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Association of *ADIPOQ* Gene Variants and Circulating Adiponectin Levels with Coronary Artery Disease Risk

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Abstract

BACKGROUND/AIMS: Coronary artery disease (CAD) is a major international health issue, closely linked with obesity and its associated metabolic complications. Adiponectin, an adipokine involved in glucose and lipid metabolism, might contribute to the development of CAD. This study investigated the association of three single nucleotide polymorphisms (SNPs) in the adiponectin gene (*ADIPOQ*), rs2241766, rs1501299, and rs266729, with CAD and serum adiponectin levels in a Turkish cohort.

MATERIALS AND METHODS: A total of 288 participants (150 CAD patients and 138 controls) were included. Serum adiponectin levels were measured, SNP genotyping was performed, and genotype-phenotype associations were evaluated using different genetic inheritance models. We also assessed the relationships among SNPs, adiponectin levels, and CAD risk. Receiver operating characteristic (ROC) analysis was used to assess the diagnostic value.

RESULTS: Serum adiponectin was significantly lower in CAD patients. ROC analysis indicated limited diagnostic value (area under the curve=0.115, 95% confidence interval: 0.074-0.156). The rs2241766 SNP showed a significant association with CAD risk under three inheritance models. Moreover, the rs2241766 SNP was strongly associated with reduced adiponectin levels in risk allele carriers.

CONCLUSION: The rs2241766 SNP in the *ADIPOQ* gene is significantly associated with both increased CAD risk and reduced serum adiponectin levels, suggesting its potential utility as a genetic biomarker. Additional studies are necessary to validate these findings in larger cohorts.

Keywords: Adiponectin, biomarker, coronaray artery disease, diagnostics, genotype, polymorphism

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INTRODUCTION

Coronary artery disease (CAD) is a major global health burden, with its prevalence increasing alongside that of global obesity.[1] Obesity, now considered the second leading cause of death globally, contributes significantly to cardiovascular morbidity by exacerbating well-known risk factors such as dyslipidaemia, hypertension (HTN), and diabetes mellitus (DM).[2] These conditions collectively increase atherogenic risk, in part by altering lipid metabolism, promoting endothelial dysfunction, and increasing systemic inflammation.[3]

Among the many molecular mediators linking obesity to cardiovascular disease, adiponectin has emerged as a particularly important adipokine. Predominantly secreted by adipose tissue, adiponectin plays critical roles in metabolic regulation, inflammation, and cardiovascular homeostasis.[4,5] Beyond its function in glucose and lipid metabolism,

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adiponectin influences endothelial function, inhibits vascular smooth muscle proliferation, and exerts anti-inflammatory effects, all of which are essential for preserving vascular integrity and myocardial function.[6]

Interestingly, despite its generally protective role, circulating adiponectin levels have shown a paradoxical association with disease severity in some clinical contexts. Although reduced adiponectin concentrations are generally linked with high CAD risk, recent findings have highlighted a paradoxical correlation between raised adiponectin levels and poor outcomes in advanced disease stages, suggesting a compensatory rather than causative role.[7,8] This paradox underscores the complex role of adiponectin in cardiovascular disease and highlights the necessity for further mechanistic and genetic investigations.

Variations in the adiponectin gene (*ADIPOQ*) are known to influence its expression and circulating levels, thereby modulating cardiometabolic risk. Several single nucleotide polymorphisms (SNPs), including rs2241766, rs1501299, and rs266729, contribute to alterations in adiponectin levels and to the gene's impact on outcome and susceptibility to CAD.[9,10] The rs2241766 SNP is located in the promoter region of adiponectin and associated with variations in *ADIPOQ* expression. Reports vary regarding its association with CAD risk, with some studies suggesting a protective effect, while others report a negative or no impact.[9,10] In addition, the rs266729 SNP, which lies in the proximal promoter region of the *ADIPOQ* gene is associated with changes in adiponectin levels and metabolic traits.[10] Similarly, the rs1501299 polymorphism, substitution of G to T in intron 2 of the *ADIPOQ* gene, it has been widely researched for its impact on adiponectin circulation and CAD susceptibility, but the results have varied, suggesting that large-scale, well-designed studies are needed to determine its actual impact on CAD susceptibility.[9] The complex association between the rs1501299 SNP and CAD risk has been reported in some studies, but others have produced inconclusive or conflicting results across studies and populations, suggesting the need for larger and ethnically diverse cohorts.[10]

Although some studies suggest that these SNPs might serve as genetic markers for CAD risk, the results have been inconsitent across different ethnicities and sample sizes. Inter-individual differences in adiponectin levels may be influenced not only by these genetic polymorphisms but also by their interaction with environmental and metabolic factors such as obesity, insulin resistance, and systemic inflammation. This complexity has made it difficult to definitively establish the role of the *ADIPOQ* gene and its genetic determinants as reliable biomarkers for CAD diagnosis or prognosis.

Given the limited data from Middle Eastern and Turkish populations and the inconsistent associations reported globally, the current study aims to explore the diagnostic and prognostic relevance of circulating adiponectin levels and the association of *ADIPOQ* gene SNPs in CAD patients. By investigating the relationship between genetic variation, its expression, and disease risk, we hope to clarify its potential utility as a molecular marker for CAD and to contribute to a more personalized understanding of cardiovascular risk stratification.

MATERİALS AND METHODS

Study Population

This case-control study, conducted between November 2007 and January 2009 included 288 subjects, comprising 150 CAD patients and 138 age- and sex-matched non-CAD patients as a control group. All patients in the CAD group underwent coronary artery bypass grafting. The detailed medical histories of the study participants were obtained during physical examinations. Coronary angiography was performed for each patient from cardiology department surgery clinic, and CAD was defined as a narrowing of 50% or more in the left main coronary artery or of 70% or more in at least one major epicardial coronary artery. Body mass index was calculated for each participant of the study. HTN was defined as resting blood pressure ≥140/90 mmHg and/or the use of antihypertensive medications. Diabetes diagnosis was determined either by the 1999 World Health Organization criteria or by the use of diabetic medications. Dyslipidemia was defined as low-density lipoprotein (LDL) cholesterol ≥130 mg/dL or current use of hypolipidemic medications. The participants in the control group who had no atherosclerotic lesions on coronary angiography were non-obese, non-diabetic, non-dyslipidemic, and none had HTN. Blood samples were drawn from a vein in the arm after the individual had fasted overnight for 12 hours. The blood samples were used for biochemical measurements, analysis of serum adiponectin levels, and extraction of genomic deoxyribonucleic acid (DNA). Written informed consent from all participants was obtained. The study followed ethical guidelines, was approved by the İstanbul Bilim University Ethics Committee (approval number: 2007/24, date: 26.10.2007), and adhered to the principles of the Declaration of Helsinki.

Biochemical Measurements

Fasting serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), fasting glucose, and fasting insulin levels were measured using standardized enzymatic methods on a Cobas 6000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The LDL-C levels were calculated using the Friedewald formula. Serum total adiponectin levels were measured using a commercially available enzyme-linked immunosorbent assay kit (ab99968; Abcam, Cambridge, UK), according to the manufacturer's instructions. The samples were assayed in duplicate to ensure reproducibility. All serum samples were stored at -80 °C until analysis. The Homeostatic Model Assessment of Insulin Resistance, calculated as [fasting glucose (mmol/L) × fasting insulin (uU/mL)] / 22.5, was employed to assess insulin resistance.

DNA Isolation and Genotyping

A total of 5 mL of whole blood was collected from each patient into ethylenediamine tetraacetic acid tubes. Genomic DNA was isolated from approximately 400 µl of whole blood using the MagNA Pure Compact DNA Isolation Kit (Roche Diagnostics GmbH, Mannheim, Germany), following the manufacturer's protocol. DNA quality and purity were determined using the NanoDrop™ 1000 spectrophotometer (Thermo Scientific, Wilmington, DE, USA), and samples were stored at -20 °C until genotyping. Genotyping of the SNPs was carried out using the LightSNiP typing assay (TIBMolBiol, Berlin, Germany) on the LightCycler® 480 system (Roche Diagnostics GmbH, Mannheim, Germany). Each reaction included a no-template control and internal controls to assess amplification specificity.

Statistical Analysis

All statistical analyses were conducted using the SPSS 25.0 software (IBM Corp., Armonk, NY, USA). The chi-square (X^2) test was used to compare the distribution of alleles for studied SNPs between the control group

and CAD patients. The Hardy-Weinberg equilibrium (HWE) was assessed using Fisher's exact test. The normality of the variables in the data was evaluated using the Shapiro-Wilk test. For linear regression, we examined the distribution of residuals and confirmed homoscedasticity and approximate normality. For continuous variables, we used the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data to compare two groups. To examine the relationship between *ADIPOQ* gene genotypes and circulating levels of adiponectin, we applied ANOVA and Kruskal-Wallis tests. Data are presented as mean ± standard deviation or as percentages, as appropriate. We assessed the diagnostic utility of serum adiponectin levels for CAD using receiver operating characteristic (ROC) curve analysis, reporting the area under the curve (AUC) values. To minimize the impact of outliers when comparing continuous variables, Spearman's correlation was employed. Additionally, linear regression analysis was performed to refine the correlation results. A p-value <0.05 was considered statistically significant.

RESULTS

Biochemical and anthropometric data for CAD patients (n=150) and controls (n=138) are summarized in Table 1. There was no statistically significant difference between the groups in age (CAD: 60.37±9.06 years; Controls: 59.33±8.81 years; p>0.05) or sex distribution (p>0.05). As we expacted the fasting plasma glucose and insulin levels were significantly increased in CAD patients in comparison with controls (p<0.05, respectively). Obesity (94.4%) and hyperlipidemia (88.7%) were the most prevalent risk factors in CAD patients, followed by type 2 DM (87.3%) and HTN (79.6%) (p=0.001). Serum TC and LDL-C were markedly elevated in CAD patients, whereas serum HDL levels were significantly higher in controls (p<0.05).

Table 1. Baseline demographic, anthropometric, and biochemical characteristics of the study groups

Variables	CAD (n=150)	Controls (n=138)	p-value*
Age (year)	60.37±9.06	59.33±8.91	0.328
Sex/male (%)	86 (57.3%)	66 (47.8%)	0.067
Weight (kg)	82.68±10.9	71.78±8.25	**0.001**
Height (cm)	162.4±8.51	164.33±9.36	0.067
BMI (kg/m^2)	31.39±3.84	28.62±4.47	**0.001**
Systolic BP (mmHg)	131.90±16.14	124.47±10.91	**0.001**
Diastolic BP (mmHg)	78.49±8.75	76.05±7.74	**0.024**
Fasting glucose (mmol/L)	8.01±2.14	4.13±0.78	**0.001**
HOMA-IR	15.15±7.98	7.52±3.11	**0.001**
Cholesterol (mmol/L)	6.89±0.95	3.62±0.72	**0.001**
HDL (mmol/L)	0.74±0.28	1.56±0.30	**0.001**
LDL-C (mol/L)	4.06±0.76	2.16±0.66	**0.001**
VLDL (mmol/L)	2.19±0.44	1.02±0.28	**0.001**
TG (mmol/L)	3.69±1.31	1.08±0.41	**0.001**

Values are presented as mean ± standard deviation. Comparisons between groups were performed using unpaired Student's t-test. *A p-value <0.05 was considered statistically significant. Bold values represent statistically significant p-values (p<0.05).
CAD: Coronary artery disease, BMI: Body mass index, BP: Blood pressure, HOMA-IR: Homeostatic model assessment of insulin resistance, HDL: High-density lipoprotein, LDL-C: Low-density lipoprotein cholesterol, VLDL: Very-low-density lipoprotein, TG: Triglycerides.

Serum Adiponectin Levels and CAD Risk

Circulating adiponectin levels were significantly lower in CAD patients (4.51±0.75 µg/mL) than in controls (7.13±1.01 µg/mL) (p=0.001) (Figure 1). To evaluate its diagnostic utility, ROC curve analysis was performed. This analysis showed an AUC of 0.115 [95% confidence interval (CI), 0.074-0.156; p=0.001] (Figure 2), which falls well below the neutral threshold of 0.5. This suggests that serum adiponectin levels are inversely associated with CAD status, i.e., higher adiponectin levels are more prevalent among controls than in CAD patients. When the direction of association is reversed, the effective discriminatory power corresponds to a corrected AUC (1 - 0.115=0.885), indicating strong predictive value as a protective biomarker (Figure 2).

Correlation Between Adiponectin and Biochemical Variables

Spearman correlation analysis in CAD patients revealed a strongly direct positive correlation between serum adiponectin and with LDL-C and a inverse relationship with fasting glucose levels (r=0.260, p=0.001, r=-0.257 p=0.001, respectively) (Figure 3). Linear regression analysis results also showed that the positive associations of LDL-C and negative associations of fasting glucose levels between adiponectin levels in CAD patients [odds ratio (OR)=5.35 95% CI=4.21-6.48 p=0.002, OR=-0.01 95% CI -0.015- -0.005, p=0.003, respectively).

Association of *ADIPOQ* Gene SNPs and CAD

Allele and genotype frequencies of the rs2241766, rs1501299, and rs266729 SNPs were analyzed in 150 patients with CAD and 120 controls (Table 2). Genotypic distributions for rs2241766, rs1501299, and rs266729 differed significantly between groups (p<0.005). Allele frequencies of rs2241766 showed a clear distinction between the groups, and genotype distributions in the control group conformed to HWE (Table 2).

In contrast, allele-level comparisons did not reach significance for rs1501299 (G allele, p=0.262) and rs266729 (C allele, p=0.07); however, genotypic models for rs1501299 did not reach statistical significance,

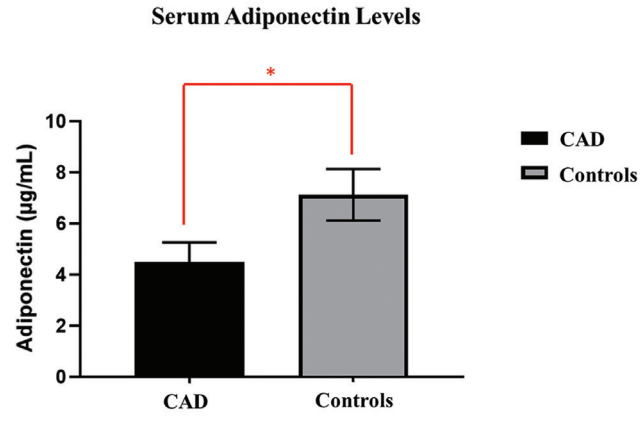

Figure 1. Serum adiponectin levels in study group. Comparison of serum adiponectin levels between CAD patients and controls. Data are presented as mean ± SD. Statistical analysis was performed using an unpaired Student's t-test. *p=0.001.

CAD: Coronary artery disease, SD: Standard deviation.

whereas rs266729 showed significance only under the dominant model (Table 3).

Further stratified analysis based on models of genetic inheritance revealed a strong relationship between rs2241766 and increased CAD risk. Under the dominant model, individuals carrying at leat one G allele (TG or GG genotypes) exhibited a significantly higher risk of CAD compared to TT homozygotes (OR=4.857; 95% CI=2.948-8.001, p<0.0001). The recessive model also demonstrated a protective effect for the TT genotype (OR=0.190, 95% CI=0.076-0.473, p<0.0001), and the additive model supported a dose-dependent increase in risk associated with the G allele (OR=3.682, 95% CI=2.503-5.416, p<0.0001). Similarly, the rs266729 variant showed a significant association with CAD under the dominant model, with carriers of the G allele (CG or GG genotypes) being at greater risk than CC homozygotes (OR=2.036, CI=1.161-3.571, p=0.012) (Table 3).

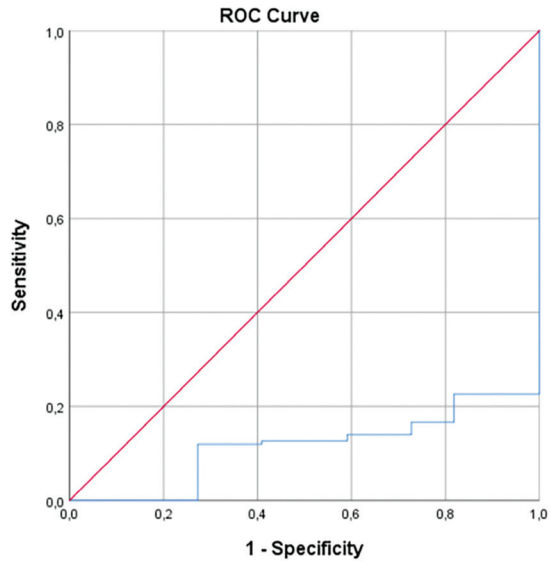

Figure 2. ROC curves of analysis of diagnostic value of serum adiponectin leves for CAD prediction. Receiver operating characteristic curve illustrating the diagnostic performance of serum adiponectin levels for predicting CAD. The area under the curve was 0.115, indicating inverse discrimination. The corrected interpretation (1 - AUC=0.885) suggests a potential protective utility.

ROC: Receiver operating characteristic, CAD: Coronary artery disease, AUC: Area under the curve.

Associations Between Studied SNPs and Serum Adiponectin Levels

To investigate the potential influence of *ADIPOQ* gene variants on circulating adiponectin levels, serum adiponectin levels were compared across genotypes for each studied SNP. A statistically significant association was observed for rs2241766: individuals carrying at least one G allele (TG or GG genotypes) had markedly lower adiponectin levels (4.263±1.49 µg/mL) than those with the TT genotype (5.053±2.14 µg/mL; p=0.039) (Figure 4A). No important differences in adiponectin levels were found for the rs1501299 variant (GT + TT genotypes: 4.395±1.05 µg/mL vs. GG genotype 4.524±1.82 µg/mL; p=0.862; Figure 4B) or for the rs266729 variant (CG + GG genotypes: 4.336±1.31 µg/mL vs. CC genotype 4.585±1.91 µg/mL; p=0.993; Figure 4C).

DISCUSSION

CAD remains a major public health concern with increasing global incidence and substantial morbidity and mortality.[11] Therefore, early prediction and risk stratification of CAD are becoming increasingly critical. A paradoxical relationship has been reported between circulating adiponectin levels and cardiovascular mortality. Some studies suggest that elevated plasma adiponectin levels are correlated with increased cardiovascular mortality.[12] However, in our study, we observed that higher adiponectin levels exert a protective effect against CAD, as CAD patients had significantly lower serum adiponectin levels than controls.

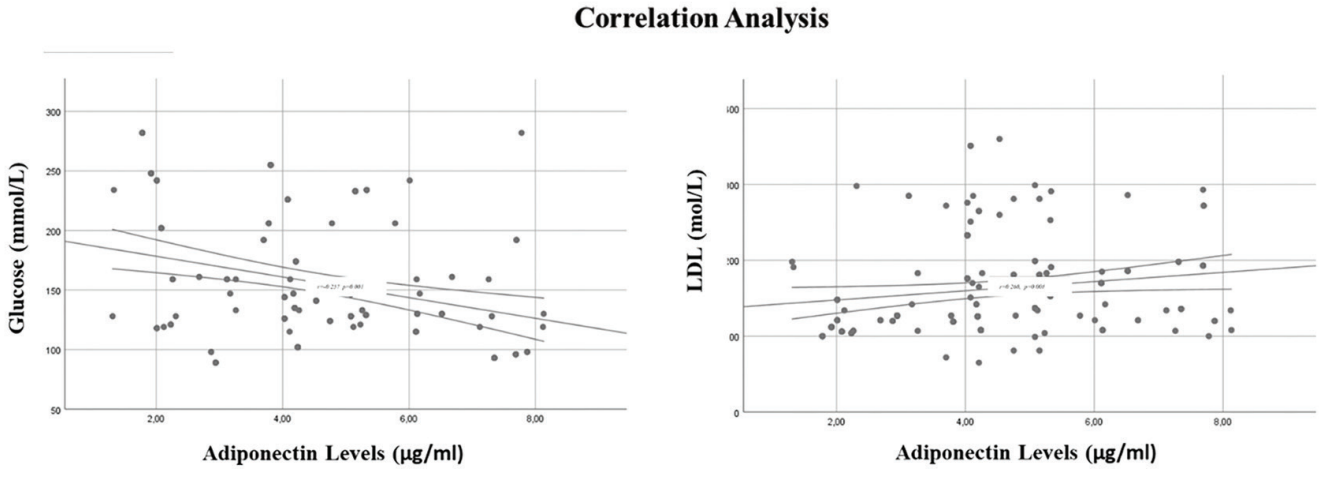

Figure 3. Correlation analysis between serum adiponectin levels and baseline biochemical characteristics in CAD patients. Correlation analysis between serum adiponectin levels and fasting glucose levels and LDL-C levels CAD patients. Correlation coefficients calculated using Spearman correlation test.

CAD: Coronary artery disease, LDL-C: Low-density lipoprotein cholesterol.

Table 2. The genotype and allele frequency distributions of *ADIPOQ* gene polymorphisms (rs2241766, rs1501299, and rs266729) in CAD patients and controls

SNP	Genotype frequencies n (%)				Allelic frequencies			
	Genotype	CAD (n=150)	Controls (n=138)	p-value	Allele CAD -controls	X^2	OR/CI (95%)	*p-value
rs2241766	TT TG GG	48 (32) 73 (48.7) 29 (19.3)	96 (69.6) 36 (26.1) 6 (4.3)	**0.001**	T/G 0.56/0.44-0.83/0.17	28.17	9.667/3.758-24.867	**0.001**
rs1501299	GG GT TT	134 (89.3) 12 (8) 4 (2.7)	120 (87) 18 (13) 0 (0)	**0.030**	G/T 0.83/0.17-0.93/0.07	3.530	8.063/0.430-15.131	0.262
rs266729	CC CG GG	105 (70) 41 (27.3) 4 (2.7)	114 (82.6) 18 (13) 6 (4.3)	**0.009**	C/G 0.64/0.36-0.89/0.11	0.240	0.724/0.199-2.636	0.07

Genotype distributions are shown as number of individuals and percentages within each group. Allele frequencies were compared using chi-square (X^2) tests. Odds ratios and 95% confidence intervals were calculated to estimate the strength of association between risk alleles and CAD status. Hardy-Weinberg equilibrium was assessed in the control group for each SNP. *A p-value <0.05 was considered statistically significant. Bold values represent statistically significant p-values (p<0.05).
CAD: Coronary artery disease, SNP: Single nucleotide polymorphism, OR: Odds ratio, CI: Confidence interval, HWE: Hardy-Weinberg equilibrium, *ADIPOQ:* Adiponectin gene.

Table 3. Association analysis of *ADIPOQ* polymorphisms with coronary artery disease under dominant, recessive, and additive genetic models

Genotype/Allele	Model	OR/CI (95%)	p-value
rs2241766			
TT vs. TG+GG	Dominant	4.857 / 2.948-8.001	**<0.0001**
GG vs. TG+TT	Recessive	0.190 / 0.076-0.473	**<0.0001**
T vs. G	Additive	3.682 / 2.503-5.416	**<0.0001**
rs1501299			
GG vs. GT+TT	Dominant	0.796 / 0.389-1.631	0.53
TT vs. GT+GG	Recessive	0.118 / 0.006-2.203	0.053
G vs. T	Additive	1.024 / 0.530-1.979	0.944
rs266729			
CC vs. CG+GG	Dominant	2.036 / 1.161-3.571	**0.012**
GG vs. CG+CC	Recessive	1.659 / 0.458-6.008	0.436
C vs. G	Additive	1.601 / 0.983-2.606	0.056

Logistic regression models were used to estimate odds ratios and 95% confidence intervals for each genetic model (dominant, recessive, and additive). ORs were adjusted for age, sex, and smoking status. p-values ≤0.05 were considered statistically significant. p-values in bold remained significant after Bonferroni correction (threshold p=0.0033). Bold values represent statistically significant p-values (p<0.05). OR: Odds ratio, CI: Confidence interval, SNP: Single nucietoide polymorphism, *ADIPOQ:* Adiponectin gene.

Moreover, ROC curve analysis yielded a low AUC of 0.115; this result should be interpreted in the context of the inverse relationship between adiponectin levels and CAD. An AUC significantly below 0.5 indicated that lower values of the tested biomarker (in this case, adiponectin) are associated with diseae presence. Therefore, reversing the classification direction (i.e., treating high adiponectin as protective) yields an effective AUC of 0.885, supporting the utility of adiponectin as a strong negative predictor and protective marker for CAD.

This finding appears to contrast with the "adiponectin paradox," in which elevated adiponectin levels have been associated with poorer outcomes in patients with advanced cardiovascular disease or heart failure.[12] However, this apparent contradiction may reflect differences in disease stage and context. In the context of primary prevention, low adiponectin levels are considered a risk factor for the development of atherosclerosis and CAD. In contrast, elevated adiponectin levels observed in late-stage disease may represent a compensatory response to metabolic or inflammatory stress, rather than a direct pathogenic factor. Therefore, our findings are consistent with the established role of adiponectin deficiency in early atherogenesis and CAD susceptibility.

Our findings are consistent with prior studies reporting that hypoadiponectinemia (low levels of adiponectin) is positively associated with CAD risk.[10,13,14] Adiponectin, an adipokine, plays a vital role in regulating the body's glucose and lipid metabolism and energy homeostasis.[15,16] In correlation analyses, we found that low adiponectin levels were significantly associated with elevated fasting glucose levels in CAD patients. Additionally, adiponectin levels showed a positive correlation with LDL cholesterol. Previous research has proposed that adiponectin may influence very-low-density lipoprotein cholesterol production, which could explain its association with circulating lipoprotein levels.[17] The associations observed in our study align with other reports linking adiponectin to lipid metabolism and the development of CAD, metabolic syndrome, and dyslipidemia-related disorders.[18,19]

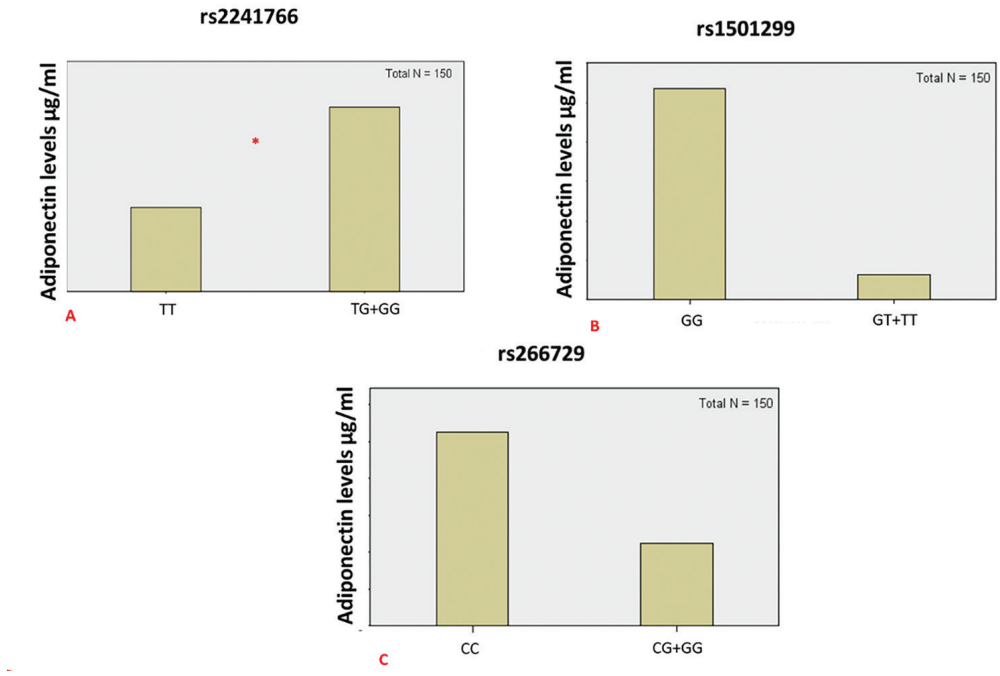

Figure 4. Serum adiponectin levels across genotypes of *ADIPOQ* SNPs. A: rs2241766 SNP, B: rs1501299 SNP and C: rs266729 SNP. Statistical comparisons were performed using the Mann-Whitney U test, and categorical field information graphs are shown. $p<0.05$ indicates a significant difference between genotype groups. *p=0.036.

SNP: Single nucietoide polymorphism, *ADIPOQ:* Adiponectin gene.

Further, we investigated the relationship between three *ADIPOQ* gene variants (rs2241766, rs1501299, and rs266729) and CAD. Our genotyping results revealed a strong association between the rs2241766 SNP and CAD risk, with significant differences in both genotypic and allelic distributions between patients and controls. The associations remained significant across dominant (TT vs. TG + GG), recessive (GG vs. TG + TT), and additive (T vs. G) inheritance models. These findings support previous meta-analyses reporting the rs2241766 variant as a genetic risk factor for CAD in diverse populations.[10,20-22]

Although the genotypic distributions of rs1501299 and rs266729 differed between CAD patients and controls, we did not observe statistically significant associations at the allelic level. Notably, the dominant genotypic model for rs266729 showed a statistically significant association with CAD risk, suggesting a potential role for this variant in disease susceptibility that may not be apparent from allele-level comparisons alone. In contrast, rs1501299 did not demonstrate a significant association in either allelic or genotypic models, indicating a limited contribution to CAD risk in our cohort. Notably, previous studies have reported inconsistent results. For instance, some investigations have supported an association between rs266729 SNP and CAD risk, particularly under dominant inheritance models,[23,24] while others found no such relationship.[25-27] Similarly, the literature is inconsistent regarding rs1501299, with some studies observing associations with CAD risk[25] and others reporting no significant link.[26,27] Given the lack of consistent statistical significance in our dataset, conclusions regarding rs1501299 and rs266729 should be considered exploratory. Future studies involving larger cohorts, haplotype-based analyses, or gene-environment interaction modeling may help clarify their roles, if any.

Moreover, we evaluated the relationship between the studied SNPs and serum adiponectin levels in CAD patients. We observed a significant association between the rs2241766 genotype and circulating adiponectin levels. Participants carrying at least one G risk allele (TG or GG) had significantly lower adiponectin levels than those with the TT genotype. This is in line with a meta-analysis that identified the G allele of rs2241766 as a determinant of reduced adiponectin levels in CAD patients,[28] suggesting that this risk allele may contribute to disease risk through decreased *ADIPOQ* gene expression. In addition, recent studies have shown that the rs2241766 genetic variation, a synonymous SNP located near an exon-intron boundary, is present in a key region of the *ADIPOQ* gene.[25,29] Even though synonymous variations do not change the protein's amino acid sequence, the location of a synonymous variation might interfere with cellular processes such as ribonucleic acid (RNA) splicing, messenger RNA stability, and protein folding.[30] Also, this rs2241766 genetic variant could ultimately lead to reduced *ADIPOQ* expression and lower adiponectin levels. No significant associations were identified between the rs1501299 and rs266729 genotypes and serum adiponectin levels in our cohort.

Study Limitations

Our study has several limitations. First, we completed the study with 288 participants (150 CAD patients and 138 controls); because this study cohort is relatively small, it may reduce the statistical power and limit the transferability of the findings. The study cohort was restricted to a single ethnic group (the Turkish population), which may limit the generalizability of the findings to populations with different genetic backgrounds. Lastly, the study examined only three *ADIPOQ* gene SNPs; other potentially relevant variants and gene-gene or gene-environment interactions were not assessed.

CONCLUSION

In conclusion, the findings of our study reinforce the role of adiponectin as a protective cardiometabolic biomarker and highlight the rs2241766 variant of the *ADIPOQ* gene as a significant genetic determinant of both serum adiponectin levels and CAD risk in the Turkish population. The observed associations suggest that genotyping of *ADIPOQ* polymorphisms, particularly rs2241766, combined with measurement of adiponectin levels, may enhance risk stratification and early detection of CAD. This integrated approach could be especially valuable in populations with high prevalence of metabolic disorders, where traditional risk markers may be insufficient for early intervention.

Clinically, the identification of individuals with high-risk genotypes and low adiponectin levels may support personalized monitoring protocols, lifestyle modification programs, or targeted pharmacological interventions aimed at improving metabolic and vascular health. Furthermore, understanding the genetic regulation of adiponectin could inform the development of novel therapeutic agents aimed at modulating its expression or downstream signaling pathways.

Future studies should aim to validate these associations in larger cohorts and explore the gene-environment interactions that may modulate adiponectin expression and CAD progression. Functional studies are also warranted to elucidate the molecular mechanisms by which *ADIPOQ* variants influence gene expression and adiponectin bioactivity. Ultimately, integrating genomic and biomarker data holds promise for advancing personalized cardiovascular medicine and improving outcomes in high-risk populations.

MAIN POINTS

- The results of the study showed that adiponectin is a protective cardiometabolic biomarker, validating its importance in metabolic and cardiovascular health.
- The rs2241766 variant of the adiponectin gene gene was identified as a significant genetic determinant of circulating adiponectin levels in Turkish patients with coronary artery disease (CAD), suggesting an association between the variant and circulating adiponectin concentration.
- The observed associations suggest that integrating genotyping of the rs2241766 polymorphism with the measurement of adiponectin levels can enhance risk stratification and early detection strategies for CAD.
- The findings support the clinical utility of this integrated approach by enabling the identification of individuals with high-risk genotypes and low adiponectin levels, which may inform personalized monitoring protocols and targeted pharmacological interventions aimed at improving metabolic and vascular health.

ETHICS

Ethics Committee Approval: The study followed ethical guidelines, was approved by the İstanbul Bilim University Ethics Committee (approval number: 2007/24, date: 26.10.2007).

Informed Consent: Written informed consent from all participants was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.G., Concept: F.A., Design: G.A., F.A., Data Collection and/or Processing: G.A., Analysis and/or Interpretation: G.A., F.A., Literature Search: S.G., F.A., Writing: G.A.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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