent form of diabetes is type 2 diabetes mellitus (T2DM), which falls in the second category and is caused by a combination of insulin resistance and an inadequate compensatory insulin secretory response [6]. Consequently, a degree of hyperglycemia occurs that might cause pathological and functional changes in different target tissues but without clinical symptoms and the condition may persist for a long time before T2DM is detected. There are other specific types of diabetes, such as exocrine pancreatic diseases, endocrinopathies, diabetes induced by drugs or chemicals, infection, uncommon forms of immune-mediated diabetes, other genetic syndromes, such as Down syndrome chromosomal abnormalities, Klinefelter syndrome, and sometimes diabetes-related Turner syndrome. Depending on the severity

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of the underlying disease, the degree of hyperglycemia can change over time [7].

Current research has shown that adipose tissue is not only an inert lipid storage depot, but also an essential endocrine organ that plays a key role in integrating endocrine, metabolic and inflammatory signals to regulate energy homeostasis. Different bioactive protein collectively called adipocytokines or adipokines, have been shown to secrete from the adipocyte into the circulation. Among the numerous adipocytokines, adiponectin - the most abundant circulating protein synthesized only in adipose tissue which acts as a hormone with anti-inflammatory, anti-diabetic and insulin-sensitizing properties, is known to play an important role in various metabolic processes including glucose control and catabolism of fatty acids [8]. A decrease in plasma adiponectin level is strongly correlated with the pathogenesis of type 2 diabetes mellitus (T2DM) and obesity [9, 10]. Animal and human metabolic studies suggest several mechanisms by which adiponectin may decrease the risk of T2DM including suppression of hepatic gluconeogenesis, stimulation of fatty acid oxidation in the liver, stimulation of fatty acid oxidation and uptake of glucose in the skeletal muscle, and stimulation of insulin secretion [11]. Therefore, adiponectin seems to be a major modulator of insulin action and its levels are reduced in diabetes, which in this condition may lead to the peripheral insulin resistance [12]. The adiponectin, a 30kDa protein, is encoded by the gene APM1/ADIPOQ consisting of three exons and two introns located on chromosome 3q27, where a locus of diabetes susceptibility was mapped [13]. Until now, 19 common polymorphisms of 14 known candidate genes have been analyzed around the world for their contribution to the prevalence and incidence of glucose intolerance [14]. While there is strong evidence that several polymorphisms are responsible for plasma adiponectin variation, the precise mechanisms underlying the association of these genetic variants in adiponectin with circulating adiponectin levels and metabolic traits remain unclear and have yet to be recognized. Single nucleotide polymorphisms (SNPs) of the adiponectin gene have been shown to be correlated with BMI, insulin sensitivity and type 2 diabetes [15]. SNPs rs266729 and rs17300539 have recently been studied extensively in the promoter of the ADIPOQ gene for type 2 diabetes [12]. Missense mutations in adiponectin have been identified in subjects with type 2 diabetes and hypoadiponectinemia, and some of these mutations have been shown to inhibit multimerisation and secretion of adiponectin, consistent with the causative role in diabetes [16]. Numerous work on the genetic polymorphism associated with diabetes are also being carried out. This study aims at defining the distribution of adiponectin gene polymorphism and also improving the level of understanding of the relationship of adiponectin gene polymorphism with diabetes mellitus. Perhaps, this is the first study that describes all the SNPs in adiponectin gene which are significantly associated with different forms of diabetes. This study would be of highly interested for the researchers in this area.

2. Adiponectin as a key mediator in ameliorating diabetes

Adiponectin (also known as AdipoQ, apM1 or Acrp30) is a tissue-specific protein of 247 amino acids that shares significant similarity with collagen VIII and X and complement protein C1q. The reduction of this protein plays a key role in obesity-related diseases, including diabetes and cardiovascular diseases [7]. Previous genome-wide linkage scans identified the chromosome 3q27 as a locus for diabetes susceptibility where the adiponectin gene is located. The adiponectin gene promoter region comprises strand sequences, 5′ untranslated region (5′UTR) and important sequence motifs in intron 1 [13]. The carrying of at least two of them, the sterol regulatory binding protein (SREBP) and the CCAAT/enhancer binding protein (C/EBP) appears to be necessary for the promoter's basal transcription activity [17]. The adiponectin occurs in plasma in oligomeric complexes, consisting of trimers (low molecular weight), hexamers (medium molecular weight), and large multimers of 12–18 subunits [high molecular weight (HMW)] [18]. The HMW isoform binds to its receptors more strongly and triggers AMP-activated protein kinase, one of the major enzymes controlling adiponectin's metabolic effects [19]. According to studies, the HMW form of adiponectin, which mediates insulin sensitivity in peripheral tissues, is the most physiologically active form in terms of glucose homeostasis [20, 21]. Only a few epidemiological research has looked into the link between HMW adiponectin and the risk of type 2 diabetes. Insulin resistance and type 2 diabetes have been linked to mutations in the adiponectin gene that induce defective multimerization and lower plasma HMW adiponectin levels, demonstrating that changes in plasma HMW adiponectin levels may be more important than changes in plasma total adiponectin levels in predicting insulin resistance [22]. Indeed, a recent study found that the ratio of HMW adiponectin plasma levels to total adiponectin levels (HMWR) is much more effective for monitoring insulin sensitivity improvement in type 2 diabetes patients responding to thiazolidinediones [23]. Oral glucose tolerance tests have also showed that the HMWR value is more significantly inversely linked with 2-hour glucose levels than total adiponectin [24]. The levels of HMW adiponectin significantly decreased in community-dwelling Japanese women 5-year follow-up period which might lead to an increased risk of cardiovascular diseases among them [25]. Females have higher levels of HMW adiponectin in both proportion and absolute numbers, however males show higher levels of trimers or hexamers [18].

According to the HapMap database (https://hapmap.ncbi.nlm), there are more than 100 SNPs that map and form 2 major haplotype blocks inside the locus of adiponectins. These polymorphisms, including uncommon variants with minor allele frequency (MAF) < 5 percent, are represented by 21 tagging SNPs (linkage with $r2 > 0.8$) [15]. Based on the NCBI database (https://www.ncbi.nlm), there are 29 SNPs in the coding region of adiponectin where 20 are missense mutations. Different SNPs were reported in ADIPOQ to be associated with adiponectin levels and/or diabetes but with inconsistent findings [26].

2.1. Mechanism of adiponectin action in insulin sensitivity

Since its discovery, adiponectin has received great attention from the scientific community. An enormous number of studies has explained its role as insulin sensitizer and the beneficial effects of adiponectin under diabetic conditions [27]. Over the years, a large body of evidence has supported a pleiotropical role of the hormone in various tissues, in which it influences varied physiological aspects in both healthy and diseased conditions. Adiponectin is known to exert a number of cellular and metabolic effects mainly through the binding of two adiponectin receptor isoforms, adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2), each having seven putative transmembrane domains (Figure 1). Adiponectin receptor isoforms have distinct patterns of distribution in different tissues where AdipoR1 predominantly expresses in the skeletal muscle, while AdipoR2 expresses exclusively in the liver [27]. Globular adiponectin (gAd) was shown to bind AdipoR1 more avidly than full-length adiponectin (fAd) in skeletal muscle cells and suppression of AdipoR1 expression with siRNA reduced the high binding affinity of gAd to the receptors. By contrast, a reduced expression of AdipoR2 caused a significant decrease in the binding of fAd, while it manifested a modest decrease in the binding of gAd [28, 29]. These observations suggest that AdipoR1 is a high-affinity receptor for gAd and a low-affinity receptor for fAd, while AdioR2 is an intermediate-affinity receptor for both fAd and gAd. As AdipoR1 and AdipoR2 are predominantly expressed respectively in the skeletal muscle and liver, this correlated the fact that gAd exerts its insulin-mimetic, insulin-sensitizing and anti-diabetic effects more effectively than fAd in the skeletal muscle and vice versa [30]. Impairment of adiponectin function in the skeletal muscle of obese T2D patients could contribute to insulin resistance development [31]. On the other hand, AdipoR2 is an intermediate-affinity receptor for both globular and full-length adiponectin, which appears to be mainly responsible for mediating the effects of full-length adiponectin in the liver. Adiponectin infusion reduces the

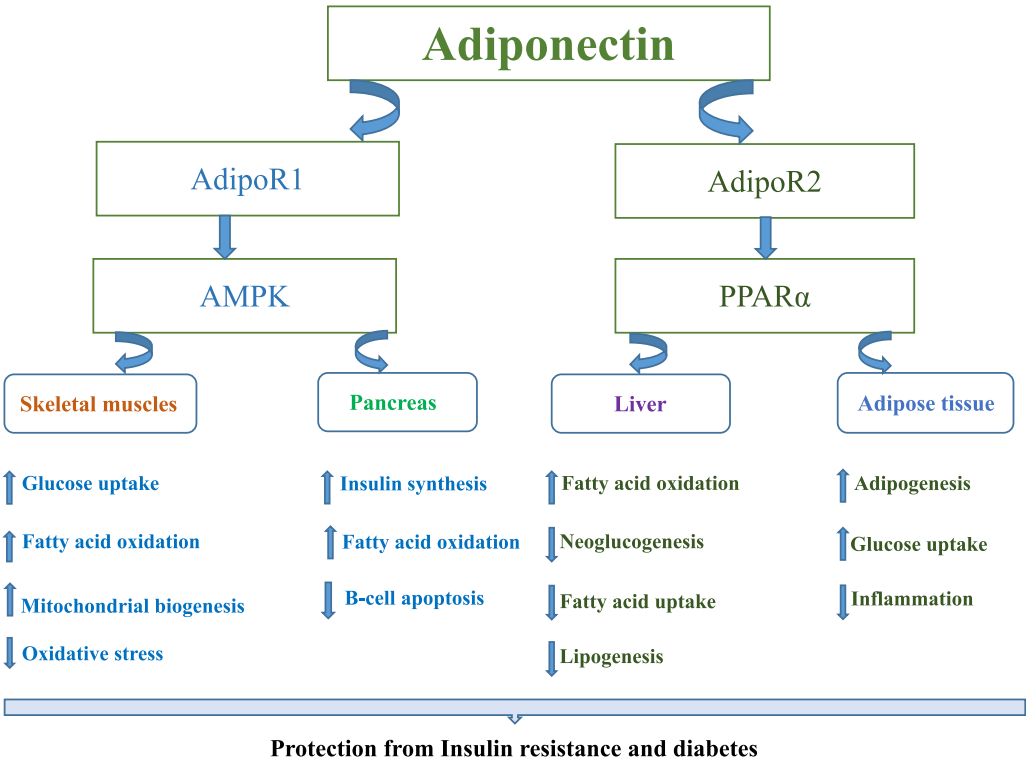

Figure 1. Mechanism of adiponectin actions in prevention of insulin resistance and diabetes. Adiponectin actions are mediated by its interaction with adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2). AdipoR1 is tightly associated with the activation of AMP-activated protein kinase (AMPK) pathway, while AdipoR2 appears to be linked to activation of peroxisome proliferator-activated receptor alpha (PPARα) pathway. AdipoR1 and AdipoR2 are expressed predominantly in skeletal muscle and liver respectively. However, both receptors express in other major organs as well. Adiponectin exerts its metabolic effects on the skeletal muscle mainly by activating the AdipoR1-AMPK signalling pathway. It boosts insulin sensitivity by stimulating glucose uptake and fatty acid oxidation, and also stimulates the expression of target genes leading to an increase in mitochondrial biogenesis while markedly reduces oxidative stress. In the pancreas, it stimulates glucose-induced insulin secretion through activation of fatty-acid oxidation and prevention of beta cell apoptosis. In case of liver, adiponectin induces fatty acid oxidation while reduces glucose production, fat formation and fatty acid uptake through activation of AdipoR2-PPARα signalling pathway; thereby exerting an insulin sensitizing effect on this organ. In adipose tissue, it exerts insulin sensitizing property by its anti-inflammatory action combined to a rise in glucose uptake and also speeds up the adipogenesis process.

expression of hepatic gluconeogenic enzymes, inhibits the production of glucose and enhances the insulin's hepatic effect [32].

2.2. Role of adiponectin in insulin sensitivity

Adiponectin is an endogenous insulin sensitizer secreted by adipose tissue. In 2001, three separate groups first described the insulin-sensitizing effect of adiponectin [8]. Adiponectin decreases the triglyceride content in tissues and improves insulin signaling. In the skeletal muscle, adiponectin up regulates the expression of molecules involved in the transport of fatty acids (e.g. CD36), fatty acid combustion (e.g. acylcoenzyme, oxidase) and energy dissipation (e.g. uncoupling protein 2), which subsequently result in decreased triglyceride (TG) content of the tissue in the skeletal muscle [27, 33]. An increase in TG content of the tissue has been demonstrated to interfere with the activation of insulin-stimulated phosphatidyl-inositol (PI) 3-kinase and subsequent glucose transporter 4 translocation, and glucose uptake by the cells, finally leading to insulin resistance. Therefore, a decrease in TG content in the muscle can be attributed to improved insulin signaling. Moreover, over-expression of adiponectin in ob/ob mice and treatment of obese diabetic or lipoatrophic mice with adiponectin resulted in increased expression of PPAR-α target genes such as CD36, acyl-coenzyme A oxidase and uncoupling protein 2, which suggest that adiponectin might activate PPAR-α [34]. In accordance with this observation, adiponectin was shown to increase the levels of PPAR-α expression *in vivo* [34]. Collectively, it could be suggested that adiponectin increases fatty acid oxidation and energy consumption, apparently via PPAR-α activation at least in part, leading to a decrease in the content of TG in the skeletal muscles and liver and consequently execute a coordinated increase in insulin sensitivity *in vivo* [35]. Adiponectin is believed to trigger insulin sensitivity by enhancing glucose utilization and fatty acid oxidation through the phosphorylation and activation of AMP-activated protein kinase (AMPK) in both skeletal muscle and liver tissue [36, 37]. Both gAd and fAd activate AMPK in skeletal muscle, whereas the kinase was activated only with fAd in the liver. Blocking of AMPK activation led to inhibition of glucose uptake and fatty-acid oxidation indicating that adiponectin mediates these effects through activation of AMPK [36].

2.3. Role of adiponectin in oxidative stress and inflammation

Oxidative stress is suggested to play a crucial role in the pathogenesis of diabetic complications. Oxidative stress results from the enhanced production of reactive oxygen species (ROS) and/or reduced ability of ROS scavenging ability which ultimately causes tissue damage [38]. In fact, the pathogenesis of several deadly diseases including diabetic, neural and vascular disorders is significantly influenced by oxidative stress. In a recent study, adiponectin gene polymorphism AdipoQ (rs1501299) and oxidative stress were found to be significantly associated with cardiovascular disease [39]. Moreover, rs266729 and rs2241766 polymorphisms in adiponectin gene significantly enhanced the risk of cardiovascular disease [40]. The rs2241766 polymorphism was also reported to be significantly associated with an increased risk of coronary artery disease in type 2 diabetic patients [41]. An increased risk of hypertension was also found to be associated with rs266729 [42].

Adiponectin is a key mediator in reducing oxidative stress by activating signaling cascades such as AMPK–eNOS and the cAMP–PKA module [43]. Ouedraogo et al. [44] demonstrated that increased nitric oxide bioavailability reduced overexpression of cell adhesion molecules

and the leukocyte–endothelium interaction. Adiponectin downstream signal was found to be involved in repairing vasculature in muscle with ischemia injury through a calreticulin/CD91–PI3K–Akt–COX2 signaling pathway. In podocytes, adiponectin decreases oxidative stress and albumin permeability. Overexpression of adiponectin ameliorates renal interstitial fibrosis and enhances podocyte and kidney function recovery after caspase 8-mediated podocyte ablation [45]. Adiponectin's anti-inflammatory properties may potentially be exerted directly on macrophages. Adiponectin alters macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2, according to both gain-of-function and loss-of-function tests [46]. Surprisingly, the M1 macrophage population reduction mediated by adiponectin partially overlaps with those reduced by adiponectin's autocrine action on adipocyte secretion [47]. According to Kadowaki and colleagues [48], full-length adiponectin, but not globular adiponectin, causes macrophages to produce IL-6. With recombinant adiponectin therapy, IL-6 is transcriptionally increased due to IκBα inhibition and recruitment of NFκB to its promoter. As a result, plasma IL-6 is able to boost hepatic IRS-2 expression and insulin signaling potency [49]. The involvement of adiponectin and its receptors in macrophages deserves additional exploration, especially given Luo and colleagues' [50] demonstration of very evident benefits from adiponectin overexpression in macrophages.

3. Adiponectin gene polymorphisms in different types of diabetes mellitus

Genetic studies on human adiponectin gene strongly suggest the role of adiponectin as a determinant of susceptibility to insulin resistance as well as its involvement in the pathogenesis of diabetes. This study found a number of SNPs in adiponectin gene directly associated with different types of diabetes including type 1, type 2 and gestational diabetes in pregnant women (Table 1).

3.1. Adiponectin gene polymorphisms involved in type 1 diabetes mellitus

Type 1 diabetes (T1D) is an autoimmune disease in which the insulin-producing beta cells within the pancreas are destroyed and thereby resulted in very little or no production of insulin. In T1D, diabetic nephropathy is associated with insulin resistance and low-grade inflammation. Serum adiponectin levels are higher in type 1 diabetic patients with nephropathy [5]. However, these are essential in that it increases anti-inflammatory functions, insulin sensitivity and soothes vascular damage. Some research implications suggest that concentrations of serum adiponectin are elevated in patients with T1D as well as in T1D complicated patients [51]. Patients with T1D and microvascular complications may have higher serum adiponectin levels than patients without complications [52]. However, nature of the ACDC gene's hereditary dominance is still uncertain [32].

Adiponectin gene ACDC spans 16 kb and comprises of three exons, in which SNP rs2241766 (+45G15G (T/G)) and rs1501299 (+276G/T) were significantly linked with T1D among Swedish Caucasians [5]. Such two SNPs impart a block of haplotypes over the world. Both single marker and haplotype analysis showed that these two SNPs were associated with T1D in a significant way. In Danish T1DM patients, the promoter polymorphism rs17300539 (-11391 A/G) in the ADIPOQ gene is related to diabetic nephropathy (DN) [53]. Another study on the same population also found that the ADIPOQ promoter polymorphism rs266729 (-11377 C/G) is related to DN in female T1DM patients. However, this study does not observe the genetic association of ADIPOQ gene polymorphisms with DN in male T1DM patients. In both male and female patients, the trend of propensity for decaying creatinine and cystatin levels in DN patients with the GG genotype relative to TT and TG carriers was a key factor in this study [54]. Another case has been found where ADIPOQ gene promoter region has four SP1 binding sites. SNP rs266729 changes the sequence at one of the SP1 binding sites in the promoter region of adiponectin. This polymorphism, together with another promoter SNP rs17300539, can confer susceptibility among the GoKinD population to the development of DN in T1D patients [53].

3.2. Adiponectin gene polymorphisms involved in type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a multicausal disease that develops slowly and in gradual order. T2DM and its complications place huge burdens on both patients and the health care system. It develops over long (years) time periods. This is where insulin resistance begins during this period of time when blood insulin levels are increasingly become ineffective. Because of this insulin resistance, the pancreas responds by producing more and more insulin in an attempt to achieve some degree of blood glucose management [6]. In contrast to T1D, plasma adiponectin level was found lower in patients with T2DM.

Table 1. List of some common SNPs of adiponectin related to diabetes mellitus.

Type of Diabetes	Associated SNP	Race/ethnicity	Study design	Reference
T1DM	rs2241766 (+45G15G (T/G))	Swedish Caucasians	Hospital based	[55]
	rs1501299 (+276G/T)	Swedish Caucasians	Hospital based	[56]
	rs17300539 (-11391 A/G)	Danish	University based	[57]
	rs266729 (-11377 C/G)	Iranian	University based	[58]
T2DM	rs2241766 (SNP+45)	Japanese, Chinese	Hospital based	[59]
	rs1501299 (SNP+276)	Iranian	Hospital based	[58]
	rs266729 (SNP–11377C > G)	Chinese	Hospital based	[60]
	rs17366743 (SNP111)	French Caucasians	Hospital based	[61]
	rs10937273	Taiwanese	Hospital based	[62]
	rs17300539 (SNP-11391)	Chinese	Hospital and population based	[63]
	rs182052 (SNP-10066)	Chinese	Hospital based	[64]
	rs822396 (SNP-3971)	South Indian	Population Based	[65]
	rs266729 (SNP–11365C > G)	Indian, Thai Taiwanese, Japanese	Hospital based	[66]
	rs17846866 (SNP+10211)	North Indian	Clinic based	[67]
	rs822393 (SNP-4522)	Chinese, South Indian	Hospital based	[68]
	rs3774261 (SNP+712)	South Indian	Population based	[65]
GDM	rs266729 (-11377C > G)	Bulgarian	Clinic based	[16]
	rs2241766 (SNP +45T > G)	Iranian	University based	[69]
	rs2241766 (SNP 45/SNP45TG)	Malaysian	Clinic based	[70]

Development of insulin resistance and T2DM was found to be positively correlated with a lower level of serum adiponectin [10]. Several SNPs in adiponectin gene have been reported to be associated with the development of T2DM.

3.2.1. rs2241766 (SNP 45/SNP+45/SNP +45TG/SNP 45T > G/SNP +45G15G (T/G))

In Japanese population, polymorphism of the adiponectin gene at position 45 was reported as a higher risk factor for developing T2DM. Thus subjects with the genotype G/T or G/G at position 45 are at significantly increased risk for T2DM [71]. Spanish individuals with both genotypes may jointly predispose to low adiponectin concentrations of the TNF-α and SNP 45 G allele of the adiponectin gene, potentially facilitating the production of impaired glucose tolerance or T2DM [72]. Adiponectin rs2241766 (SNP45T > G) polymorphism is closely linked to T2DM prevalence in South Indian population [6] and Singaporean Chinese adults [73]. The rs2241766 SNP (SNP45 T/G) of adiponectin gene is a risk factor for the development of T2DM in Iraqi population [74]. Impaired glucose tolerance subjects with the G-allele of SNP >45 is at higher risk to convert in T2DM [75].

3.2.2. rs1501299 (SNP 276/SNP 276G > T/SNP +276(G/T))

The rs1501299 polymorphism of the adiponectin gene at position 276 (SNP276) is associated with insulin resistance and pathogenesis of T2DM. SNP rs1501299 in intron 2 (G/T) showed fascinating phenotypes with respect to levels of plasma adiponectin, insulin resistance and susceptibility to T2DM in Japanese population. Subjects with the G/G genotype at position 276 had lower levels of plasma adiponectin, higher insulin resistance index and increased risk of developing T2DM compared to those with the T/T genotype [71]. Similar findings for the rs1501299 in adiponectin gene with insulin resistance and susceptibility to T2DM have been observed in other ethnic groups [76, 77, 78]. The rs1501299 alone or together with rs2241766 (as a haplotype) in exon 2 was found to be linked with obesity and insulin resistance in German and American Caucasians [77, 78]. Impaired glucose tolerance subjects with the T-allele of SNP rs1501299 are also at higher risk to convert in T2DM. Although regular exercise is suggested for the betterment of the patients with T2DM, however, the adiponectin gene polymorphism rs1501299 is not correlated with the magnitude of the impact of twice-weekly exercise training on total and high molecular weight levels of adiponectin [79].

3.2.3. rs266729 (SNP -11377/SNP -11377C > G)

Adipocytes have diverse endocrine, paracrine and autocrine functions. Adiponectin is a cytokine which is specifically secreted through adipose tissue. In the Chinese population, adiponectin -11377 G allele was reported to be associated with increased risk of developing T2DM, and thus the G allele is considered as a candidate SNP that may confer T2DM [80]. G allele contributes to the development of T2DM at this site. Persons bearing the G allele can develop T2DM more easily than those without the G allele [81]. Two SNPs, rs17300539 (SNP-11391) and rs266729 (SNP-11377), in the promoter region of the adiponectin gene were radically associated with the development of hypoadiponectinemia and T2DM in French Caucasians [76].

3.2.4. rs17366743 (SNP 111)

Functional polymorphisms in APM1, which modulate the fat-secreted adiponectin hormone levels, are correlated with levels of adiponectin and contribute to the genetic risk of T2DM. In French Caucasians, two unusual mutations - G90S and Y111H (rs17366743) - in the exon 3 of the adiponectin gene were associated with the genetic risk of T2DM [76]. His111 allele carriers were at higher risk of developing type 2 diabetes and tended to have a lower serum adiponectin in white populations.

3.2.5. rs10937273

Adiponectin gene polymorphisms in the rs10937273 (intronic region) position are statistically associated with early T2DM development in Taiwanese population [62]. These types of polymorphisms within adiponectin gene have been linked to affect the adiponectin plasma levels that are inversely associated with obesity and hyperinsulinemia.

3.2.6. rs17300539 (SNP -11391/SNP -11391 G/A)

The GG genotype −11391 G/A (rs17300539) is associated with higher concentrations of insulin and triacylglyceride and also with a higher risk of clinical manifestations of insulin resistance and metabolic syndrome [82]. According to Frederic Fumeron [12], the risk of developing hyperglycemia was significantly associated with two SNPs, rs17300539 and rs2241766, for normoglycemic subjects at baseline.

3.2.7. rs182052 (SNP -10066)

In African Americans, the rs182052 SNP in the adiponectin gene is associated with T2DM [83]. Adiponectin gene SNP rs182052 is also substantially correlated with T2DM in Chinese population [84].

3.2.8. rs822396 (SNP-3971/SNP -3971 A/G)

In the South Indian population, the association of the polymorphism rs822396 (SNP -3971 A/G) with T2DM is mediated by obesity where the association with T2DM is lost after BMI adjustment [65]. The association between the rs822396 SNP and obesity was an unprecedented finding from this study. The variant −3971 A/G lending risk to T2DM has an impact on the function of the adiponectin gene as these intronic variations can result in alternative spliced mRNAs and gradually affect the permanence or processing of the mRNA.

3.2.9. rs266729 (SNP-11365)

The promoter polymorphism rs266729 (-11365 C/G) in the adiponectin gene is linked to plasma adiponectin levels [85]. In the South Indian population, rs266729 is substantially correlated with T2DM [65]. Some researchers have placed the importance of locating adiponectin gene polymorphism in the promoter region and showed that the promoter function is performed by either of these gene variants with higher BMI measures and lower rates of adiponectin among Japanese female population [86].

3.2.10. rs17846866 (SNP +10211/SNP +10211 T/G)

The adiponectin gene variant rs17846866 (SNP +10211) was related to altered levels of circulatory adiponectin. The TT genotype may be the main contributor to raising the levels of circulatory adiponectin in T2DM. In North Indians, however, the G allele could increase the risk of developing T2DM. Among Asian Indians, polymorphism rs17846866 (+10211 T/G) in the first intron of the adiponectin gene is associated with T2DM, obesity and hypoadiponectinemia [87].

3.2.11. rs3774261 (SNP +712/SNP +712 G/A)

The variants of the adiponectin gene and the haplotype contribute to the development of type 2 diabetes, obesity, and hypoadiponectinemia in the population of South India. The genetic association of rs3774261 (SNP +712 G/A) in South Indian population is significantly linked to T2DM [65]. But it has been observed that the AA genotype of +712 G/A (rs3774261) SNP conferred approximately 0.65 times less risk to developing T2DM. However, few studies found a significant association with this type of variant in relation to T2DM and obesity among the Korean population [88].

3.2.12. rs822393 (SNP-4522/SNP -4522 C/T)

The rs822393 SNP is significantly associated with insulin sensitivity in white subjects [89]. This observation found an association between circulating adiponectin and insulin and also showed that adiponectin (administered intravenously or through genetic up-regulation) increases insulin sensitivity in rodents and emphasized the ideas that changes in adiponectin levels or activity result in insulin resistance and T2DM. The rs822393 (SNP -4522 C/T) polymorphism is substantially correlated with T2DM in the South Indian population, which in those populations

conferred two folds of higher risk to develop T2DM. On the other hand, this SNP was also associated with hypoadiponectinemia in the White population [65].

3.3. Adiponectin gene polymorphisms involved in gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is known to be an allergy of glucose with initiation or first decision during pregnancy. The prevalence of obesity and diabetes globally raises the incidence of GDM in recent years and adverse health effects for women and children associated with GDM in both the short and long term. Since nearly two-thirds of American women now begin pregnancy either overweight or obese, the strong link between maternal obesity during pregnancy and metabolic syndrome in childhood is of particular concern [90]. GDM has become more common in recent decades, and its prevalence is linked to the prevalence of type 2 diabetes in the same population (ranging from 1.7 to 11.6 percent) [91]. GDM and T2DM share common pathophysiological atmospheres including dysfunction of beta cells and resistance to insulin. Women with GDM also have an increased risk of developing type 2 diabetes later in life [92]. Low circulating levels of adiponectin in pregnant women with obesity or gestational diabetes mellitus are associated with large babies with increased fat mass. They are more likely to experience perinatal complications and later develop metabolic syndrome [93]. A number of SNPs in adiponectin gene are discussed here which are known to be associated with GDM in women.

3.3.1. rs2241766 (SNP +45T > G/SNP45/SNP 45TG)

A number of SNPs in adiponectin gene are discussed here which are known to be associated with GDM in women. The rs2241766 (+45T/G) polymorphism of the adiponectin gene has been found to be associated with circulating adiponectin levels in Iranian GDM populations [69]. When compared to other groups, Malaysian gestational diabetic patients with the TG/GG genotype in adiponectin rs2241766 (SNP45) had lower plasma adiponectin levels, suggesting a role for adiponectin SNP rs2241766 in circulating plasma adiponectin levels and subsequent risk of GDM [70]. The TG/GG genotype of rs2241766 in the Iranian population was a significant risk factor of GDM. The genotype GT/GG and G-allele of SNP rs2241766 (+45T > G) in the adiponectin gene were more common in patients with GDM than in non-GDM patients [69]. The adiponectin SNP rs2241766 could be associated with the outbreak of GDM in Nantong area women in China. Pregnant women with adiponectin SNP rs2241766 genotype TG + GG have lower concentrations of plasma adiponectin and greater occurrences of macrosomia and neonatal hypoglycemia. The adiponectin gene allele +45G could be combined with reduced plasma adiponectin levels and the worst outcomes of pregnancy [94]. GDM patients carrying rs2241766 G allele or TG/GG genotype have a substantially higher proportion of adiponectin than normal subjects carrying the T allele or TT genotype [95]. Gestational diabetic patients during the early trimester have slightly lower levels of plasma adiponectin than normal individuals do. Adiponectin SNP rs2241766 was found to be combined with GDM in a significant way. Malaysian gestational diabetic patients with TG/GG genotype in adiponectin SNP rs2241766 had lower plasma adiponectin levels compared to other groups, indicating the role of adiponectin SNP rs2241766 in the circulation of plasma adiponectin levels and subsequent GDM risk [70].

3.3.2. rs266729 (SNP -11377C > G)

The polymorphism of the adiponectin promoter rs266729 is linked to gestational diabetes. The sequence altered by rs266729 could have a different role in pregnant and non-pregnant women's adipocytes. One could therefore assume that the G allele, which was obtained by many to reduce the expression of ADIPOQ in non-pregnant individuals, could make the promoter less responsive to the inhibition combined with gestation [16]. There was a statistically significant correlation between the ADIPOQ rs266729 gene polymorphism and GDM [96]. An increase in the presence of the G allele (genotypes GG and CG) was observed among women with GDM. Multivariate logistic regression analysis, taking into account age, pregnancy BMI, past pregnancies and gene polymorphism ADIPOQ rs266729, revealed that a G allele is an independent risk factor for GDM. Meta-analysis of the SNPs in adiponectin gene indicates that variation of ADIPOQ rs266729 may increase the risk of GDM in Asian and European countries [97].

4. Burden due to polymorphism in adiponectin gene

The role of the adipocyte-derived peptide adiponectin that has just been described is still poorly understood. Nonetheless, it is believed to play pivotal role including glucose and lipid metabolism control, cardiovascular function and insulin resistance improvement, and to have anti-inflammatory, anti-diabetic and anti-atherogenic properties [98]. In some cross-sectional studies, SNPs of the adiponectin gene were found to be linked to body mass index (BMI), insulin sensitivity and type 2 diabetes, but these associations were not found in each and every case. Polymorphisms of the adiponectin gene are involved in type 1, type 2 and gestational diabetes mellitus [5, 6, 52]. Beside diabetes, SNPs in adiponectin gene are also associated with increased risk of several diseases including colorectal cancer [99], metabolic related nonalcoholic fatty liver disease (NAFLD) [100], coronary artery disease [101], coronary heart disease [102], knee osteoarthritis [103], diabetic peripheral neuropathy [104], atherosclerosis [105], late-onset of Alzheimer's Disease [106], obesity in adults [107], polycystic ovary syndrome [108], diabetic kidney disease [109], rheumatoid arthritis [110].

5. Remarks and future directions

Current research in human and animal models of obesity, diabetes and atherosclerosis has suggested the possible role of adiponectin and adiponectin receptors in these metabolic diseases [32]. As the production of endogenous adiponectin is impaired as an effect of obesity and related pathologies, use of pharmacological or dietary interventions to restore the ability of adipose tissue to secrete adiponectin is a practical therapeutic approach. Transplantation of genetically modified mesenchymal stem cells harboring adiponectin gene, as a mean of genetic and cellular combined therapy, would release adiponectin in to systematic circulation for compliment of the endogenous adiponectin [111]. Moreover, a native, functional and deleterious SNP free form of the adiponectin gene could be obtained through gene editing by using CRISPR (clustered regularly interspaced short palindromic repeats)-Cas9 (CRISPR associated protein 9) technique. These unique strategies are likely to serve as potential novel and innovative therapeutic approaches for the treatment of metabolic diseases in the near future, although more research is needed to understand the underlying mechanisms controlling adiponectin levels, including dietary and lifestyle interventions, which can target adiponectin as a therapeutic intervention in metabolic syndrome [112]. In addition to established risk factors, future studies should evaluate whether adiponectin is useful for the prediction of type 2 diabetes using statistical techniques appropriate for prognostic analyses. Although a number of SNPs have been reported to be associated with the development of diabetes, it is yet to understand the precise role of each of the SNPs or their assorted contribution in the pathogenesis as well as their mechanistic role in the occurrence of the disease among various populations.

Genetics has been widely promoted as a method to unravel the pathogenesis of chronic types of diabetes, but the complexity of the issue has defied simple solutions. Lots of essential adiponectin questions await further analysis. It is important to elucidate the mechanisms by which adiponectin is synthesized and secreted, as do the signals that reduce adiponectin expression in adipocytes and the importance of its complex interplay with adiponectin receptors and other regulatory proteins such as AMPK, PPAR-α and their downstream signaling molecules. Similarly, the role and regulation of the oligomerisation of adiponectin must be

defined [113]. The answers to these and other intriguing questions will without doubt provide further insight into the metabolic roles of this adipocyte hormone and the association of the adiponectin variants in pathogenesis of various diseases particularly diabetes.

6. Limitations of the study

Adiponectin is an important protein hormone that possesses anti-inflammatory, anti-diabetic and insulin-sensitizing properties, and consequently takes part in various metabolic processes including glucose and fatty acid metabolism [8]. Low level of plasma adiponectin is associated with insulin resistance, diabetes especially T2DM and obesity [9, 10]. However, adiponectin singly can't exert its biological functions; instead the protein hormone acts through binding with its receptors, AdipoR1 and AdipoR2 [30]. Therefore, not only the genetics of adiponectin, but also the genetics of AdipoR1 and AdipoR2 are important in the pathogenesis of diabetes and other metabolic diseases associated with adiponectin. This study only focuses on the genetic polymorphisms of adiponectin gene, but not its receptors, associated with the pathogenesis of diabetes. Moreover, this descriptive review followed only the findings of selected articles and didn't apply any statistical method to check the reliability and validity of the quoted studies. It is clear that more researches are needed regarding diabetes in terms adiponectin genetic variability. Further studies are suggested to conduct that will apply meta-analysis with other appropriate statistical models to check the reliability and validity of the related literatures which will be collected from all over the world using the systematic review in order to gain a clear view of the contribution of adiponectin gene polymorphisms in the pathogenesis of diabetes.

7. Conclusion

Adiponectin has attracted tremendous scientific interest in recent years due to its various beneficial effects, and has been extensively studied in both human and animal models. Although these epidemiological studies cannot establish causality, the consistency of the association across diverse populations, the dose-response relationship and the supporting findings in mechanistic studies indicate that adiponectin is a promising target for the reduction of the risk of diabetes [114]. Although diabetes is a multifactorial disease, polymorphisms in adiponectin gene showed significant correlation with all forms of the disease i.e. type 1, type 2 and gestational diabetes mellitus. An increasing number of SNPs e.g. rs2241766, rs1501299, rs266729, rs17366743, rs17300539, rs182052, rs822396, rs17846866, rs3774261 and rs822393 in adiponectin gene have been found to be significantly associated with the pathogenesis of diabetes. Among these mutational variants, SNP rs2241766 is significantly linked to all three forms of the disease. However, the presence of a particular SNP may vary among different populations and even it may not be present in a certain set of individuals suffering from diabetes. This variation may depend on the genetics, environmental factors and life style of the patients. Thus not a single mutation but the presence of a number of SNPs in adiponectin gene could be considered as the risk factor, along with other known causes, for developing diabetes among the patients globally. There is still more work to be done to turn knowledge of this gene into benefits for patients. The greatest benefit will probably come from new and better therapies derived from a better understanding of the disease's etiology.

Declarations

Author contribution statement

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