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# Single-Nucleotide Polymorphism of rs11061971 (+219 A>T) in Adiponectin Receptor 2 (AdipoR2) Gene and its Association with Risk of Type 2 Diabetes among Iranian Population

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**ABSTRACT**

**Background & Objective:** Genetic modifications in the adiponectin receptor 2 (AdipoR2) gene can affect phenotypes associated with insulin resistance and diabetes. The purpose of this study was to evaluate the possible role of genetic modifications in the AdipoR2 gene, to determine the frequency of genotypes and polymorphism alleles of this gene at rs11061971 (+219 A>T), and to investigate its correlation with type 2 diabetes (T2D) and its related metabolic profile.

**Materials & Methods:** In this case-control study, the single-nucleotide polymorphism (SNP) of AdipoR2 in 116 T2D patients and 102 controls was evaluated using RFLP PCR and FOK 1 enzyme. Fasting blood sugar, cholesterol, triglyceride, insulin, HDL-C, LDL-C and HbA1c were also measured and their correlation with the studied genetic modifications was assessed. The collected data were analyzed using Chi-square test and Hardy-Weinberg equation.

**Results:** There was a significant association in AT and TT genotypes in rs11061971 (+219 A>T) with T2D. However, no significant difference was observed in the frequency of alleles between the case and control groups. In addition, in LDL-C and total cholesterol in the control group, there was a significant difference between AA and TT genotypes as well as with AA and AT genotypes. However, no correlation was found between the other studied serum parameters and the genotype of individuals in the rs1106197171 polymorphism.

**Conclusion:** It can be concluded that rs11061971 (+219 A>T) polymorphism is associated with T2D incidence. The findings suggest that AT and TT genotypes in this gene compared to AA genotype increase the risk of diabetes.

**Keywords:** Polymorphism, Adiponectin receptor, Diabetes, Glucose, Lipid, Insulin



## Introduction

Diabetes, as the most common metabolic disorder, is characterized by chronic hyperglycemia due to impaired insulin secretion by β-cells in the islets of Langerhans or insulin resistance (1, 2). Of the four major groups of diabetes, type 2 diabetes (T2D) accounts for 90 to 95% of diabetic patients, and is of great importance (1,3). Diabetes mellitus is a multifactorial condition influenced by environmental and genetic factors (1). According to a report, the prevalence of T2D in Iran is the highest among developing countries (4).

The adipose tissue acts not only as the fat-storing parenchymal cells, but also as an endocrine organ and the immune system. One of the most abundant adipocytokines secreted exclusively by adipose tissue is adiponectin, which is a protein hormone that regulates several metabolic processes, including glucose homeostasis and fatty acid catabolism (5). Adiponectin is the most abundant adipose tissue-derived cytokine, which has anti-inflammatory, anti-diabetic, and anti-atherogenic properties (6, 7); moreover, its low circulating level is associated with central obesity, insulin resistance (IR), metabolic syndrome (MetS) and T2D (8-10). Dysregulation of adiponectin and its receptors, which reduces its level, contributes to the development of various diseases, including obesity, IR, chronic kidney disease (CKD), type 1 diabetes (T1D) and T2D (11,12). Through its insulin-sensitizing properties, adiponectin regulates glucose and lipid homeostasis, and appears to be associated with the development and progression of T2D

at lower levels (13, 14). Adiponectin has a direct role in insulin sensitivity. It can activate AMPK and PPAR in skeletal muscle and liver, thereby increasing insulin sensitivity (15, 16).

Adiponectin plays an important role in insulin sensitivity and T2D risk through adiponectin receptors 1 and 2 (AdipoR1/AdipoR2) signaling pathways (8, 17). The adiponectin receptors are found at all sites essential for glucose metabolism (17, 18). AdipoR2 gene is located on chromosome p13.3112, which consists of eight exons (19). The concomitant impairment of AdipoR1 and AdipoR2 in rats prevents adiponectin binding, leading to processes such as increased tissue triglyceride content, inflammation, and oxidative stress, causing IR and glucose intolerance. The alterations in adiponectin-mediated pathways have been shown to be associated with glucose intolerance, IR, obesity, and T2D. Genetic modifications in AdipoR2 gene can affect IR and T2D-related phenotypes (20, 21).

According to the mentioned points, adiponectin receptor genes that mediate the anti-diabetic metabolic actions of adiponectin are influential factors in the pathogenesis of diabetes. Genetic studies have yielded different results regarding the role of AdipoR1/AdipoR2 genes and the context of T2D risk (22). Laura G. Rasmussen et al., concluded that AdipoR1/AdipoR2 genes influence insulin sensitivity (23); however, Kim et al. (2009) found that none of the SNPs in AdipoR1 or AdipoR2 genes has been accompanied with the T2D risk in Korean patients (21). Moreover, Haibing Yu et al., in 2021 concluded that some single nucleotide polymorphisms (ADIPOR2 rs1044471, PCK1 rs1042531, GLUT1 rs127 18444) in the adiponectin signaling pathway may be associated with T2D (24).

To the best of our knowledge, the SNPs of AdipoR2 gene in T2D have not yet been fully studied and the effect of their genetic variants have not been extensively revealed in Iran. Therefore, the purpose of this study was to evaluate the frequency of single-nucleotide polymorphism of rs11061971 (+219 A>T) in AdipoR2 gene and its association with diabetes risk in an Iranian population with type 2 diabetes. Moreover, the possible role of this genetic modification in related metabolic properties was examined.

## Materials and Methods

### Subjects

This case-control study was conducted on a statistical population including T2D patients and a healthy group. The diabetic subjects included 116 T2D patients aged 40 to 70 years, who had glucose levels above 126 mg/dl and HbA1C above 6.5% (case group). The control group consisted of 102 healthy individuals without any underlying disease and with normal glucose levels. One of the exclusion criteria was the subject's history of other systemic diseases. In both groups, half were men and the other half were women, who were selected by convenience sampling from the people referring to the diabetes control centers in Tehran-Iran. The protocol of this research was reviewed and approved by the ethic committee of Faculty of Medical Sciences at the Islamic Azad University of Shahrood, Iran (IR.IAU.SHAHROOD.REC.1399.048). All patients' information remained private and confidential. Informed written consent was obtained from the patients, without any external compulsion or pressure.

### Sampling

After obtaining the consent of the subjects, 10 ml of venous blood was taken after a 12-hour fasting. About 3 ml was poured into a Falcon tube containing EDTA to measure HbA1c, and the rest was poured into an anticoagulant-free test tube to separate serum, and centrifuged for 10 minutes at 3000 ×g. The serum samples were separated and stored at -20°C until analysis.

### Measurement of lipid, glucose, HbA1c and insulin profiles

A part of the separated serum was analyzed to measure fasting blood sugar, triglycerides, cholesterol, HDL-C and LDL-C levels using a BT 35i Autoanalyzer and Biorexfars kits. The HbA1c level was measured by ion exchange chromatography (Audicom). The insulin level was also measured by ELISA using the Diagnostic Automation/Cortez Diagnostics Inc. (DACDI) Kit (USA). The used insulin kit was based on the sandwich ELISA method.

### DNA extraction

DNA extraction from white blood cells was performed using a DNA extraction kit (SinaClon Co., Iran) in accordance with the manufacturer's instructions. The quantity of extracted DNA was determined using NanoDrop, and the optical density (OD) ratio was measured at 260 to 280 nm.

### PCR procedure

The PCR procedure was performed using PCR 2x Master Mix in which all the necessary materials except DNA template and primers were present. Primers suitable for the desired polymorphism site were designed using Oligo software.

The characteristics of the used primers in this study were as follow:

Forward: sequence: GGTGATAATGACAGCCACCAAG, length 22 bp, Tm 59.32 ˚C.

Revers: sequence: CCATCCTCCCTCCAGCAATG, length 20 bp, Tm 60.18 ˚C.

The length of amplicon was 182 bp.

The final mastermix was prepared using 1 µl of each primer, 6.5 µl of injected water and 10 µl of pre-prepared mastermix. Then, each of the microtubes was added in1.5 µl of the template DNA corresponding to each patient or control sample and placed in a thermocycler. After PCR,

the products were randomly confirmed by 1.5% agarose gel electrophoresis.

### PCR-RFLP method protocol

The restriction enzyme of FOK 1 was selected in accordance with the designed primers and amplified fragments. Thus, 4 µl of PCR product, 1 µl of enzyme, 1 µl of enzyme buffer and 4 µl of sterile deionized water were mixed and the enzymatic digestion was performed according to the kit protocol. Finally, the restricted product was electrophoresed on 3% agarose gel.

### Statistical analysis

Data analysis and charting were performed using SPSS v.18 and Microsoft Office Excel 2013 software, respectively. One-way ANOVA was used for statistical analysis. P-value less than 0.05 was considered as significance level. Hardy-Weinberg equilibrium test was also performed. Statistical comparison of means was carried out by Mann-Whitney U test for non-parametric data. Comparisons of age and gender ratio were performed using independent t-test and Chi-square test respectively. Odds ratio (95% confidence level, 95%CI) was applied to investigate the role of rs11061971 polymorphism in T2D risk. Pearson correlation test and correlation coefficient (r) were used to evaluate the correlation between blood parameters in studied subjects.

## Results

### Demographic characteristics of study participants

A total of 218 subjects participated in the present study, of whom 103 were male (47%) and 115 were female (53%). This study was performed on two groups of individuals including the control group (n=102, 47%) and the case group (n=116, 53%); their demographic profiles are listed in Table 1. According to the results, 82 patients (38%) had a family history of diabetes, and the rest had no family history. There was no significant difference in age and sex between the case and control groups. Duration of diabetes in case group was 6-13 years.

**Table 1. Comparison of demographic characteristics of all subjects**

| Variables | Gender | Case group | Control group | P-value |
|---|---|---|---|---|
| Age (year) | Female | 63.10±8.44 | 60.56±8.57 | 0.091 |
| | Male | 59.58±8.35 | 61.29±8.31 | 0.301 |
| Gender | Female (%) | 61 (28.0%) | 54 (24.8%) | 0.185 |
| | Male (%) | 55 (25.2%) | 48 (22.0%) | |

### Measurement of serum glucose and lipid levels

Both the case and control groups were tested for biochemical parameters related to blood glucose for the diagnosis of diabetes, including fasting blood sugar, HbA1c, TG, HDL-C, LDL-C and Chol, and fasting insulin; the findings are shown in Table 2. Total cholesterol levels in healthy individuals and patients showed no significant difference. Moreover, LDL-C levels were not significantly different between the case and healthy women. However, the levels of other studied parameters in diabetics were significantly different from healthy individuals.

**Table 2. Comparison of blood parameters of the subjects by gender**

| Variables | Gender | Control group, Mean ± standard deviation | Control group, Mean ± standard deviation | P-value |
|---|---|---|---|---|
| Fasting blood sugar | Female | 165.33±15.00 | 83.74±9.18 | P<0.001 |
| | Male | 164.95±12.02 | 85.00±8.82 | P<0.001 |
| HbA1c (%) | Female | 7.40±0.54 | 5.33±0.40 | P<0.001 |
| | Male | 7.23±0.41 | 5.18±0.48 | P<0.001 |
| Triglyceride (mg/dl) | Female | 155.20±42.30 | 110.39±7.70 | P<0.001 |
| | Male | 175.02±29.51 | 110.44±10.99 | P<0.001 |
| HDL-C (mg/dl) | Female | 44.26±6.33 | 53.20±5.92 | P<0.001 |

| Variables | Gender | Control group, Mean ± standard deviation | Control group, Mean ± standard deviation | P-value |
|---|---|---|---|---|
| LDL-C (mg/dl) | Male | 40.35±5.36 | 50.81±3.13 | P<0.001 |
| | Female | 145.16±31.79 | 131.13±35.46 | 0.100 |
| Total cholesterol (mg/dl) | Male | 150.22±40.03 | 135.65±30.91 | 0.043 |
| | Female | 204.43±28.38 | 194.89±36.08 | 0.299 |
| Fasting insulin (pmol/L) | Male | 207.55±38.15 | 197.08±31.19 | 0.134 |
| | Female | 107.46±48.63 | 71.19±43.06 | 0.050 |
| | Male | 104.76±52.92 | 64.96±41.20 | P<0.001 |

### Evaluation of Hardy-Weinberg equilibrium

Expected genotype frequency was calculated by Hardy-Weinberg equation. According to statistical analysis, all genotype frequencies followed this equilibrium (Table 3).

**Table 3. Evaluation of Hardy-Weinberg equilibrium in all studied samples**

| Parameters | Observed frequency | Observed percentage | Expected frequency | Expected percentage |
|---|---|---|---|---|
| Wild homozygous genotype (AA) | 26 | 11.93 | 26.50 | 12.15 |
| Heterozygous genotype (AT) | 100 | 45.87 | 99.01 | 45.42 |
| Homozygous mutant genotype (TT) | 92 | 42.20 | 92.50 | 42.43 |
| Wild allele A | 152 | 34.86 | -- | -- |
| Mutant allele T | 284 | 65.14 | -- | -- |
| Chi-square test results | 0.021832332 | | P-value: 0.882534 | |
| Outcome | The population is in Hardy-Weinberg equilibrium. | | | |

### Rs11061971 alleles and genotypes in AdipoR2 gene and their correlation with diabetes risk

The images obtained by agarose gel electrophoresis were evaluated to determine the genotype of individuals in the rs11061971 polymorphism in the AdipoR2 gene (Figure 1).

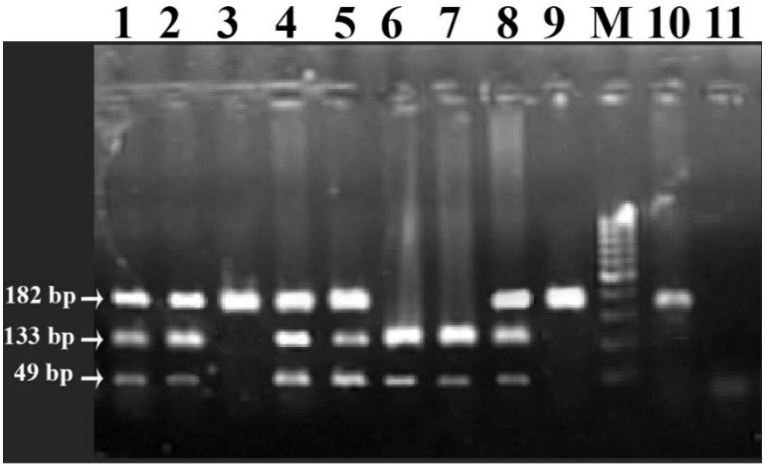


**Figure 1. Analysis of the bands appeared on agarose gel electrophoresis for genotyping of adiponectin receptor gene. (M: 50-bp marker, 11: negative control (NTC), 1, 2, 4, 5 and 8: heterozygous AT, 10: undigested PCR product (UnDigest), 3 and 9: homozygous AA, 6 and 7: homozygous TT)**

According to the obtained results, the frequency and percentage of genotypes in all diabetic and control subjects were determined. Allele A was the wild allele and allele T was the mutant allele. The genotype AT (46%) had the highest frequency in participants, followed by TT (42%) and AA (12%). The Odds Ratio (95%CI) was applied to investigate the role of rs11061971 polymorphism in T2D risk. AA genotype, OR=1 (95%CI), was considered as wild allele in this study. Individuals with AT and TT genotypes in rs11061971 had higher odds ratio for T2D risk than those with genotype AA as wild genotype. Moreover,

the frequency of genotypes in rs11061971 region was determined in male and female groups among the subjects (Table 4), and the T2D risk rate (95%CI) in men and women was examined separately.

**Table 4. Genotype frequency in rs11061971 region of AdipoR2 gene in subjects by gender**

| Gender | Genotypes | Case group frequency/percentage | | Control group frequency/percentage | | OR (CI=95%) | P-value |
|---|---|---|---|---|---|---|---|
| Female | AA | 8 | 6.9% | 5 | 4.9% | - | - |
| | TT | 25 | 21.6% | 23 | 22.5% | 0.679 | 0.019 |
| | AT | 28 | 24.1% | 26 | 25.5% | 0.673 | 0.012 |
| Male | AA | 7 | 6.0% | 6 | 5.9% | - | - |
| | TT | 25 | 21.6% | 19 | 18.6% | 1.128 | 0.016 |
| | AT | 23 | 19.8% | 23 | 22.5% | 0.857 | 0.019 |

Regression analysis was performed; according to the results, the risk of T2D in men and women with AT and TT genotype compared to AA wild genotype showed a significant increase.

The frequencies of wild A and mutant T alleles in this SNP in both patient and control populations are shown in Table 5. The frequency of A and T alleles in both diabetic and control groups revealed no significant difference, in other words, neither was associated with a significant change in T2D risk.

**Table 5. Allele frequency in the rs11061971 region of AdipoR2 gene in both groups**

| Alleles | Case group, frequency(percentage) | Control group, frequency(percentage) | OR (CI=95%) | P-value |
|---|---|---|---|---|
| Wild A allele | 81 (34.9%) | 71 (34.8%) | 0.995 | 0.208 |
| Mutant T allele | 151 (65.1%) | 133 (65.2%) | | |

**Serum glucose and lipid profile in different genotypes of AdipoR2 gene**

Mean values of biochemical parameters in terms of genotype were examined in both control and case groups. There was no significant correlation between different genotypes and the mean fasting blood sugar level in either of the studied groups. In addition, there was no statistically significant correlation between the mean level of HbA1c and different genotypes in the two groups. The statistical analysis of TG, HDL-C and fasting insulin showed similar results. However, there was a significant difference in serum LDL-C and cholesterol level between AA and TT genotypes as well as between AA and AT genotypes in the control group ($P<0.05$).

## Discussion

Diabetes, with high prevalence and mortality, is associated with other diseases. The disease is associated with biochemical and functional abnormalities in liver, including changes in the metabolism of carbohydrates, lipids and proteins. These changes are especially important because of their effect on liver function of blood glucose homeostasis.

A direct correlation between diabetes and Adipor2 gene polymorphism has been shown in literature. The important role of AdipoR2 in T2D, as observed in the present study, may be due to the unique function of this receptor on the effects of adiponectin in the liver. This organ has been suggested as the main site of adiponectin bioactivity. Adiponectin affects lipid metabolism and increases the fatty acid oxidation by activating AMP-activated protein kinase (AMPK) system. Adiponectin also lowers hepatic glucose levels by reducing expression of the enzymes involved in hepatic gluconeogenesis. Thus, elevated serum triglycerides may reflect low levels of lipid oxidation in patients with metabolic syndrome, leading to the accumulation of toxic intracellular lipid metabolites in the liver and other peripheral tissues and thus inhibiting the insulin signaling (20). Studies show that AdipoR2 down regulation or dysfunction may be responsible for the IR appearance in peripheral tissues (25). Therefore, in the present study we hypothesized that genetic diversity in AdipoR2 may support increased susceptibility to T2D. We investigated this hypothesis by examining the AdipoR2 gene polymorphism in the rs11061971 region and the correlation between the observed sequence change and T2D in a small population of Tehran (Iran).

The present study was performed on blood samples of 102 controls and 116 T2D patients using PCR-

RFLP. The results showed significant difference in genotypes between the two studied groups. Therefore, we can suggest the association of these two genotypes (AA and TT) with T2D risk. Subsequently, we examined the frequency of alleles and statistical analysis showed no significant difference between the two groups.

Putapov et al., in Russia reported that individuals with the TT genotype at rs11061971 had a higher risk of diabetes (OR=4.45) (20). They also stated that the T allele of rs11061971 shows a greater correlation with diabetes risk (OR=2.05). On the other hand, the A allele of rs11061971 was associated with a reduction in T2D risk (OR=0.49). They concluded that the diversity and types of AdipoR2 increase the T2D risk and correlate with some IR-related phenotypes in the Russian study population (20), while, the allele frequency revealed no significant difference in our study.

In a study by Ismail et al., in 2016, the AdipoR2 gene SNP was involved in the pathogenesis of T2D with CVD in Al-Najaf Governorate of Iraq (26). In their study, the homozygous TT and heterozygous AT genotypes of rs11061971 had a strong association and increased risk of T2D with CVD (26). Moreover, the T allele frequency of rs11061971 was correlated with increased risk of T2D with CVD. Adiponectin receptors also play an important role in the metabolism of VLDL cholesterol and triglycerides (26). Similarly, Damcott et al., reported that the T allele of rs11061971 was significantly associated with a higher risk of T2D in the population of Old order Amish (25).

Richardson et al., found a strong correlation between AdipoR2 polymorphism and plasma triglycerides levels, which may have important implications for atherogenesis or dyspepsia due to the potential effect of AdipoR2 genetic modifications on the metabolism of triglyceride-rich lipoproteins in Mexican Americans (27). Collins et al., meanwhile, suggested that AdipoR2 may not be the most important risk factors for T2D and IR in the UK population; although, more detailed analysis of the gene variants may be needed to determine their potential role in IR and glucose homeostasis (28).

In a study (2018) on Japanese elderly, it was found that there was a significant correlation between AdipoR2 SNP rs12230440 and renal function and the effects of this polymorphism on the adiponectin receptor may affect renal function in elderly Japanese (29).

Nikitin et al., (2015) in Russia indicated that the AdipoR2 gene polymorphism was correlated with T2D risk in the Russian population, but there was no correlation between T2D and the AdipoQ or AdipoR1 gene polymorphism (30). Moreover, recently we have studied two adiponectin gene polymorphisms (ADIPOQ rs266729 and rs1501299) in an Iranian T2D population and reported that ADIPOQ rs266729 but no rs1501299 is associated with higher risk of T2D (6).

In another study conducted in 2019, the authors concluded that AdipoR1 polymorphisms (rs1342387 G>A & rs12733285C>T) are not associated directly with T2DM in an Iraqi population (31). However, they suggested an indirect impact via directing of insulin resistance and BMI (31).

As can be seen, different results have been obtained in various studies. This discrepancy in findings may be related to racial differences or environmental factors faced by members of the studied community. On the other hand, in biochemical pathways, a protein similar in function to a defective protein may compensate for its defective activity, or at least the function of a defective protein may be sufficient to progress the pathway.

## Conclusion

The results of the present study, which was conducted for the first time in Iran, revealed a direct correlation between type 2 diabetes (T2D) and adiponectin receptor 2 (AdipoR2) gene polymorphism. The genetic linkages observed between certain types of AdipoR2 and T2D in several studies, including this one, introduce AdipoR2 as a promising target for the treatment of T2D patients, especially those with obesity, insulin resistance and dyslipidemia. Since we could not cover adequate SNPs in the regulatory region, to further elucidate the role of AdipoR2 polymorphisms in the pathogenesis of type 2 diabetes, further analyses in other populations with larger samples, more SNPs, as well as more functional studies are suggested.

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## Conflict of Interest

The authors declare no any conflict of interest regarding the publication of this article.

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