Original Article

Role of Adiponectin Polymorphism (rs1501299) in Diabetes with Nephropathy and Its Association with Renal Biomarkers

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Abstract

Background: Diabetic nephropathy (DN) is a major cause of end-stage kidney disease, associated with severe complications. Numerous studies have found connections between variations in the *ADIPOQ* gene and both type two diabetes mellitus (DM) and DN. **Objective:** The objective of the present investigation is to evaluate the correlation between the *ADIPOQ* polymorphism (rs1501299) and the exposed to DN in the Iraqi patients. **Materials and Methods:** A case-control study involved 121 subjects divided into three groups: 45 type 2 diabetes (T2DM) patients with nephropathy, 39 T2DM patients without nephropathy, and 37 healthy subjects. Biochemical analysis was carried out on all participants and PCR method was utilized for genotyping the adiponectin polymorphism (rs1501229). **Results:** In the DN group, the genotype models frequencies were 22.2% for genotype (GG), 33.3% for heterozygous genotype (GT), and 44.4% for homozygous (TT), while the DM group had frequencies of 29.7% for GG, 51.3% for GT, and 23% for TT. When comparing the polymorphism between the control group and the DN group, T allele carriers had a high significant risk of DN under the codominant TT model ($P = 0.01$), the dominant GT + TT model ($P = 0.04$), and the recessive model ($P = 0.01$). In the T2DM group, the risk of DN was notably higher among T allele carriers under the recessive model ($P = 0.04$). Additionally, in the codominant model, the rs1501299 polymorphism genotypes were significantly associated with elevated levels of serum fasting blood sugar, HbA1c, urea, creatinine, and estimated glomerular filtration rate in the study participants. **Conclusion:** Our findings demonstrate a substantial association between the polymorphism (rs1501299) and an increased susceptibility to DN among individuals with T2DM in the Iraqi patient population.

Keywords: *ADIPOQ* gene polymorphism, gene mutation, type 2 diabetic nephropathy

Introduction

Diabetes mellitus (DM) is a cluster of metabolic disorders marked by elevated levels of glucose in the blood (known as hyperglycemia), which arise from abnormalities in the secretion of insulin, its action, or both.[1] The persistent elevation of glucose levels in diabetes is linked to the long-term impairment, dysfunction, and deterioration of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[2] Type 2 diabetes (T2DM) is the most prevalent form of diabetes, it is characterized by elevated blood glucose levels, insulin resistance (IR), and a relative deficiency of insulin.[3] DM is a complex disease that gives rise to various disruptions in the body's metabolism. These metabolic disruptions manifest as different types of small-vessel diseases, including diabetic nephropathy (DN), retinopathy, and neuropathy.[4] T2DM is a prevalent, long-lasting, and intricate condition that is, rapidly increasing on a global scale.[5] It is characterized by IR in the peripheral tissues and a deficiency in insulin secretion. Between 1980 and 2008, the number of individuals with T2DM increased more than doubled worldwide. This increase is strongly influenced by genetic factors, and a family history of the disease.[6,7] T2DM is influenced by a combination

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of genetic and environmental factors. Extensive efforts have been made to identify the genes that contribute to the disease, aiming to enhance our understanding of its underlying mechanisms, identify new targets for therapeutic interventions, and determine prognostic and predictive factors.[8]

DN is a prevalent and recurring complication of diabetes that directly leads to end-stage renal disease (ESRD). Roughly 30% to 40% of individuals diagnosed with T2DM may be experience the development of DN.[9,10] DN is a complex disorder that arises from a combination of factors, including elevated levels of glucose, genetic predisposition, and renal damage in susceptible individuals. Consequently, in-depth research the specific genes and genetic variations that contribute to the development of DN is crucial to investigate.[11] The natural history of diabetic kidney disease includes glomerular hyperfiltration, progressive albuminuria, declining glomerular filtration rate (GFR), and ultimately, ESRD.[12] This condition is associated with the progressive decline of kidney function in individuals with DM. Also, there can be significant protein loss in the urine as the damage occurs to the glomeruli, there can be leading to reduced serum albumin levels, generalized body swelling (edema), and the onset of nephrotic syndrome. Similarly, the estimated glomerular filtration rate (eGFR) can steadily decline from a normal level of over 90 mL/min/1.73 m² to less than 15, at which point the patient is diagnosed with ESRD.[13,14]

Adiponectin, a hormone secreted by adipocytes,[15] is classified as an adipokine. It plays a crucial role in controlling insulin function, as well as regulating glucose and lipid metabolism. Additionally, it has beneficial effects in preventing atherosclerosis and reducing inflammation.[16]

The *ADIPOQ* gene codes for a protein called adiponectin, primarily produced in adipose tissues, and it plays a crucial role in the development of obesity and T2DM. Adiponectin, a significant protein secreted by adipocytes in the human bloodstream, acts as a regulator of energy and is involved in maintaining glucose tolerance. The *ADIPOQ* gene is situated on chromosome 3q27, which has been identified as a susceptibility locus for T2DM.[6]

The variation in the *ADIPOQ* gene is associated with metabolic conditions and health disorders such as IR, abdominal obesity, compromised glucose tolerance, abnormal lipid profiles, high blood pressure, and elevated blood sugar levels.[17] Dysregulation in controlling both adiponectin levels and its receptors has been noted in the progression of various conditions, including obesity, IR, chronic kidney disease, type 1 diabetes (T1DM), and T2DM.[18]

The aim of the current study was to assess the association of the *ADIPOQ* polymorphism (rs1501299) with DN susceptibility in Iraqi patients.

Materials and Methods

Ethical issues

Each patient and control provided written informed consent for a genotypic analysis in addition to all other biochemical evaluations. The Kerbala Medical College Ethics Committee of Kerbala University gave its approval to this investigation (October 18, 2023-MEC-71).

Study design

The present research was structured as a case-control study, involving the categorization of participants into three distinct groups: individuals with type 2 DM and nephropathy (DN group), those with T2DM without nephropathy (DM group), and healthy subjects (HC group) serving as the control group. A total of 121 individuals were included in the study based on the prevalence and incidence of the disease as well as confirmed through equation of sample size calculation, comprising 45 DN patients (22 males and 23 females), 39 T2DM patients without nephropathy (19 males and 20 females), and 37 apparently healthy individuals (24 males and 13 females) serving as the control group. Ethical approval for the study was obtained from the Ethical Research Committee at the College of Medicine, University of Kerbala, and the Kerbala Health Directorate. Blood samples were collected from all study participants, both healthy subjects and patients, at Al-Hussein Teaching Hospital and Al-Hujjah Hospital. The study was conducted between December 2019 and February 2020. Participants with an eGFR of less than 60 mL/min/1.73 m² and urinary albumin excretion (UAE) exceeding 300 mg/day were categorized as the DN group, while those with an eGFR greater than 60 mL/min/1.73 m² and UAE less than 30 mg/day were classified as the DM group and the control group.

A 5 mL of venous blood were obtained from all participants using a disposable syringe. The drawn blood was subsequently divided into two portions: The initial portion, comprising 3 mL, was placed into two gel tubes and subjected to centrifugation at 4000 times the force of gravity ($\times g$) to isolate serum. This serum sample was utilized for the automated analysis of various parameters, including blood glucose, urea, creatinine, lipid profile, and other biomarkers. The remaining 2 mL of blood were collected in two Ethylenediaminetetraacetic acid (EDTA) tubes. The first EDTA tube, containing 1 mL of blood, was automatically analyzed for HbA1c, while the second EDTA tube was preserved at −20°C for subsequent Deoxyribonucleic Acid (DNA) extraction using the Geneaid kit. Polymerase chain reaction (PCR) amplification was carried out using allele-specific amplification refractory mutation system PCR (ARMS-PCR), a rapid and straightforward technique employed to identify single nucleotide polymorphisms (SNPs). In this study, ARMS-PCR was specifically employed to detect the *ADIPOQ* polymorphism known as (+276 G/T) (rs1501299). The sequences of the primers are presented in Table 1.

Table 1: The primer sequences for alleles of the *ADIPOQ* polymorphism (rs1501299)

Primers	Sequences of primers (5′ to 3′)
Forward outer primer	GAG CTG TTC TAC TGC TAT TAG CTC TGC
Reverse outer primer	GAA TAT GAA TGT ACT GGG AAT AGG GAT G
Forward inner primer (G allele)	CCT CCT ACA CTG ATA TAA ACT ATA TGA GGG
Reverse inner primer (T allele)	TGT GTC TAG GCC TTA GTT AAT AAT GAA CGA

Table 2: The PCR program protocol for the *ADIPOQ* SNP (rs1501299)

Steps	Temperature (°C)	Time	Cycles
Initial denaturation	95	5 min	1
Denaturation	95	30 s	35
Annealing	61	27 s	
Extension	72	25 s	
Final extension	72	5 min	1

The PCR outcomes were examined through electrophoresis on a 1% agarose gel, and their visualization was facilitated by applying diamond safe stain (Promega, USA). Details of the PCR cycling conditions can be found in Table 2.

Statistical analysis

The data that obtained from all groups were analyzed by SPSS v.20.0 software (Chicago, IL). Demographic and clinical data were showed as mean ± SD. Anthropometric indices and genotype/allele frequencies were compared using the *t* test and Chi-square (χ^2) test. Hardy–Weinberg equilibrium (HWE) was performed by SNP-Analyzer (version 1.1.5 ga) Magna Græcia University ($P > 0.05$) using gene frequencies of the healthy participants. Sanger sequence analysis was done by MEGA software. The statistical significance was considered at $P < 0.05$.

Results

The biochemical characteristics of the patients such as BMI and age did not have a significant difference but the other biochemical parameters had significant difference between the DN and DM groups [Table 3, $P \leq 0.05$]. GFR was very low in the DN group, compared to the DM and control groups, while serum urea and creatinine were very high in the DN group.

Lipid profile is dysregulated in both DM and DN groups was observed, with elevated LDL-C, TC, and TG levels in DM and altered HDL-C in both DM and DN groups.

Genotyping levels of the *ADIPOQ* polymorphism were not compatible with the HWE in the DN groups ($P = 0.04$), which may be due to the small number of samples, while the DM and HC groups were consistent with the HWE ($P = 0.8$ and $P = 0.23$), respectively. The data analysis indicated that the genotype frequencies of the *ADIPOQ* polymorphism (G > T) (rs1501299) for homozygous wild genotype (GG), heterozygous genotype (GT), and homozygous (TT) in the DN group, [Table 4] were 22.2%, 33.3%, and 44.4%, respectively. While in the DM group, the genotype frequencies were 29.7%, 51.3%, and 23%, and in the HC group were 43.2%, 37.8%, and 18.9%, respectively.

In the HC group, compared with the DN group, a higher risk of DN was found among carriers of T allele under codominant TT [observed risk (OR) = 4.5, 95% confidence interval (CI): 1.42−14.7, $P = 0.01$], dominant GT + TT (OR = 2.6, 95% CI: 1.02−6.94, $P = 0.04$), and recessive model (OR = 3.4, 95% CI: 1.2−9.4, $P = 0.01$). While in the DM group, compared with the DN, the risk of DN was significantly higher among carriers of T allele under recessive model (OR = 2.6, 95% CI: 1.03−6.88, $P = 0.04$), as shown in Table 5.

The amplification of the *ADIPOQ* (+276 G/T) showed two bands (476 and 244 bp) for homozygous (GG), and also two bands (476 and 292 bp) for homozygous (TT), while the heterozygous (GT) revealed three bands (476, 292, and 244 bp), as shown in Figure 1. As shown in Figure 2, the sequencing of the amplicon was run to corroborate this discovery, and the findings were consistent with the earlier discovery made by ARMS-PCR.

The data analysis showed that in the DN group, the genotypes harboring the T allele showed higher significant levels of blood glucose, urea, creatinine, and eGFR, compared to the GG genotype ($P < 0.05$). The other parameters in Table 6 did not show any significant differences between GG, GT, and TT genotypes, in the DN group. This illustrates that these parameters are not associated genetically, while in the DM group (without nephropathy), expect blood glucose and HbA1c, no significant difference in other biochemical parameters

Table 3: The clinical and biochemical characteristics of study subjects

Parameters	HC ($N = 37$) mean ± SD	DM ($N = 39$) mean ± SD	DN ($N = 45$) mean ± SD
No. (M/F)	37 (24/13)	39 (19/20)	45 (22/23)
Age (year)	55.4 ± 9.1	55.1 ± 9.2	55.1 ± 9.3
BMI (Kg/m^2)	27.9 ± 3.7	29.6 ± 3.8	27.6 ± 4.2
RBS (Mmol/L)	4.9 ± 0.8	11.1 ± 4.5[a]	14.4 ± 5.7[b,c]
HbA1c (%)	5.3 ± 0.8	9.3 ± 1.7[a]	8.0 ± 1.4[b,c]
Insulin	32.5 ± 8.1	151.9 ± 22.1[a]	173.9 ± 24.2[b]
HOMA-IR	0.6 ± 0.1	3.8 ± 1.2[a]	4.9 ± 1.7[b]
Urea (mg/dL)	32.2 ± 5.2	29.9 ± 12.4	150.4 ± 38.4[b,c]
Creatinine (mg/dL)	0.68 ± 0.1	0.82 ± 0.2	7.8 ± 2.0[b,c]
eGFR (L/min/1.73 m^2)	127.3 ± 39.7	99.4 ± 28.2[a]	6.9 ± 2.7[b,c]
TC (mg/dL)	145.6 ± 22.6	166.1 ± 30.5	143.2 ± 23.5[c]
LDL-C (mg/dL)	83.4 ± 21.2	118.4 ± 34[a]	81.7 ± 17.8[c]
HDL-C (mg/dL)	44.2 ± 2.7	39.1 ± 13.7[a]	39.7 ± 8[b]
TG (mg/dL)	133.1 ± 47	170.8 ± 20.2[a]	119.3 ± 32.1[c]

N: number, M: male, F: female, Y: year, BMI: body mass index, FBS: fasting blood sugar, HbA1c: hemoglobin A1c, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, eGFR: estimated glomerular filtration rate

Data were expressed as mean ± SD. P value < 0.05 is significant, by one way ANOVA test

[a]Significant difference between DM and HC

[b]Between DN and HC

[c]Between DN and DM

Table 4: The results of polymorphic allele frequency for the *ADIPOQ* polymorphism (rs1501299) in the DN, DM, and HC groups

Study groups	Genotype			X	*P* value	Frequency	
	Common Homozygote GG	Heterozygote GT	Recessive Homozygote TT			G	T
DN (N = 45)							
Observed N (%)	10 (22.2%)	15 (33.3%)	20 (44.4%)	4.0	0.04	0.39	0.61
Expected (N)	6.8	21.4	16.8				
T2DM (N = 39)							
Observed N (%)	11 (29.7%)	19 (51.3%)	9 (23%)	0.02	0.88	0.53	0.47
Expected (N)	10.8	19.4	8.8				
HC (N = 37)							
Observed (N) (%)	16 (43.2%)	14 (37.8%)	7 (18.9%)	1.4	0.23	0.62	0.38
Expected (N)	14.3	17.4	5.3				

DN: diabetic nephropathy, DM: diabetes mellitus, HC: healthy control (GG, GT, and TT) alleles, χ^2: chi-square, G: guanine, T: thymine

$P < 0.05$ statistically significant

between the TT and GT genotypes ($P > 0.05$) was found. In the HC group, no significant difference was found in all biochemical parameters between the GT, TT, and GG genotypes ($P > 0.05$).

Discussion

Several genetic variants in the *ADIPOQ* had been identified and their associations with T2DM were studied; however, the finding were inconsistent among different studies. To the best of our knowledge, there are no more studies concerning the role of *ADIPOQ* polymorphisms in the Iraqi T2DM and/or DN patients. Here, in this study shows correlation of the *ADIPOQ* polymorphism (+276 G/T) with T2DM and/or DN in the Iraqi population The results of this study indicated that subjects carrying TT and GT genotypes had a greater chance to develop DN. In addition, the results indicated that there is a significant association between the *ADIPOQ* polymorphism (rs1501299) and the etiology of DN.

The relationship between lipid profile, diabetes, and DN involves a complex interplay of metabolic factors. Dyslipidemia is both a consequence of diabetes and a contributor to the progression of diabetic complications, including nephropathy. Managing lipid levels is an integral part of the comprehensive care of individuals with diabetes to mitigate the risk of cardiovascular events and renal complications.[19]

The baseline characteristics of clinical parameters that is, blood sugar, HbA1c, serum creatinine, serum urea, eGFR, fasting serum insulin, HOMA-IR, and lipid profile were significantly elevated in the DN groups, compared with other groups ($P < 0.05$); DN usually

Table 5: The genotype and allele frequencies of the polymorphism (rs150299) between the DM and DN groups

SNP (rs150299) G > T	DM *N* = 39	DN *N* = 45	OR (95% CI)	*P* value
Codominant				
GG (reference allele)	11	10		
GT	19	15	0.86 (0.2−2.5)	0.8
TT	9	20	2.4 (0.76−7.8)	0.1
Dominant				
GT + TT	28	35	1.3 (0.5−3.7)	0.5
Over dominant				
GG + TT	20	30		
GT	19	15	0.5 (0.2−1.2)	0.1
Recessive				
GT + GG (reference allele)	30	25		
TT	9	20	2.6 (1.03−6.88)	0.04
Additive				
2TT + GT	37	55	1.6 (0.6−4.2)	0.3

SNP: single nucleotide polymorphisms, DM: diabetes mellitus, DN: diabetic nephropathy, OR: observed risk, CI: confidence interval
P value < 0.05 is significant

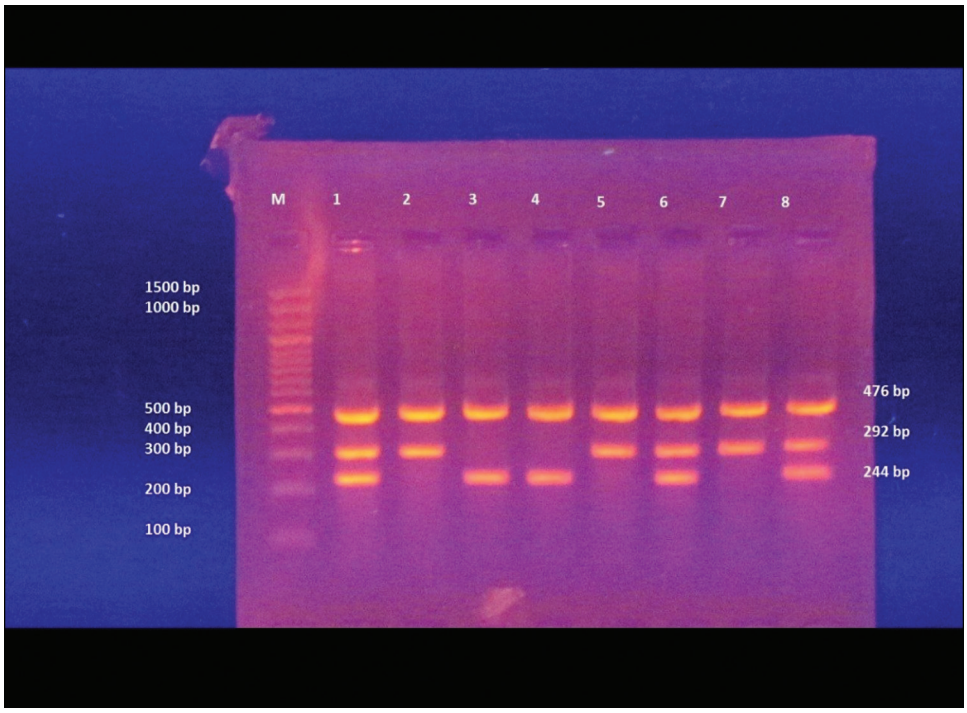

Figure 1: The gene polymorphism products on agarose gel electrophoresis for the adiponectin rs1501299 G\T polymorphism; M, DNA marker, 100 bp, lane 3 and 4 (GG), lane 1, 6, and 8 (GT), and lane 2, 5, and 7 (TT)

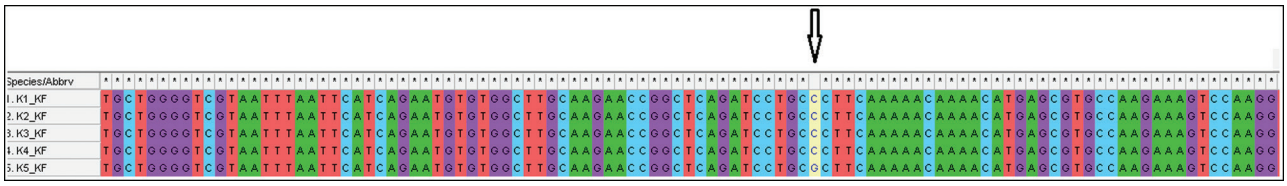

Figure 2: The sequence results of the outer amplicon of PCR

develops in patients with poor glycemic control. The rate of glycemic control is an important predictor of terminal kidney damage.[20,21] Serum creatinine and urea are the established indicators of glomerular filtration rate (GFR). Serum creatinine and urea are the known indicators of GFR. Serum creatinine is a more

Table 6: The biochemical characteristics in the DN group with respect to genotype, in the codominant model ($N = 45$)

Parameters	GG ($N = 10$) Mean ± SD	GT ($N = 15$) Mean ± SD	TT ($N = 20$) Mean ± SD
Age	58.6 ± 10.4	61.1 ± 8.2	57.6 ± 8.3
BMI (Kg/m^2)	25.7 ± 3.6	28.3 ± 4.5	28 ± 4.2
RBS (Mmol/L)	10.7 ± 3.3	14.3 ± 3.4[a]	16.4 ± 4.2[b]
HbA1c (%)	7.1 ± 1.1	8.02 ± 1.7[a]	8.5 ± 1.2[b]
Insulin	166.7 ± 20.1	170 ± 22.7	180.4 ± 14.2[b,c]
HOMA-IR	4.6 ± 0.3	4.6 ± 1.1	5.3 ± 2.6
Urea (mg/dL)	125.6 ± 23.7	151.7 ± 37.8[a]	161.9 ± 40.5[b,c]
Creatinine (mg/dL)	6.4 ± 1.2	8.4 ± 2[a]	8.1 ± 1.9[b]
eGFR (L/min/1.73 m^2)	8.9 ± 2.8	6.7 ± 2.9[a]	6.2 ± 2.2[b]
TC (mg/dL)	152.9 ± 30.7	141.7 ± 15.1	139.5 ± 24.4
LDL-C (mg/dL)	75.1 ± 18.7	85.2 ± 9	82.2 ± 21.7
HDL-C (mg/dL)	43.2 ± 11.2	37.7 ± 6.6	39.4 ± 6.9
TG (mg/dL)	120 ± 94.8	121 ± 20.4	97.6 ± 28.3[b]

BMI: body mass index, RBS: random blood sugar, eGFR: estimated glomerular filtration rate, TC: total cholesterol, HDL-C: high-density lipoproteins cholesterol, LDL-C: low-density lipoproteins cholesterol, DN: diabetic nephropathy

Data were expressed as mean ± SD

P value < 0.05 is significant, by one way ANOVA test

[a]Significant difference between GG and GT

[b]Between GG and TT

[c]between GT and TT

delicate index of kidney activity, relative to the serum urea level. This occurs because creatinine fulfills most of the requirements of a perfect filtration marker;[10] creatinine is known to be increased with high glucose levels, in uncontrolled diabetics and often correlates with severity of kidney damage; an increase of creatinine in diabetic patients indicates progressive renal damage.[10]

In this study, the TT allele frequency is the dominant one in the DN group (20/45), but in the DM group, the dominant allele is GT (19/39), this explains that the risk of T allele in total (GT and TT) alleles (35/10 = 3.5) is higher in the DN group than DM (28/11 = 2.5). In another word, the T allele makes the risk of developing DM two and half folds more than the G allele, and the risk increases three and half times for developing DN. Other environmental factors and patients' characteristics like old age, prolongation more than 2 years after diagnosis, and poor glycemic control together with the abovementioned genetic factors, make the risk of developing DN higher.

The comparison of the DM and DN groups, presented in Table 5, showed that under the recessive model, statistically the (GT + GG) had a significant effect for risk development of DN represent as 2.6 folds with respect to those of the homozygous TT (GT + GG vs. TT $P = 0.04$, OR = 2.6, 95% CI: 1.03−6.88). Another study showed a lack of association between the *ADIPOQ* polymorphism (rs1501299) and nephropathy in the African-American T2DM diabetic population,[22] also no microvascular complications were associated with the *ADIPOQ* polymorphism (rs1501299), in the DN group.[16]

In another study, they found that GT genotype and T allele may confer protection from micro/macroalbuminuria in T2DM patients.[23] The difference in our data and the other in the world is due to the difference in age and the duration of disease, in addition to the sample size.

The association between different allele frequencies and other biochemical characteristics are shown in Table 6. The serum creatinine levels were elevated in the GT and TT genotypes, compared to the GG genotype. A higher serum creatinine level was found in the DN patients who carried the GT and TT genotypes and had a higher frequency of T allele. Higher serum FBS, HBA1c, and urea levels were found when the mean and frequency of TT allele is higher than GG, GT alleles, leading to the increased risk of DN, compared to the other genotypes due to the presence of the T allele.

Conclusions

1. The *ADIPOQ* polymorphism (G > T) was found to be significantly associated with the progression of type 2 DM in the Iraqi population.
2. Genotypic frequency of T allele at the rs1501299 locus is a risk factor for DN, in the Iraqi population.
3. FBS, HbA1c, urea, creatinine, and eGFR are considered risk factors for developing DN.
4. Dyslipidemia of various abnormalities is considered a risk factor for developing DN.

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Conflicts of interest
There are no conflicts of interest.

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