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Potential association of GCK rs2268576 and rs741038 polymorphisms with type 2 diabetes mellitus in the Turkish population

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ABSTRACT

Objective: Polymorphisms, defined as variations in specific genes, are common in human populations and usually do not cause disease. However, some may influence disease susceptibility or progression. This study aimed to investigate the potential association of two glucokinase (GCK) gene polymorphisms (rs2268576 and rs741038) with the development and metabolic regulation of type 2 diabetes mellitus.

Patients and Methods: A total of 134 individuals were enrolled, including 58 patients with type 2 diabetes and 76 non-diabetic controls from outpatient clinics. Genomic DNA was extracted from peripheral blood samples, and genotyping for rs2268576 and rs741038 was performed using real-time polymerase chain reaction (PCR). Genotypic distributions were compared between groups and correlated with laboratory parameters obtained during clinical follow-up.

Results: No significant differences were found in the genotypic distributions of rs2268576 and rs741038 between diabetic patients and controls (P> 0.05). Similarly, no association was observed with fasting glucose, postprandial glucose, or HbA1c. However, individuals with the GG genotype of rs741038 had significantly higher microalbumin/creatinine ratios (P = 0.03), suggesting a potential genetic link to diabetic nephropathy despite no association with diabetes development.

Conclusion: Although no relationship was found between these GCK polymorphisms and diabetes itself, the rs741038 GG genotype may indicate risk for diabetic nephropathy, independent of glycemic control.

Keywords: Type 2 diabetes, MODY2, GCK rs741038, GCK rs2268576, Diabetic nephropathy

1. INTRODUCTION

Diabetes is a significant health problem affecting approximately 537 million people worldwide and 10.5% of individuals aged 20 to 79 years [1,2]. Diabetes mellitus (DM) is defined by relative insulin deficiency or insulin resistance in peripheral tissues. These conditions lead to hyperglycemia, which causes multisystem complications and establishes DM as a chronic metabolic disease.

Maturity-onset diabetes of the young (MODY) is a rare, autosomal dominant form of diabetes caused by monogenic defects that impair pasancreatic β-cell function. It is frequently misdiagnosed as type 1 or type 2 diabetes, particularly in young adults [3,4]. MODY should be suspected in individuals diagnosed before age 25, with a family history spanning at least two generations, and stable glycemic control with minimal or no insulin (<0.5 U/kg). Other features include absence of autoimmune markers, no signs of insulin resistance (e.g. obesity, acanthosis nigricans, dyslipidemia), and the presence of mild to moderate hyperglycemia [5,6].

Among the subtypes, MODY 2 is caused by mutations in the glucokinase (GCK) gene and accounts for approximately 30–60% of all MODY cases. The GCK gene, located on chromosome 7p15.3–p15.1, encodes GCK, a key enzyme that acts as a glucose sensor in pancreatic β-cells. It plays a central role in glucose homeostasis by catalyzing the phosphorylation of glucose to glucose-6-phosphate. Individuals with MODY 2 typically exhibit mild, stable fasting hyperglycemia and rarely develop severe diabetic complications. Therefore, early diagnosis is

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crucial for preventing unnecessary insulin therapy and for guiding appropriate clinical management [6].

Type 2 diabetes mellitus (T2DM) remains a prevalent and growing health challenge, associated with both microvascular and macrovascular complications. Between 2000 and 2019, the age-adjusted mortality rate due to diabetes increased by 3%. In 2019 alone, diabetes and related kidney diseases were estimated to be responsible for approximately 2 million deaths worldwide [1,2]. These statistics highlight the importance of early diagnosis, timely initiation of treatment, and a comprehensive understanding of the factors involved in glucose regulation.

Lifestyle modifications, such as regular physical activity, healthy diet, maintaining normal body weight, and avoiding tobacco use have a key role in preventing and managing T2DM. However, in addition to environmental and behavioral factors, genetic predisposition plays a crucial role in disease susceptibility. In particular, GCK gene variations affecting glucose phosphorylation may influence both the development and regulation of T2DM. Understanding the effects of these polymorphisms is essential for a comprehensive view of the disease.

The aim of this study was to investigate whether GCK gene polymorphisms rs741038 and rs2268576 were associated with type 2 diabetes and whether they were related to the biochemical and demographic profiles of patients.

2. PATIENTS and MATERIALS

This study involved a total of 134 participants, including 58 individuals diagnosed with type 2 diabetes and 76 non-diabetic volunteers from the same outpatient internal medicine clinics. All participants were aged 18 years or older. Peripheral blood samples were collected into EDTA-containing tubes from all participants to prevent coagulation. The samples were stored at +4 °C until genomic DNA isolation was performed. Information about the participants and additional laboratory data were obtained and evaluated from the results of routine tests recorded in the hospital information system. The study was approved by the Yeditepe University Clinical Research Ethics Committee under protocol number 2170 (CREC Decision No. 1435, date: 05.05.2021) and was conducted in accordance with ethical and scientific standards.

Genomic DNA was extracted from peripheral blood samples using the Pure Link Genomic DNA Mini Kit (Invitrogen, Life Technologies; Thermo Fisher Scientific Inc., Waltham, MA, USA), following the manufacturer's instructions. DNA concentrations were measured using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific Inc., Waltham, MA, USA). The OD260/OD280 absorbance ratio was used to assess DNA purity, and only samples with a ratio between 1.8 and 2.0 were included in the study.

Genotyping was performed using the EZ-PCR method on a 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). The genotyped target regions were the GCK gene variants rs2268576 and rs741038, for which specific primers and probe sets, termed "TaqMan Genotyping Assays," were utilized.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation. The distribution of the continuous variables was assessed using the one-sample Kolmogorov-Smirnov test. For comparisons between two groups, the independent samples t-test was applied for normally distributed data, whereas the Mann–Whitney U test was used for non-normally distributed data. Comparisons among more than two groups were performed using one-way ANOVA for parametric data and the Kruskal–Wallis test for nonparametric data. Categorical variables were analyzed using the Chi-square (χ^2) test. Probability values were evaluated as two-tailed, and a P-value less than 0.05 was considered statistically significant.

3. RESULTS

This study involved a total of 134 participants, including 58 individuals diagnosed with type 2 diabetes in the patient group and 76 non-diabetic volunteers in the control group from the same outpatient clinics. The mean age of the participants was 51.96 ±11.43 years. There was no statistically significant difference in age between the diabetic and non-diabetic groups (53.60 ±10.07 vs. 50.70 ±12.25; P = 0.145). Demographic characteristics of the study groups are presented in Table I.

Table I. *Demographic characteristics of the patient and control groups*

PARAMETRE	Patient (n=58)	Control (n=76)	P Value
Height (cm)	165.68±10.77	166.2±9.82	0.774
Weight (kg)	78.93±15.39	79.28±17.76	0.907
BMI (kg/m^2)	28.62±4.1	28.74±5.37	0.889
FBG (mg/dl)	139±33.65	88.66±7.88	0.000*
HbA1C (%)	6.67±0.8	5.39±0.27	0.000*
T. Cholesterol (mg/dl)	189.45±38.41	202.56±36.7	0.051
Triglyceride (mg/dl)	190.44±123	143.01±85	0.014*
HDL (mg/dl)	50.78±12.18	52.2±13.43	0.533
LDL (mg/dl)	106.23±32.13	124.96±35.5	0.003*
AST (U/L)	20.13±9.36	21.4±10.87	0.484
ALT (U/L)	19.16±5.79	19.86±6.12	0.509
Creatinine (mg/dl)	0.84±0.18	0.77±0.15	0.018*

BMI: Body Mass Index: FBG: Fasting blood glucose, HbA1C: Glycated haemoglobin, HDL:High density lipoprotein, LDL: Low density lipoprotein, AST: Aspartate transaminase, ALT: Alanine transaminase. n=number of samples, (Mean ± Standard Deviation), P<0.05 values in the table indicate statistical significance (P). Differences in categorical data between groups were examined with the chi-square test and differences between the means of two independent samples were examined with the Student's t-test.*

When demographic data were compared, as expected, blood glucose, HbA1c, triglyceride, low-density lipoprotein (LDL)-cholesterol, and creatinine values were significantly higher in the patient group than in the control group (P<0.005). There was no significant difference in the genotypic (P = 0.236) and allelic (P =

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0.699) distribution of the C > T variation in the rs2268576 region of the GCK gene between the patient and control groups (Table II).

As shown in Table III, no statistically significant associations were observed between genotypes of the GCK rs2268576 polymorphism and laboratory parameters. Specifically, HbA1c, blood glucose, lipid profile, and liver and kidney function tests did not differ significantly among the genotypic groups (P > 0.05). However, although not statistically significant, participants with the CT genotype tended to have higher HbA1c levels compared to those with the CC and TT genotypes (P = 0.253).

Consistent with previous findings, subgroup analyses in diabetic (Table IV) and non-diabetic control participants (Table V) similarly showed no statistically significant differences among rs2268576 genotypes in relation to laboratory parameters (p > 0.05). However, although not statistically significant, participants with the CT genotype tended to have higher microalbumin levels compared to those with the CC and TT genotypes (P = 0.139).

Table II. *Comparison of genotypic and allelic distribution in the GCK gene rs2268576 region between patient and control groups*

Genotype rs2268576	Patient (n=58)	Control (n=76)	P value
CC	12 (%20.7)	23 (%30.3)	0.236
TT	14 (%24.1)	22 (%28.9)	
CT	32 (%55.2)	31 (%40.8)	
Allele	**Allele Frequency**		
C	56 (%48.3)	77 (%50.7)	0.699
T	60 (%51.7)	75 (%49.3)	

n=number of samples, (%) percentage of samples, P<0.05 values indicate statistical significance. Differences in categorical data between groups were examined with the Chi-square test.

Table III. *Comparison of laboratory parameters according to GCK rs2268576 genotypes in all participants*

		CC N:35	TT N:36	CT N:63	P Value
FBG (mg/dl)	Mean±SD	105.83±21.24	113.05±43.12	116.81±36.84	0.478
	Median (IQR)	97(21)	97(33)	109(46)	
PBG (mg/dl)	Mean±SD	124.28±53.11	158.75±74.58	154.45±86.71	0.476
	Median (IQR)	105(68)	139(133)	125(123)	
HbA1c (%)	Mean±SD	5.79±0.76	5.95±0.92	6.05±0.86	0.253
	Median (IQR)	5(0.8)	6(0.7)	6(1.3)	
BMI (kg/m^2)	Mean±SD	28.49±5.57	28.82±4.89	28.74±4.41	0.957
	Median (IQR)	29(7.3)	29(6.3)	28(6.1)	
AST (U/L)	Mean±SD	20.53±11.84	22.91±11.57	19.8±8.2	0.423
	Median (IQR)	16(12.3)	20(16.5)	18(9.5)	
ALT (U/L)	Mean±SD	19.66±4.6	21.27±8.78	18.49±4.19	0.310
	Median (IQR)	20(6.6)	19(8.3)	18(6.3)	
Total Cholesterol (mg/dl)	Mean±SD	199.34±39.3	196.33±34.1	195.78±39.7	0.905
	Median (IQR)	185(54.7)	194(54.6)	198(47.2)	
Triglyceride (mg/dl)	Mean±SD	143.1±105.88	157.07±74.79	178.41±118.7	0.076
	Median (IQR)	116(64.3)	134(91.6)	148(117.6)	
LDL (mg/dl)	Mean±SD	119.96±32.82	113.95±29.37	117.61±40.06	0.773
	Median (IQR)	114(47.5)	114(53)	115(40.1)	
HDL (mg/dl)	Mean±SD	54.76±14.03	51.55±12.82	49.86±12.1	0.197
	Median (IQR)	54(18.7)	48(16)	47(15)	
Creatinine (mg/dl)	Mean±SD	0.78±0.16	0.8±0.17	0.81±0.17	0.896
	Median (IQR)	1(0.23)	1(0.26)	1(0.22)	

FBG: Fasting blood glucose, PBG: Postprandial blood glucose, HbA1C: Glycated haemoglobin, BMI: Body Mass Index, AST: Aspartate transaminase, ALT: Alanine transaminase HDL:High density lipoprotein, LDL: Low density lipoprotein. n=number of samples, (Mean ± Standard Deviation), Median (interquartile range), p<0.05 values in the table indicate statistical significance. Differences in categorical data between groups were examined with Kruskal Wallis test.(Comparisons performed among CC, TT, and CT genotypes.)

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Table IV. *Comparison of laboratory parameters according to GCK rs2268576 genotypes in diabetic patients*

		CC N:12	TT N:14	CT N:32	P Value
FBG (mg/dl)	Mean±SD	129.08±28.35	150.5±48.85	143.15±33.58	0.641
	Median (IQR)	133(55.8)	141(67)	133(34)	
PBG (mg/dl)	Mean±SD	160±54.63	203.28±65.58	209.61±83.09	0.324
	Median(IQR)	152(80)	167(125)	193(116)	
HbA1c (%)	Mean±SD	6.58±0.75	6.76±1.02	6.67±0.74	0.954
	Median(IQR)	7(0.9)	7(1.6)	7(0.85)	
BMI (kg/m^2)	Mean±SD	28.5±2.04	29.33±5.54	28.35±4.03	0.982
	Median(IQR)	29(3.2)	29(5.54)	27(5.1)	
AST (U/L)	Mean±SD	17.42±6.09	25.96±14.99	18.54±5.57	0.303
	Median(IQR)	16(10.47)	20(21.8)	17(7.9)	
ALT (U/L)	Mean±SD	18.57±3.02	22.28±9.59	17.98±3.63	0.485
	Median(IQR)	18(3.2)	19(13.8)	18(6.7)	
Total Cholesterol (mg/dl)	Mean±SD	207.74±43.63	189.37±36.85	182.4±35.81	0.315
	Median(IQR)	184(50.3)	190(61.6)	180(42.4)	
Triglyceride (mg/dl)	Mean±SD	169.24±78.82	172.82±77.52	206.6±150.88	0.907
	Median(IQR)	142(172)	151(114.3)	161(180.8)	
LDL (mg/dl)	Mean±SD	122.14±35.61	103.38±31.18	100.63±29.8	0.224
	Median(IQR)	112(35.1)	102(36.7)	99(92.7)	
HDL (mg/dl)	Mean±SD	53.65±13.56	53.01±14.87	48.66±10.16	0.586
	Median(IQR)	52(17.2)	50(23)	47(13.5)	
Creatinine (mg/dl)	Mean±SD	0.8±0.19	0.86±0.16	0.85±0.19	0.623
	Median(IQR)	1(0.365)	1(0.16)	1(0.31)	
Microalbumin/creat. (mg/g)	Mean±SD	15.77±14.81	9.81±8.3	34.45±63.05	0.110
	Median(IQR)	9(14.7)	5(13)	10(28.7)	

FBG: Fasting blood glucose, PBG: Postprandial blood glucose, HbA1C: Glycated haemoglobin, BMI: Body Mass Index, AST: Aspartate transaminase, ALT: Alanine transaminase HDL:High density lipoprotein, LDL: Low density lipoprotein. n=number of samples, (Mean ± Standard Deviation), Median (interquartile range), p<0.05 values in the table indicate statistical significance(p). Differences in categorical data between groups were examined with Kruskal Wallis test.(Comparisons were performed among CC, TT, and CT genotypes.)*

Table V. *Comparison of laboratory parameters according to GCK rs2268576 genotypes in control participants*

		CC N:23	TT N:22	CT N:31	P Value
FBG (mg/dl)	Mean±SD	93.15±6.9	89.22±9.6	88.72±8.21	0.560
	Median (IQR)	92(10)	87(5.9)	88(8.3)	
PBG (mg/dl)	Mean±SD	88.57±12.29	96.4±22.72	89.27±19.45	0.727
	Median(IQR)	85(23)	95(40.5)	84(22)	
HbA1c (%)	Mean±SD	5.35±0.23	5.44±0.26	5.39±0.31	0.560
	Median(IQR)	5(0.4)	5(0.4)	5(0.3)	
BMI (kg/m^2)	Mean±SD	28.48±6.78	28.46±4.49	29.13±4.82	0.858
	Median(IQR)	28(9.4)	28(7.5)	28(6.7)	
AST (U/L)	Mean±SD	22.23±13.86	20.97±8.61	21.1±10.18	0.946
	Median(IQR)	17(17.9)	20(12.6)	18(10)	
ALT (U/L)	Mean±SD	20.25±5.23	20.62±8.4	19.02±4.7	0.543
	Median(IQR)	21(8.4)	19(5.9)	18(6.2)	
Total Cholesterol (mg/dl)	Mean±SD	194.76±36.98	200.76±32.28	209.59±39.32	0.495
	Median(IQR)	190(135)	200(53)	210(162)	
Triglyceride (mg/dl)	Mean±SD	128.84±117.31	147.04±73.03	150.22±65.15	0.066
	Median(IQR)	105(54)	123(93)	137(103)	
LDL (mg/dl)	Mean±SD	118.77±32.01	120.68±26.72	132.39±42.35	0.554
	Median(IQR)	114(50.1)	118(42.2)	130(61.1)	
HDL (mg/dl)	Mean±SD	55.37±14.55	50.63±11.61	51.06±13.84	0.332
	Median(IQR)	55(18.9)	48(14.7)	47(18.7)	

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Creatinine (mg/dl)	Mean±SD	0.77±0.14	0.77±0.18	0.77±0.13	0.868
	Median(IQR)	1(0.17)	1(0.29)	1(0.24)	
HOMA-IR	Mean±SD	2.85±2.89	2.66±3.09	1.94±0.87	0.645
	Median(IQR)	2(1.7)	2(1.4)	2(1.6)	

FBG: Fasting blood glucose, PBG: Postprandial blood glucose, HbA1C: Glycated haemoglobin BMI: Body Mass Index, AST: Aspartate transaminase, ALT: Alanine transaminase HDL:High density lipoprotein, LDL: Low density lipoprotein. n=number of samples, (Mean ± Standard Deviation), Median (interquartile range), p<0.05 values in the table indicate statistical significance. Differences in categorical data between groups were examined with Kruskal Wallis test.(Comparisons were performed among CC, TT, and CT genotypes.)

Table VI presents the genotypic and allelic distribution of the *GCK* gene polymorphism rs741038. No statistically significant differences in genotype frequencies were observed between the patient and control groups (P = 0.759). Similarly, the allele-based comparison showed no significant association between the G and A alleles and diabetes status (P= 0.496).

Similar to the findings for rs2268576, no statistically significant differences were observed in laboratory parameters among the different genotypes of rs741038 when all participants were analyzed (P > 0.05). As shown in Table VII, although participants with the AA genotype of the GCK rs741038 polymorphism exhibited higher mean levels of fasting blood glucose (120.85 ± 43.49 mg/dL), postprandial blood glucose (192.66 ± 87.59 mg/dL), and HbA1c (6.05 ± 0.82%) compared to those with GG and GA genotypes, these differences were not statistically significant (FBG P = 0.919; PBG P= 0.227; HbA1c p = 0.854). Even though there were no statistically significant results, for postprandial blood glucose (PBG, P = 0.227), LDL cholesterol (p = 0.170), and total cholesterol (P = 0.187), a statistical trend was noted, with the AA genotype showing higher levels than the GG and GA groups.

According to the data presented in Table VIII, no statistically significant differences were observed among rs741038 genotypes in diabetic patients with respect to FBG, PBG, HbA1c, BMI, and standard liver and kidney function tests. However, a significant difference was detected in the microalbumin/creatinine ratio (P= 0.03), which was markedly higher in participants with the AA genotype (44.48 ± 72.97 mg/g) and lower in those with the GA genotype (9.61 ± 7.95 mg/g).

Table VI. *Comparison of genotypic and allelic distribution in the GCK gene rs741038 region between patient and control groups*

Genotype rs741038	Patient (n=58)	Control (n=76)	P value
GG	23 (%39.6)	35 (%46)	0.759
AA	7 (%12.1)	8 (%10.6)	
GA	28 (%48.3)	33 (%43.4)	
Allele	**Allele Frequency**		
G	74 (%63.8)	103 (%67.8)	0.496
A	42 (%36.2)	49 (%32.2)	

n=number of samples, (%) percentage of samples, P<0.05 values indicate statistical significance. Differences in categorical data between groups were examined with the chi-square test.

Table VII. *Comparison of laboratory parameters according to GCK rs741038 genotypes in all participants*

		GG N:58	AA N:15	GA N:61	P Value
FBG (mg/dl)	Mean±SD	110.90±35.56	120.85±43.49	113.1±35.08	0.919
	Median (IQR)	99(32)	111(68.1)	97.5(42.6)	
PBG (mg/dl)	Mean±SD	141.86±77.58	192.66±87.59	139.77±69.69	0.227
	Median (IQR)	130(73.8)	179(166.8)	115(93.2)	
HbA1c (%)	Mean±SD	5.95±0.92	6.05±0.82	5.94±0.8	0.854
	Median (IQR)	6(11.5)	6(1.52)	6(1.3)	
BMI (kg/m^2)	Mean±SD	28.98±4.74	27.98±4.1	28.59±5.14	0.791
	Median (IQR)	29(6.2)	28(30.8)	27(7)	
AST (mg/dl)	Mean±SD	21.68±10.61	21.06±11.55	20±9.61	0.487
	Median (IQR)	20(11.7)	19(10.9)	16(10.5)	
ALT (mg/dl)	Mean±SD	20.48±7.58	19.8±5.14	18.62±4.03	0.643
	Median (IQR)	19(7.4)	18(7.2)	18(5.8)	
Total Cholesterol (mg/dl)	Mean±SD	190.65±31.4	213.54±50.59	198.61±39.15	0.187
	Median (IQR)	186(42.7)	220(53)	201(55)	
Triglyceride (mg/dl)	Mean±SD	165.59±118.1	169.71±77.02	159.95±99.92	0.664
	Median (IQR)	134(110.6)	145(145.1)	133(97.1)	

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LDL (mg/dl)	Mean±SD	110.77±28.76	127.97±50.05	120.35±35.81	0.170
	Median (IQR)	109(36.1)	131(32.7)	114(45.5)	
HDL (mg/dl)	Mean±SD	49.99±12.62	54.33±13.95	52.41±12.87	0.335
	Median (IQR)	47(14)	52(19.4)	51(15.6)	
Creatinine (mg/dl)	Mean±SD	0.79±0.17	0.82±0.16	0.81±0.17	0.652
	Median (IQR)	1(0.23)	1(0.27)	1(0.31)	

FBG: Fasting blood glucose, PBG: Postprandial blood glucose, HbA1C: Glycated haemoglobin BMI: Body Mass Index, AST: Aspartate transaminase, ALT: Alanine transaminase HDL:High density lipoprotein, LDL: Low density lipoprotein. n=number of samples, (Mean ± Standard Deviation), Median (interquartile range), p<0.05 values in the table indicate statistical significance(p). Differences in categorical data between groups were examined with Kruskal Wallis test.(Comparisons were performed among GG, AA, and GA genotypes.)*

Table VIII. *Comparison of laboratory parameters according to GCK rs741038 genotypes in diabetic patients*

		GG N:23	AA N:7	GA N:28	P Value
FBG (mg/dl)	Mean±SD	140.45±40.47	156.67 ±32.61	139.64±35.36	0.329
	Median (IQR)	127(59.2)	152(39.9)	132(36.2)	
PBG(mg/dl)	Mean±SD	186±80.81	212.2±82.03	197.5±64.23	0.634
	Median (IQR)	155(147.5)	196(153.5)	189(113.7)	
HbA1c (%)	Mean±SD	6.72±1.01	6.71±0.62	6.62±0.66	0.950
	Median (IQR)	7(1.4)	7(1.3)	7(0.8)	
BMI (kg/m^2)	Mean±SD	29.51±4.22	26.83±3.08	28.33±4.15	0.198
	Median (IQR)	29(3.5)	26(6)	27(5)	
AST (U/L)	Mean±SD	23.04±12.58	16.28±4.49	18.81±6.43	0.389
	Median (IQR)	19(14.1)	16(8.8)	18(10)	
ALT (U/L)	Mean±SD	20.68±7.95	17.56±3.37	18.37±3.82	0.614
	Median (IQR)	18(8.4)	17(6.9)	18(6.9)	
Total Cholesterol (mg/dl)	Mean±SD	182.84±29.17	200.34±47.93	191.92±42.61	0.713
	Median (IQR)	183(37.1)	183(49.1)	190(57)	
Triglyceride (mg/dl)	Mean±SD	218.43±154.87	185.7±101.12	169.64±96.75	0.562
	Median (IQR)	162(80.2)	141(105.3)	145(97.9)	
LDL (mg/dl)	Mean±SD	98.24±23.29	110.5±45.62	110.74±33.7	0.436
	Median (IQR)	102(33)	109(21.3)	101(32)	
HDL (mg/dl)	Mean±SD	47.24±10.82	58.57±15.26	51.61±11.75	0.114
	Median (IQR)	46(14.6)	55(22.3)	50(13.4)	
Creatinine (mg/dl)	Mean±SD	0.85±0.19	0.79±0.15	0.85±0.19	0.837
	Median (IQR)	1(0.25)	1(0.23)	1(0.29)	
Microalbumin/ Creatinine (mg/g)	Mean±SD	44.48±72.97	22.42±21.18	9.61±7.95	0.03*
	Median (IQR)	20(40.5)	9(34.8)	6(7.2)	

FBG: Fasting blood glucose, PBG: Postprandial blood glucose, HbA1C: Glycated haemoglobin BMI: Body Mass Index, AST: Aspartate transaminase, ALT: Alanine transaminase HDL:High density lipoprotein, LDL: Low density lipoprotein. n=number of samples, (Mean ± Standard Deviation), Median (interquartile range), p<0.05 values in the table indicate statistical significance(p). Differences in categorical data between groups were examined with Kruskal Wallis test.(Comparisons were performed among GG, AA, and GA genotypes.)*

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As shown in Table IX, no statistically significant associations were observed between rs741038 genotypes and laboratory parameters in the control group (P> 0.05).

Table IX. *Comparison of laboratory parameters according to GCK rs741038 genotypes in Control participants*

		GG N:35	AA N:8	GA N:33	P Value
FBG (mg/dl)	Mean±SD	91.48±9.01	85.04±6.57	89.89±7.85	0.123
	Median (IQR)	90(13)	82(9.7)	89(9.8)	
PBG (mg/dl)	Mean±SD	88.9±18.67	95±01	91.67±18.51	0.762
	Median (IQR)	84(16)	95(0)	90(27.8)	
HbA1c (%)	Mean±SD	5.44±0.31	5.38±0.23	5.34±0.24	0.087
	Median (IQR)	5(0.4)	5(0.5)	5(0.3)	
BMI (kg/m²)	Mean±SD	28.61±5.11	28.99±4.79	28.82±5.9	0.934
	Median (IQR)	28(7.7)	29(5.5)	28(8.5)	
AST (U/L)	Mean±SD	20.82±9.26	25.83±14.68	21.05±11.72	0.541
	Median (IQR)	20(11.9)	23(30.9)	16(13.4)	
ALT (U/L)	Mean±SD	20.35±7.46	22.04±5.85	18.84±4.26	0.397
	Median (IQR)	19(6.1)	23(4.3)	19(6.2)	
Total Cholesterol (mg/dl)	Mean±SD	195.56±32.17	225.08±53.14	204.65±35.35	0.190
	Median (IQR)	186(48.2)	225(48.1)	213(43.5)	
Triglyceride (mg/dl)	Mean±SD	132.38±72.24	155.72±51.2	151.47±103.38	0.294
	Median (IQR)	115(91)	148(60)	118(102.8)	
LDL (mg/dl)	Mean±SD	117.58±29.44	143.25±51.52	128.46±36.03	0.247
	Median (IQR)	116(49.2)	132(34.8)	128(41.7)	
HDL (mg/dl)	Mean±SD	51.72±13.49	50.62±12.5	53.11±13.92	0.806
	Median (IQR)	48(20.4)	46(16.9)	51(16.8)	
Creatinin(mg/dl)	Mean±SD	0.75±0.15	0.85±0.17	0.77±0.14	0.379
	Median (IQR)	1(0.20)	1(0.37)	1(0.22)	
HOMA-IR	Mean±SD	1.65±0.84	2.36±0.55	3.06±3.26	0.183
	Median (IQR)	1(1.05)	2(1.03)	2(1.87)	

FBG: Fasting blood glucose, PBG: Postprandial blood glucose, HbA1C: Glycated haemoglobin BMI: Body Mass Index, AST: Aspartate transaminase, ALT: Alanine transaminase HDL:High density lipoprotein, LDL: Low density lipoprotein. n=number of samples, (Mean ± Standard Deviation), Median (interquartile range), p<0.05 values in the table indicate statistical significance. Differences in categorical data between groups were examined with Kruskal Wallis test. (Comparisons were performed among GG, AA, and GA genotypes.)

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4. DISCUSSION

Mutations refer to permanent changes in the DNA sequence that can impair protein function, structure, or expression and are often linked to pathological conditions. By contrast, polymorphisms are stable genetic variants with a minor allele frequency of at least 1% in the population, and they are generally not associated with disease phenotypes.

In this study, we examined the potential associations between two GCK gene polymorphisms (rs2268576 and rs741038), with the development and regulation of diabetes. Although certain genotypes of these variants showed a trend toward increased susceptibility, the associations did not reach statistical significance. Notably, analysis of the microalbumin/creatinine ratio, a clinical marker of diabetic nephropathy, revealed a statistically significant difference among rs741038 genotypes.

In a study by Ansari and colleagues involving 180 individuals with T2DM and 120 controls, it was found that the GCK rs1799884 SNP was associated with T2DM development, with the A allele identified as a major risk factor relative to the G allele [7]. Similarly, a meta-analysis by Li et al. confirmed the role of the A allele in GCK rs1799884 in T2DM development [8]. Zang et al., examined six GCK single nucleotide polymorphisms (SNPs) and found significant associations with T2DM for rs2971672 and rs12702070, while the remaining variants showed no such relationship [9]. In line with our findings, Yılmaz et al., investigated four GCK variants (rs2268574, rs2268576, rs758898, and rs741038) and reported no statistically significant differences in genotype frequencies between diabetic and control groups [10].

Sun and colleagues studied 499 individuals with T2DM and 499 healthy subjects, finding that the genotypic distribution of GCK rs12702070 differed between the diabetes and control groups, while rs2268573, rs2268549, and rs1476891 showed no significant differences [11]. A Finnish study evaluated six GCK-related polymorphisms among the 35 most common SNPs to assess their relationship with DM. Among these, GCK rs2244164 was associated with DM, while no correlation was found with rs2284769, rs2284773, rs12534623, rs2268573 and rs882020 [12]. In a study conducted by Frigeri et al., no relationship was found between the GCK rs144723656, rs2268574, and rs2268575 polymorphisms and the presence of T2DM [13].

In our study, two GCK-related SNPs (rs2268576 and rs741038) were compared for their relationship with diabetes. The CT genotype of GCK rs2268576 was more common in T2DM patients than in controls (55% vs. 40.8%), but the difference was not statistically significant (P =0.236). Similarly, GCK rs741038 genotype distributions showed no significant difference between T2DM patients and the control group (p = 0.759).

In addition to studies focusing on the presence of diabetes, numerous investigations have examined the effects of *GCK* gene polymorphisms on laboratory parameters. Holmkvist et al., reported that rs758989, rs2244164, rs1303722, and rs1799884 were not associated with T2DM. However, the rs1799884 variant was significantly associated with elevated fasting plasma glucose concentrations [14]. Winkler et al., analyzed 22 common *GCK* gene variants and identified a significant association between rs1799884 and fasting blood glucose levels. In addition, the presence of the A allele in maternal rs1799884 was associated with an increase of 32 grams in offspring birth weight [15]. In a study involving 870 non-diabetic and 835 diabetic women, the GCK rs1799884 polymorphism was significantly associated with gestational diabetes mellitus (GDM), whereas no other SNPs showed a significant association. Additionally, individuals with the TT genotype of GCK rs4607517 had significantly higher fasting blood sugar levels compared to those with other genotypes [16]. A meta-analysis including 2632 diabetic and 2050 non-diabetic Japanese individuals found that GCK rs4607517 was significantly associated with HbA1c levels, but not with fasting glucose [17]. In our study, individuals with the CC genotype for GCK rs2268576 had lower FBG, PPG, and HbA1c values than other genotypes, while those with the CT genotype had higher values. However, these differences were not statistically significant. Similarly, for GCK rs741038, individuals with the AA genotype showed slightly higher fasting blood glucose, postprandial blood glucose, and HbA1c values compared to other genotypes, but these differences were not statistically significant.

Hyperlipidemia and its regulation remain major concerns in diabetic patients due to their critical role in the development of cardiovascular complications. In a study by Yılmaz et al., which investigated the association between four *GCK* gene polymorphisms and diabetes, the rs2268574 variant was associated with high-density lipoprotein (HDL) levels, while no associations were found with other lipid parameters. Additionally, individuals with the GG genotype of rs741038 exhibited higher LDL levels compared with other genotypes [10]. In our study, participants with the CT genotype of rs2268576 showed elevated triglyceride and reduced HDL levels, whereas those with the AA genotype of rs741038 had increased levels of triglycerides, LDL, and HDL. Although these differences did not reach statistical significance, the trends observed suggest that lipid profiles may vary according to GCK genotype, and further investigation into their potential contribution to hyperlipidemia risk may be warranted.

There are limited studies examining the association between GCK polymorphisms and diabetic nephropathy. In a study conducted by Leak and colleagues on 638 African American individuals, it was suggested that GCK rs730497 plays a role in the development of end-stage renal disease (ESRD) [18]. In our study, we explored whether there were differences in the genotypes of GCK polymorphisms and microalbumin/creatinine ratios, as early indicators of diabetic nephropathy, among diabetic patients. Microalbumin/creatinine ratios were significantly higher in individuals with the GG genotype for GCK rs741038 compared to others (P= 0.03). Although microalbumin/creatinine ratios were higher in individuals with the CT genotype for GCK rs2268576 than in those with other genotypes, this difference did not reach statistical significance (P = 0.110). In our study, since FBG, PPG, and HbA1c values were higher in individuals with the AA genotype for GCK rs741038 compared to other groups, and microalbumin/creatinine ratios were elevated in those with the GG genotype for GCK rs741038, the GG genotype may be considered an independent risk factor for the development of microalbuminuria, regardless of high blood sugar levels.

In conclusion, GCK polymorphisms rs2268576 and rs741038 were not found to exert significant effects on diabetes development or blood sugar regulation. However, individuals with the GG genotype for GCK rs741038 appear to have a significant risk of nephropathy, independent of blood sugar regulation. We suggest that the varying results across studies on GCK gene polymorphisms in T2DM likely arise from differences in ethnicity, environmental factors, and lifestyle.

Limitations

This study has several limitations that should be acknowledged. First, the sample size, particularly the diabetic patient group (n=58) was relatively small, which may have reduced the statistical power to detect subtle genotype– phenotype associations. Second, the study was conducted at a single center, and all participants were of Turkish origin, which may limit the generalizability of the findings to other populations. Finally, the cross-sectional design prevents the establishment of any causal relationships between GCK polymorphisms and clinical outcomes.

Conclusion

Despite the limitations, this study provides valuable preliminary data and serves as an important reference point for future research. Larger, multicenter studies with expanded sample sizes can build upon these findings, but our results contribute meaningful insights into the potential role of GCK polymorphisms in diabetes and its complications.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Yeditepe University Clinical Research Ethics Committee under protocol number 2170 (CREC Decision No. 1435, date: 05.05.2021) and was conducted in accordance with ethical and scientific standards.

Conflict of interest: The author declare that there is no conflict of interest.

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Author contributions: YS: Main author. Responsible for study design, patient follow-up, data analysis, statistical evaluation, and manuscript writing, SGY: Contributed to the study design and coordination of the research process, FTA: Contributed to laboratory procedures and sample processing, SIG: Assisted in laboratory testing and technical work, OEU: Supported patient monitoring and data collection, MS: Assisted with patient monitoring and contributed to the manuscript drafting process, HA: Supervisor of the thesis. Provided support in study design and manuscript preparation, TI: Contributed to study design, laboratory supervision, and manuscript editing.

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