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Low adiponectin levels and *ADIPOQ* +276G>T single nucleotide polymorphism are associated with type 2 diabetes mellitus in the Sudanese population: case-control study

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Abstract

Aim: Type 2 diabetes mellitus is a polygenic disorder influenced by multiple genes and environmental factors. Polymorphisms in the adiponectin gene are linked to insulin resistance, serum adiponectin levels, and type 2 diabetes mellitus. This study investigated the association between adiponectin levels, the *ADIPOQ* +276G>T single nucleotide polymorphism (SNP), and type 2 diabetes in the Sudanese population.

Methods: A case-control study involved 202 individuals with type 2 diabetes and 100 controls, after providing written informed consent. Blood samples were collected after overnight fasting for measurements of fasting blood glucose (FBG), and hemoglobin A1C (HbA1c) levels were measured using enzymatic methods. Participants' body mass index (BMI) was calculated based on weight and height measurements. Adiponectin levels were measured by sandwich ELISA. Adiponectin gene +276G>T SNP was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: Patients with type 2 diabetes had significantly lower adiponectin levels compared to controls ($P < 0.001$). The distribution of the +276G>T SNP genotypes and the T allele was significantly different between diabetic patients and controls, with TT, GT, and T allele more frequent in diabetics ($P < 0.05$). Adiponectin levels varied by genotype, with GG carriers having higher levels than GT and TT carriers, who exhibited significantly lower levels ($P < 0.001$).

Conclusions: The +276G>T SNP in the adiponectin gene is associated with reduced adiponectin levels in individuals with type 2 diabetes in the Sudanese population.

Keywords

type 2 diabetes mellitus, adiponectin, single nucleotide polymorphism

Introduction

Diabetes mellitus (DM) is a complex metabolic disorder characterized by sustained hyperglycemia resulting from either pancreatic β-cell dysfunction or insulin resistance [1]. It ranks among the top ten causes of mortality worldwide and is strongly associated with an increased risk of death, disability, and reduced quality of life due to severe complications such as nephropathy, retinopathy, neuropathy, and arteriosclerosis [2, 3].

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, accounting for approximately 90% of all cases and affecting nearly 14% of the global population [4, 5]. T2DM is a polygenic disorder resulting from the interaction of multiple genetic variants with environmental and lifestyle factors [6–8]. Genetic predispositions play a significant role in the disease's pathogenesis across diverse populations. Individuals with genetic susceptibility have a higher risk of developing T2DM compared to those without such predispositions [9]. Genetic studies of T2DM have primarily used genome-wide association studies (GWAS), candidate gene studies (comparing single nucleotide polymorphisms [SNPs] between patients with diabetes and controls in selected genes coding for proteins involved in the pathogenesis of T2DM), and linkage analysis. Numerous genes, loci, and genetic polymorphisms have been identified as being associated with susceptibility to T2DM and associated complications [10, 11]. One of these genes is adiponectin [12].

Adiponectin, a protein hormone produced by adipocytes, influences insulin sensitivity and inflammation, both of which are closely involved in the development of T2DM [13]. Adiponectin is one of the most abundant adipokines, consisting of 244 amino acids and is a collagen-like protein secreted exclusively by the adipocyte [14]. Adiponectin is a collagen-like protein composed of 244 amino acids and is exclusively secreted by adipocytes [13]. It plays a crucial role in the metabolism of fats and carbohydrates. It exerts anti-inflammatory and insulin-sensitizing effects through several mechanisms, including promoting hepatic fatty acid oxidation, inhibiting hepatic gluconeogenesis, enhancing skeletal muscle glucose uptake, and stimulating insulin secretion [13, 15, 16]. Based on human genome-wide scans, the gene encoding adiponectin, *ADIPOQ*, located at chromosome 3q27, was identified as the T2DM genetic locus in various populations [13]. The levels of adiponectin are also regulated by genetic variations in the *ADIPOQ* gene. It is estimated that between 30 and 70 percent of variations in the normal levels of adiponectin in the blood can be attributed to genetic factors [13, 17]. Various SNPs in the adiponectin gene have been reported in association with insulin resistance, serum adiponectin levels, and T2DM [12, 18]. The alteration of base guanine (G) by thymine (T) at the adiponectin gene rs1501299 (+276G>T) results in three different genotypic distributions (GG, GT, and TT). This SNP occurs when the normal wild-type allele of the gene G is replaced by the T allele (GT or TT). This was associated with low adiponectin levels and T2DM, and this association was subsequently found in different ethnic groups, such as Japanese, Korean, Indian, Malay, Egyptian, and Afro-American. Although inconsistent, many studies have also found a relationship between this genetic variation and adiponectin levels in different study groups [18–20]. The aim of this study was to investigate the association between adiponectin levels and the SNP *ADIPOQ* +276G>T with T2DM in the Sudanese population.

Materials and methods

Design, setting, and study population

This case-control study was conducted at the Jabir Abu Eliz Diabetic Center in Khartoum, Sudan. 202 T2DM patients between the ages of 40 and 59 years participated in this study. A subject was considered to have diabetes if their fasting blood glucose (FBG) was 7 mmol/L (126 mg/dL) or higher, or if the 2-hour glucose result during a 75 g oral glucose tolerance test (OGTT) was 11.1 mmol/L (200 mg/dL) or higher [21]. All T2DM patients who visited the Jabir Abu Eliz Diabetic Center between February 2014 and 2017 met the inclusion criteria for the diabetic subjects. The subsequent exclusion criteria were implemented: individuals with T1DM and women with gestational diabetes were excluded; participants were also eliminated if they were seriously ill, had any other chronic diseases, had a history of steroid use, or refused to participate in this study. A total of 100 healthy nondiabetic volunteers from the Khartoum State

community were selected as a control group matched by age. Each control participant exhibited normal FBG levels (FBG < 110 mg/dL) and hemoglobin A1C (HbA1c) values and was not a family member of the patients. The sample size was calculated using the single proportion formula $n = Z^2pq/d^2$ [22]. Where n is the sample size, Z is the standard normal deviation, usually set at 1.96, which corresponds to the level of the 95% confidence interval (CI); p is the estimated proportion in the target population estimated to have a particular characteristic; q (complementary proportion) is simply the remainder of the population, and equal to $1 - p$, if $p = 0.5$, then $q = 0.5$, and d is the degree of accuracy desired, set at 0.07. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethical Research Committee of the Board of Medical and Health Sciences, University of Khartoum, Khartoum State, Sudan (December 4, 2013). Informed written consent was obtained from all participants. Data were collected from all participants using a questionnaire, which included information on age, sex, duration of the disease, and details related to diagnosis and follow-up. A clinical examination was performed.

Laboratory analyses

Blood samples were collected from all subjects in the morning after a 6–8 h overnight fast. FBG was measured using enzymatic colorimetric methods; the percentage of HbA1c was measured using boronate-affinity binding enzymatic methods using NycoCard Reader II (Axis-Shield, Norway) [23]. Serum levels of adiponectin were measured using a quantitative Human Adiponectin Immunoassay kit (Biorbyt, Cambridge, UK) (Catalogue number: orb54803). The assay was performed according to the manufacturer's instructions [24].

Venous blood samples from each subject were collected in EDTA-coated tubes and subsequently used for DNA extraction using the phenol-chloroform DNA extraction method [25]. Isolated DNA was used to determine adipokine gene SNPs. The adiponectin gene SNP (*ADIPOQ* +276 G/T or rs1501299) was genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). *ADIPOQ* +276 G/T was amplified using previously published primers and methods [26]. SNP +276 was chosen based on its established associations with adiponectin levels and its potential relevance to T2DM according to previous studies [16, 18, 20]. The following primers were used for SNP +276 genotyping:

Forward primer 5'- TCTCTCCATGGCTGACAGTG-3' and reverse primer 5'-AGATGCAGCAAAGCCAAAGT-3' [26].

PCR reactions were conducted in a total volume of 25 µL reaction mixture, containing 5 µL Maxime PCR Premix kit (for 20 µL rxn, 96 tubes), StarTaqTM DNA (Catalog 25165, iNtRON Biotechnology, Inc., South Korea). The components of the kit were i-StarTaqTM DNA polymerase (2.5 U), dNTPs (2.5 mM each), reaction buffer (1×), and gel loading buffer (1×). A total of 2 µL of template DNA, 1 µL of forward primer, 1 µL of reverse primer, and 16 µL of distilled water (sterile nuclease-free water) were added to Maxime PCR Premix tubes. PCR-amplified products were analysed by electrophoresis in 2% agarose gel in 1 PCR reaction. Reactions were conducted in a total volume of 25 µL reaction mixture, containing 5 µL Master Mix of Maxime PCR Premix kit (iNtRON Biotechnology, Seongnam, Korea). The components of the kit were i-StarTaqTM DNA polymerase (2.5 U), dNTPs (2.5 mM each), reaction buffer (1×), and gel loading buffer (1×). Two µL of template DNA, 1 µL of forward primer, 1 µL of reverse primer, and 16 µL of distilled water (sterile nuclease-free water) were added to Maxime PCR Premix tubes. The TBE (Tris-boric acid-EDTA) was stained with 3 µL ethidium bromide at 95 V for 40 minutes, and bands were visualised under UV light using an Agel documentation system (Biometra BioDocAnalyze series compact set model 034-050 digital gel documentation system, Analytik Jena in Germany). The amplified 468-bp PCR product was digested with Bacillus stearothermophilus (BsmI) restriction endonuclease (Catalog R0134S, New England Biolabs, United States) at 37°C. Incubate overnight. For detection of the 276G>T SNP, the presence of a single 468-bp band indicates wild homozygosity for the G allele (G/G); the presence of two fragments, 320 and 148 bp, indicates homozygosity for the T allele (T/T); and the presence of three fragments, 468, 320, and 148 bp, indicates heterozygosity for the G & T alleles (G/T) [25].

Statistical analyses

SPSS Statistics (V.20.0; IBM Corp., USA, 2010) was used for analysis of data. The distribution of variables in the study groups was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were compared with an independent samples *t*-test and expressed as mean ± standard deviation (SD), while non-normally distributed variables were compared with the Mann-Whitney *U* test and expressed as medians (min–max). Categorical variables were described using numbers and percentages. Genotype and allele frequencies were expressed as percentages. The statistical difference in genotype distribution and allele frequencies in both case and control subjects was analyzed using the Chi-square test, odds ratios (ORs) with 95% CIs, and *P* values < 0.05 were considered statistically significant. Correlations of genotypes with serum adiponectin levels were evaluated by using ANOVA One way analysis of variance test.

Results

This study comprised 202 patients with T2DM and 100 healthy control participants. The patients with T2DM group comprised 107 males (53%) and 95 females (47%), whereas the control group included 66 males (66%) and 34 females (34%). The mean ages of the patient and control groups were similar, at 51.9 and 51.02 years, respectively, with no significant difference observed ($P > 0.05$). Patients with T2DM had a significantly higher body mass index (BMI, mean ± SD: 25.80 ± 3.65) compared to the control group (mean ± SD: 24.60 ± 4.81) ($P < 0.05$). FBG levels were significantly elevated in patients with T2DM (mean ± SD: 180.81 ± 47.15) compared to the control group (mean ± SD: 100.06 ± 13.18) ($P < 0.001$). HbA1c levels were significantly elevated in patients with T2DM (mean ± SD: 8.77 ± 2.36) compared to the control group (mean ± SD: 5.09 ± 0.67) ($P < 0.001$). Additionally, patients with type 2 diabetes exhibited notably lower serum adiponectin levels (mean ± SD: 16.98 ± 10.41) than the control group (mean ± SD: 21.95 ± 13.85) ($P < 0.001$). No significant difference in adiponectin levels was observed between male (mean ± SD: 17.90 ± 10.70) and female (mean ± SD: 16.20 ± 10.17) patients with T2DM ($P > 0.05$). Among patients with type 2 diabetes, serum adiponectin levels were significantly lower in obese, overweight, and normal-weight individuals compared to the control group ($P < 0.05$) (Table 1).

Table 1. Adiponectin levels among study subjects according to BMI.

Variable	T2DM patients (*n* = 202) Mean ± SD	Control group (*n* = 100) Mean ± SD	*P*-value
Normal (< 25 kg/m^2)	17.90 ± 14.20	29.00 ± 15.40	0.04
Overweight BMI (25–29 kg/m^2)	17.44 ± 9.40	22.33 ± 16.40	0.04
Obese BMI (≥ 30 kg/m^2)	16.34 ± 9.90	20.54 ± 11.73	0.02

Independent samples *t*-test; data are shown as mean ± standard deviation (SD). *P*-value < 0.05 is considered significant. BMI: body mass index; T2DM: type 2 diabetes mellitus.

The genotype distribution and allele frequencies of +276 G/T and their corresponding ORs were shown in Tables 2 and 3. GT was more common among patients 43.6% than healthy controls 24.0% (OR = 1.82, 95% CI: 1.24–2.70), $\chi^2 = 12.8$, $P < 0.05$. TT genotype distributions among patients were 7.9%, and in the healthy control group were 6% (OR = 1.32, 95% CI: 0.51–3.27), $\chi^2 = 12.8$, $P < 0.05$. GT + TT genotypes were more common among patients 51.5% than in the control group 30.0% (OR = 1.72, 95% CI: 1.24–2.40), $\chi^2 = 12.5$, $P < 0.001$ (Table 2). T allele was more common among patients 29.7% than in the healthy control group 18% (OR =1.70, 95% CI: 1.18–2.24), $\chi^2 = 9.6$, $P < 0.05$ (Table 3).

Table 2. Genotype distribution of SNP +276 G/T among patients with T2DM and the control group.

Genotype	T2DM patients (*n* = 202)	Control group (*n* = 100)	χ^2 test *P*-value	Odds ratio (OR)	95% CI
GG (%)	98 (48.5%)	70 (70.0%)	χ^2 =12.8	0.70	0.24–0.70
GT (%)	88 (43.6%)	24 (24.0%)	*P* = 0.002	1.82	1.24–2.70

Table 2. Genotype distribution of SNP +276 G/T among patients with T2DM and the control group. (*continued*)

Genotype	T2DM patients (*n* = 202)	Control group (*n* = 100)	χ^2 test *P*-value	Odds ratio (OR)	95% CI
TT (%)	16 (7.9%)	6 (6.0%)		1.32	0.51–3.27
GT + TT (%)	104 (51.5%)	30 (30.0%)	χ^2 = 12.5	1.72	1.24–2.40
			P < 0.001		

Data are numbers (*n*) and percentages (%). Chi-square test (χ^2); *P*-value < 0.05 is considered significant. CI: confidence interval; SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

Table 3. Allele frequencies of SNP +276 G/T among patients with T2DM and the control group.

Genotype	T2DM patients (*n* = 202)	Control group (*n* = 100)	χ^2 test *P*-value	Odds ratio (OR)	95% CI
G (%)	284 (70.3%)	164 (82.0%)	χ^2 = 9.6	0.90	0.78–0.94
T (%)	120 (29.7%)	36 (18.0%)	*P* = 0.002	1.70	1.18–2.24

Data are numbers (*n*) and percentages (%). Chi-square test (χ^2); *P*-value < 0.05 is considered significant. CI: confidence interval; SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

Correlations of SNP +276 G/T genotypes with biochemical measurements of study subjects were shown in Table 4. The means of FBG, HbA1c, and BMI, were not significantly different in three genotypes of SNP +276 G/T in T2DM patients and control group ($P > 0.05$), except for the means of BMI in control group GG (24.6 kg/m^2), GT (25.7 kg/m^2), and TT (20.5 kg/m^2) that showed significant differences $P < 0.05$. There was a significant difference between the means of adiponectin levels in three genotypes of SNP +276 G/T in T2DM patients, GG genotype (20.0 ± 11.00), GT (14.4 ± 9.40), and TT (12.7 ± 6.54), P <0.001.

Table 4. Correlations of SNP +276 G/T genotypes with biochemical measurements of study subjects.

Biochemical variables	Genotype	T2DM patients Mean ± SD (*n* = 202)	*P*-value	Control group Mean ± SD (*n* = 100)	*P*-value
FBG	GG	179.7 ± 42.5	0.5	101.4 ± 8.71	0.2
	GT	184.3 ± 52.6		95.8 ± 21.8	
	TT	168.4 ± 42.7		101.0 ± 9.40	
	GT + TT	182 ± 51.30	0.7	97.0 ± 20.0	0.1
HbA1c	GG	8.6 ± 2.40	0.4	5.06 ± 0.80	0.9
	GT	9.0 ± 2.40		5.14 ± 0.44	
	TT	8.5 ± 2.17		5.13 ± 0.64	
	GT + TT	9.0 ± 2.40	0.3	5.14 ± 0.50	0.6
BMI	GG	25.8 ± 3.62	0.9	24.6 ± 3.40	0.009
	GT	25.7 ± 3.70		25.7 ± 4.51	
	TT	25.6 ± 4.04		20.5 ± 3.50	
	GT + TT	25.7 ± 3.70	0.8	25.0 ± 4.80	0.9
Adiponectin	GG	20.0 ± 11.00	< 0.001	21.3 ± 13.40	0.7
	GT	14.4 ± 9.40		22.9 ± 16.50	
	TT	12.7 ± 6.54		25.3 ± 8.16	
	GT + TT	14.0 ± 9.00	< 0.001	23.4 ± 15.8	0.5

One-way analysis of variance (ANOVA) test. *P*-value < 0.05 is considered significant. BMI: body mass index; FBG: fasting blood glucose; HbA1c: hemoglobin A1C; SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

Discussion

Several genetic variants in the *ADIPOQ* gene have been identified, and their associations with T2DM were studied. The +276G>T SNP of the adiponectin gene is thought to be a significant recognized genetic risk factor for the development of insulin resistance and T2DM [27, 28]. The aim of the present study was to provide supportive evidence about the possible association between these SNPs, low adiponectin levels, and T2DM in the Sudanese population. In this study, patients with T2DM had considerably lower levels of

adiponectin than the control group. These results are consistent with previous studies showing that adiponectin is involved in the metabolism of glucose, and that patients with T2DM often have low adiponectin levels [29–31]. Patients with T2DM tend to exhibit reduced adiponectin levels, which are associated with impaired glucose and lipid metabolism, thereby worsening insulin resistance [32]. Adiponectin has been shown to enhance the functional capacity of pancreatic beta cells and improve insulin sensitivity by promoting hepatic insulin signaling through the upregulation of insulin receptor substrate 2 (IRS-2) expression [33]. The glucose-lowering effects of adiponectin may also result from several mechanisms, including the inhibition of hepatic gluconeogenesis, the stimulation of fatty acid oxidation in the liver, and the promotion of glucose uptake and fatty acid oxidation in skeletal muscle tissue [34].

In this study, significant differences were found in the genotype distribution of *ADIPOQ* +276G/T among patients with T2DM and the control group. The +276G>T SNP of heterozygous GT and homozygous TT genotypes were significantly more frequent in T2DM patients compared to the control group, similar to the findings in a study of Taiwan (China) patients with T2DM [35]. Patients with T2DM had a higher distribution of the TT + GT genotype, which was consistent with that found in some of the previous studies [36–39]. In the current study, the T allele was found to be significantly higher among patients compared with healthy controls. These findings agree with the data presented by Zacharova et al. [39].

In the current study, adiponectin levels were estimated in various genotypes of SNP +276 of the *ADIPOQ* gene; it was observed that the adiponectin levels of TT and GT genotype carriers were significantly lower than those of GG genotype in T2DM patients compared with the control group. This finding is supported by several other studies [36, 40]. This suggests that the SNP +276 G/T of the *ADIPOQ* polymorphism had a significant role in the development of insulin resistance, and this can be due to changes in adiponectin expression and ultimately reduction in adiponectin levels and its biological effects.

Despite the fact that the adiponectin +276G>T SNP has been examined in several populations, the Sudanese population, which has a distinct genetic history and way of life, has received very little attention. This study is novel since it is the first to look into the relationship between type 2 diabetes, the adiponectin +276G>T SNP, and low adiponectin levels in the Sudanese population. By addressing a major knowledge gap and offering insightful information to this population, the findings may enhance healthcare outcomes. Additionally, this study may help improve risk assessment, preventative measures, and focused therapies for these people.

This study faced a number of inevitable limitations. First, while the results are encouraging, the sample size is relatively small; more research with a larger participant group is required to validate these findings. Second, all of the patients in the study came from a single diabetic clinic, which may restrict how broadly the findings may be applied. Third, Sudan lacks money and resources for comprehensive studies, including restricted access to kits and specialized reagents for testing adiponectin levels. Large-scale studies can be problematic since these materials can be expensive and difficult to get and keep in the nation. Other confounding factors and their covariate effects were not considered during the analysis of the association of the +276G>T SNP with adiponectin levels, such as diabetes medications.

Conclusions

In conclusion, this study provided significant evidence that adiponectin is a novel susceptibility gene for T2DM in the Sudanese population; *ADIPOQ* +276G/T polymorphism and its haplotype combinations are associated with insulin resistance, which might be mediated through alterations in adiponectin expression and serum levels, which may have contributed to the pathogenesis of T2DM.

Abbreviations

BMI: body mass index

CI: confidence interval

DM: diabetes mellitus

FBG: fasting blood glucose

G: guanine

HbA1c: hemoglobin A1C

ORs: odds ratios

PCR: polymerase chain reaction

SNPs: single nucleotide polymorphisms

T: thymine

Declarations

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Author contributions

HBE: Conceptualization, Data curation, Methodology, Investigation, Writing—original draft, Formal analysis, Visualization. EMA: Conceptualization, Methodology, Investigation. AM: Writing—review & editing. AOM: Conceptualization, Methodology, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval

This study was approved by the Ethical Research Committee of the Board of Medical and Health Sciences, University of Khartoum, Khartoum State, Sudan (December 4th, 2013), and was carried out in compliance with the Declaration of Helsinki.

Consent to participate

Informed written consent was obtained from all subjects before participating in the study.

Consent to publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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