RESEARCH ARTICLE

GLUCOKINASE (GCK) RS4607517 POLYMORPHISM FREQUENCY AND NUTRITIONAL HABITS IN PATIENTS WITH TYPE 2 DIABETES

Nazan SON ERENOĞLU[1], Osman SON[2], Evrim Suna ARIKAN SÖYLEMEZ[3*]

[1]Department of Nutrition and Dietetic, Faculty of Health Sciences, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey
[2]Endocrinology and Metabolism Diseases Polyclinic, Eskişehir Private Anadolu Hospital, Eskişehir, Turkey
[3]Department of Medical Biology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

*Corresponding Author : arikanmt@gmail.com

ABSTRACT

Background: The aim of this study was to investigate nutritional habits, biochemical markers and the allele and genotype frequencies of *GCK* rs4607517 - 30G>A polymorphism of patients with Type 2 Diabetes Mellitus (T2DM).

Methods: The study was conducted with 200 T2DM patients and 100 controls. The analysis of *GCK* Gene rs4607517 - 30G>A polymorphism was performed by Real-Time PCR method. The Attitude Scale for Healthy Nutrition was applied to the intervention group. Additionally, the sociodemographic data of the patients were collected, anthropometric measurements were performed and their biochemical markers were examined.

Results: The mean duration of diabetes of the patients was 7.94±5.81 years, the mean age 55.88±12.23 years, the mean BMI 30.14±5.91 kg/m^2, and the mean HbA1c value was 7.74±1.97. There was no difference between allele and genotype frequencies of two groups (p>0.05). The anthropometric and biochemical values of the patients with different genotype was similar (p0,05). Furthermore, as the HbA1c values of the patients increased, the Malnutrition score was found to increase, and there was a statistically significant found between the groups (p=0.012).

Conclusion: Although there are studies related to the effect of rs4607517 polymorphism in the GCK gene on the development of T2DM, the fact that the frequency of polymorphism of the patient group in our study was similar to the control group makes it necessary for the variant to be screened in larger patient populations. The majority of patients with T2DM were found to have high levels of HbA1c, LDL cholesterol, and triglycerides, inadequate level of nutrition knowledge and were obese.

Keywords: Type 2 diabetes, Nutrition, *GCK*, rs4607517.

INTRODUCTION

Diabetes, which comes from Diabetes Mellitus (DM) in Latin[1], is a metabolic disease that occurs with the decrease and/or disappearance of the function of the insulin hormone in the body.[2] DM has become a major health problem all over the world due to its increasing prevalence. Currently, it is estimated that approximately 422 million adults worldwide have diabetes and 1.6 million individuals die from diabetes and its complications per year.[3] Statistics report that 347 million people worldwide had diabetes in 2017, with more than 90% of cases being T2DM. These numbers are estimated to increase by 55% until 2035 unless necessary measures are taken.[4,5] The most important cause of this rapid increase in DM is obesity, which is increasing like an epidemic all over the world. Medical nutrition therapy (MNT), medical treatment, lifestyle change, and physical activity recommendations have been noted as the treatment methods of DM.[4-6] The fact that MNT is included in all of the treatment options recommended for a good glycaemic control indicates the importance of MNT to control the disease.[7]

Glucokinase (GCK) is an enzyme involved in glucose metabolism and glucose-stimulated insulin secretion. GCK is a hexokinase isozyme (hexokinase IV) that catalyzes glucose to glucose-6-phosphate (G6P) and is involved in the first step of both glycolysis and glycogen synthesis. *GCK* is predominantly expressed in hepatocytes and pancreatic beta cells. The pancreatic beta-cell isoform is an important enzyme in regulating glucose-stimulated insulin secretion

and is considered a glucose sensor. The liver isoform plays a central role in the regulation of glucose homeostasis and is an essential component of the hepatic glucose sensing system involved in glucose synthesis, glycolysis, and storage of glucose.[8-10] Mutations in this gene that alter the enzyme activity have been associated with congenital diabetes and hyperinsulinemic hypoglycemia. Furthermore, rare heterozygous inactivating mutations in *GCK* lead to Maturity-Onset Diabetes of the Young (MODY), which emerges fundamentally due to reduced insulin secretion stimulated by glucose.[11] Rare mutations in GCK lead to MODY, while common variants in other populations have been associated with HbA1c levels, fasting glucose concentrations, and T2DM.[12-14]

In this study, allele frequencies and genotype frequencies of *GCK* rs4607517 - 30G>A polymorphism were determined in 200 T2DM patients and 100 control individuals. The effect of demographic characteristics on the nutritional habits of patients with T2DM was evaluated and the relationship between the nutritional habits of diabetic patients and the variables related to diabetes has been revealed. A comparison was performed between the biochemical parameters of the T2DM patients with their attitudes towards healthy nutrition.

METHODS

In this study, a 2cc blood sample was taken into one-5cc EDTA tube from 200 volunteer patients, who were diagnosed with T2DM, and 100 healthy control groups who applied to Eskişehir Private Anadolu Hospital Endocrinology and Metabolism Diseases Polyclinic. The Attitude Scale for Healthy Nutrition (ASHN), taking approximately 5 minutes to complete, was also applied. The height of the participants was measured with a fixed millimetric height scale, and their body weight was measured with a fixed floor scale by the same person. BMI values were calculated after the body weight and height data of the participants were recorded on the personal information forms [Formula: Body Mass Index (BMI) = Body Weight (kg)/Height $(m)^2$]. In individuals with diabetes, other anthropometric values (waist/hip) were measured by the same person using a tape measure. Furthermore, age, gender, duration of diabetes, which food group they consume more in their daily nutrition were asked and noted. The results of fasting blood sugar (FBS), creatinine, ALT, uric acid, LDL-cholesterol, triglyceride, HbA1c, hemoglobin and hematocrit values were recorded from the biochemical parameters of patients with T2DM.

The Attitude Scale for Healthy Nutrition (ASHN)

The Turkish Validity and Reliability Study of the scale were conducted by Tekkurşun Demir and Cicioğlu in 2019. The ASHN has a structure consisting of 21 items and 4 sub-dimensions. These sub-dimensions have been named Information on Nutrition (IN), Emotion for Nutrition (EN), Positive Nutrition (PN), and Malnutrition (MP). A higher value of the total score of the scale (TSS) obtained from the scale indicates healthy nutritional habits. The participants would be considered to have a very low level of attitude towards healthy nutrition with a score of 21 from the ASHN, a low level with a score of 22-42, a medium level with a score of 43-63, a high level with a score of 64-84 and high level of attitude towards healthy nutrition at an ideal level with a score of 85-110.[15]

Genetic Analysis

Total DNA Isolation from Peripheral Blood Samples: Genomic DNA was obtained from peripheral blood using the relevant DNA isolation procedures (Invitrogen™ PureLink™ Genomic DNA Mini Kit, Cat No: K182002, USA) and its quantity and purity were determined with Promega QuantiFluor E6090 (Promega, Madison, USA) and stored at -20°C until use.

Genotype Analysis of GCK Gene rs4607517 - 30G>A Polymorphism: Genotype analysis of the GCK gene rs4607517 (-30G>A) polymorphism was performed using the Applied Biosystems 3130XL Genetic Analyzer (USA). MyTaq™ HS DNA Polymerase (Bioline, Meridian Bioscience, Tennessee, USA) was used in the reaction mixture, and the relevant primers were designed by Sentebiolab (ANKARA). Based on the results of the sequence analysis, the cases were determined as wild, heterozygous, and homozygous, and the frequencies of alleles and genotypes of the rs4607517-30G>A polymorphism were calculated.

Statistical analysis: In this study, the data were entered in SPSS-19 version, while "Student's *t*-test" or "Fisher's exact test", "Kruskal-Wallis Test" and "x^2" test methods were used for the comparison of age, BMI, gender, alleles and genotype frequencies between the patients with T2DM and control group. Odds ratio (OR) was calculated by logistic regression analysis at a 95% confidence interval to determine the relationship between disease and age, gender, and genotype. Allele and genotype frequencies of the studied gene polymorphism and its relationship with T2DM were analyzed with the “chi-square” test. The deviation from the Hardy-Weinberg Equilibrium was tested with the "chi-square test". P0.05 was considered significant. The Kruskal Wallis test was used for the evaluation of the relationship between genotype groups and clinical data.

This study was approved by the Ethics Committee of Afyonkarahisar Health Sciences University (05.06.2020/248) and informed consent was obtained from all the participants.

RESULTS

Of the 200 patients with T2DM included in the study, 59.5% were female and 40.5% were male. The mean duration of diabetes of the patients was 7.94±5.81 years, the mean of was age 55.88±12.23 (22-75) years, the of mean BMI 30.14±5.91 kg/m^2, and the of mean HbA1c value was to was 7.74±1.97. The majority of the patients in the study were either overweight (36.5%) or obese (46%) (p<0.001). As the HbA1c level increases, the level of nutrition knowledge decreases (p=0.004). Although there was no statistically significant difference the increasing of LDL cholesterol values increased as the HbA1c levels of the patients'. Although there was no statistically significant difference found, the triglyceride levels of the obese and overweight patients were found to be higher compared to normal-weight patients in the study (p=0.11).

In the grouping of the HbA1c values, the HbA1c values of the patients have increased along with the increase increasing of FBS, duration of DM and Triglyceride levels, and there was a statistically significant difference (P<0.001). With an increase in the HbA1c values of the patients, LDL cholesterol, ALT, Hematocrit, and Creatinine values increased systematically at minimal levels, however, there was no statistically significant difference between the groups. The ASHN, which was applied to measure the patients' attitudes towards healthy nutrition and their nutritional habits, and HbA1c grouping were cross-compared. The IN (P=0.003), PN (P=0.023), EN (P=0.281), TSS (P=0.003) scores were found to decrease with an increase in the HbA1c values of the patients, and there was a statistically significant difference between the groups in terms of IN, PN, and TSS. Furthermore, according to the results, the MN score was found to increase with an increase in the HbA1c values of the patients and there was a statistically significant difference between the groups (P=0.012) (Table 1).

Table 1. Comparison of patients' HbA1c grouping and clinical data

		HbA1c Grouping				
		<=6 (n=37) mean±sd. (min-max)	**6.1-7.9 (n=91) mean±sd. (min-max)**	**8-9.9 (n=43) mean±sd. (min-max)**	**10 = > (n=29) mean±sd. (min-max)**	**p**
Age Year		54.81±13.81 (23-75)	56.17±12.37 (22-75)	56.81±12.64 (23-75)	54.96±9.08 (33-70)	0.706
Duration of DM		5.00±4.89 (1-20)	7.52±4.85 (1-20)	10.95±6.59 (1-25)	8.59±6.50 (1-25)	< 0.001
BMI (kg/m^2)		30.41±6.18 (22-47)	29.86±5.57 (18-50)	30.25±6.93 (18-61)	30.49±5.22 (22-45)	0.936
FBS mg/dl		121.00±58.35 (77-450)	131.71±31.72 (58-220)	181.95±54.10 (90-360)	256.41±85.26 (89-499)	< 0.001
ALT		21.89±17.69 (8-104)	26.00±23.25 (7-162)	24.06±20.70 (5-101)	23.10±10.25 (11-53)	0.290
LDL (mg/dl)		127.40±30.68 (84-190)	136.67±33.99 (65-245)	124.04±34.28 (64-234)	211.00±126.68 (47-211)	0.113
Hematocrit (%)		42.38±3.93 (36-55)	43.03±6.75 (30-92)	41.39±4.77 (28-51)	44.15±4.60 (32-53)	0.056
Creatinine (U/L)		0.88±0.23 (0.5-2)	0.81±0.18 (0.5-2)	0.85±0.27 (0.5-2)	0.88±0.39 (0.5-2.5)	0.643
Uric Acid (mg/dl)		5.65±1.57 (3-10)	5.00±1.84 (1-17)	4.61±1.11 (2-7)	4.64±1.50 (2-8)	0.003
Triglycerides (mg/dl)		166.70±103.69 (59-547)	170.95±93.25 (41-489)	185.90±104.48 (58-513)	209.72±21.92 (54-1192)	< 0.001
ASHN	**IN**	17.75±3.95 (11-25)	16.21±4.00 (6-25)	14.76±4.49 (7-25)	14.20±4.46 (7-24)	0.003
	EN	24.16±2.90 (17-30)	22.81±3.93 (14-30)	23.11±4.50 (12-30)	22.27±4.60 (14-30)	0.281
	PN	21.64±2.38 (16-25)	20.74±2.88 (12-25)	19.79±3.29 (12-25)	19.89±2.60 (14-25)	0.023
	MN	21.78± 3.21 (14-25)	20.32±3.93 (10-25)	20.06±4.17 (9-25)	18.44±4.32 (10-25)	0.012
	TSS	85.35±8.72 (68-105)	80.10±10.66 (46-105)	77.74±11.86 (49-97)	74.82±12.08 (54-94)	0.003

Kruskal-Wallis Test

Genotype Data: Genotype ratios and allele frequencies of the *GCK* gene rs4607517 -30G>A polymorphism was determined for 200 T2DM patients and 100 healthy controls. Genotype data of all analyzed samples were obtained. The *GCK* gene rs4607517 -30G>A polymorphism is found in humans in the form of three different genotypes: GG (wild type) (Figure 1), GA (heterozygous) (Figure 2) and AA (mutant). The A risk allele sometimes appears in the form of the C risk allele. However, there were no cases with GC or CC genotypes in our study.

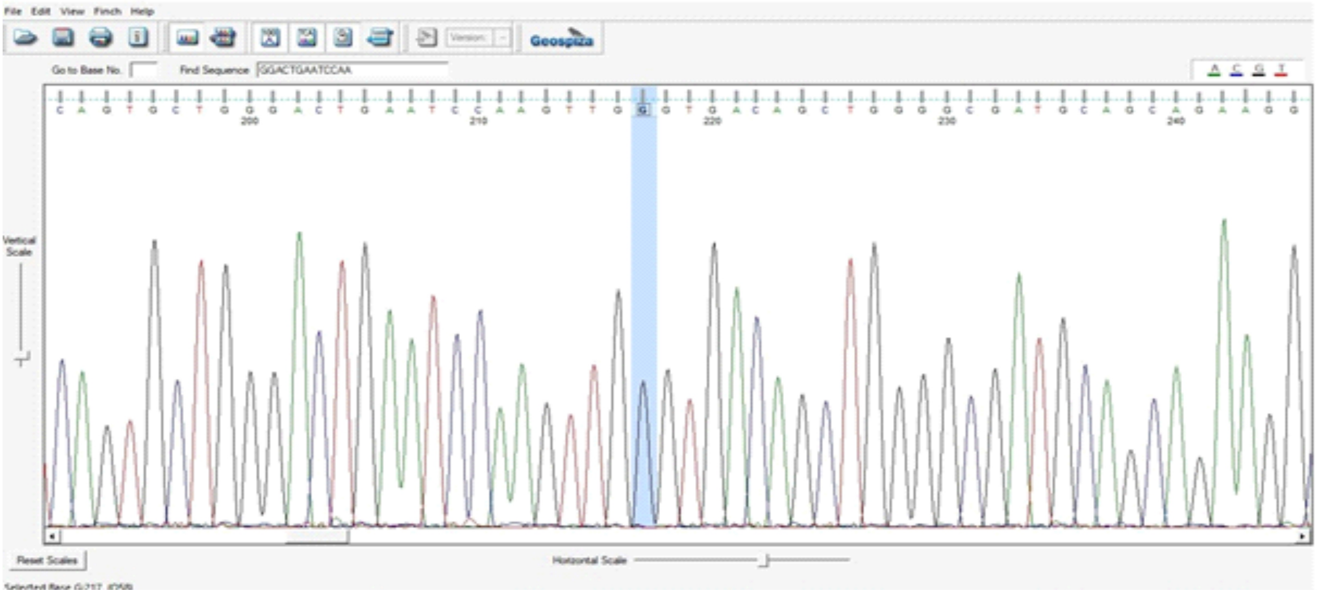

Figure 1. GG type genotype

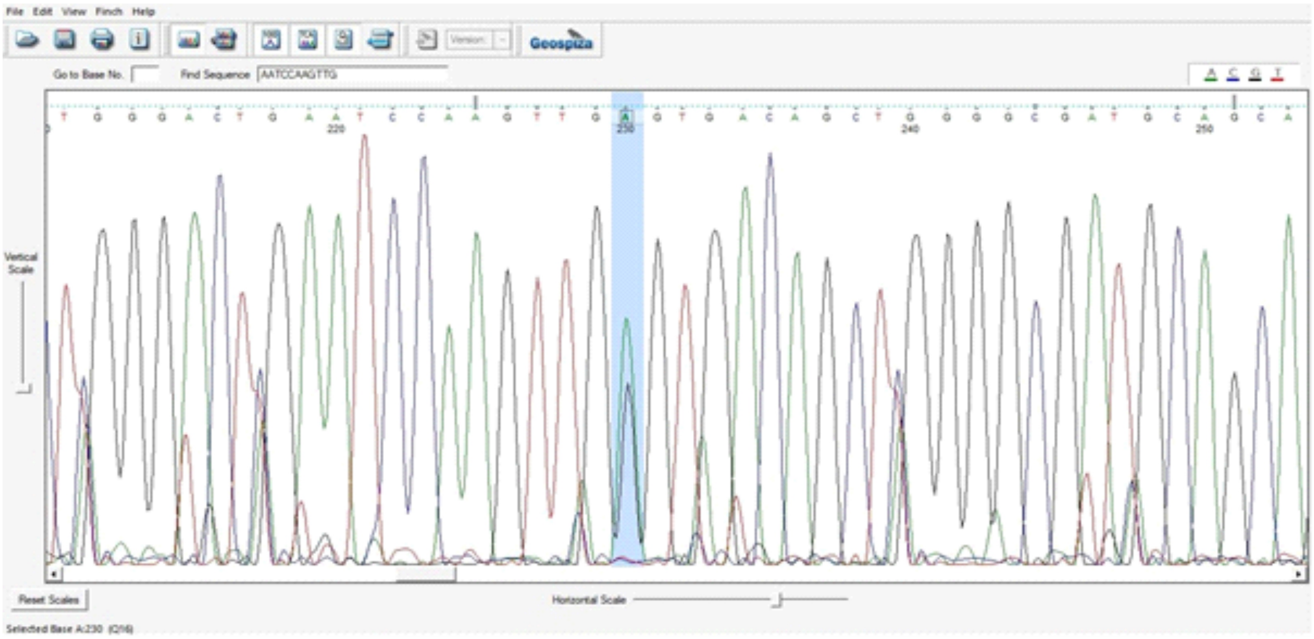

Figure 2. GA type genotype

Genotype Ratios of *GCK* Gene rs4607517 -30G>A Polymorphism: In the control group, 70 (69.72%) of the participants were with the GG genotype, 27 (27.56%) the GA genotype, and 3 (2.72%) the AA genotype. In the patient group, 136 (68.48%) of them were with the GG genotype, 59 (28.55%) the GA genotype, and 5 (2.98%) the AA genotype. When the patient and control groups were compared statistically using the x^2 test, there was no difference observed in terms of genotype ratios between the groups (p>0.05) (Table 2).

Table 2. Genotype distribution of *GCK* Gene rs 4607517-30G>A polymorphism

Genotype	Control Group *n*=100	T2DM *n*=200	P
GG	70 (69.72%)	136 (68.48%)	0.88
GA	27 (27.56%)	59 (28.55%)	
AA	3 (2.72%)	5 (2.98%)	

Allele Frequencies of *GCK* Gene rs4607517 -30G>A Polymorphism: The frequency of the G allele was found to be 331 (82.75%) and the frequency of the A allele was 69 (17.25%) in the group with T2DM patients, while in the control group, the frequency of the G allele was 167 (83.5%) and the A allele was 33 (16.5%). G and A allele frequencies of the *GCK* Gene rs4607517 -30G>A polymorphism were analyzed using the x^2 test. There was no difference between the allele frequencies of the groups (P>0.05) (Table 3).

Table 3. Distribution of allele frequencies of the *GCK* Gene rs4607517 -30G>A polymorphism

Allele	Control Group *n*=38	T2DM Patient Group *n*=34	P	OR (95% CI)
G	167 (83.5%)	331 (82.75%)	0.82	1.055 (0.670-1.662)
A	33 (16.5%)	69 (17.25%)		

DISCUSSION

Diabetes mellitus (DM) is a lifelong disease that develops as a result of insulin deficiency and/or ineffectiveness, accompanied by acute and chronic complications characterized by hyperglycemia.[16] DM is an important disease because if it uncontrolled, its frequency and complications may increase mortality and morbidity, and thus brings an economic burden on both the individual and the society. It has been shown that acute/chronic diabetic complications can be prevented or delayed with good glycemic control.[17,18] T1DM is associated with insulin deficiency, while T2DM is associated with obesity and insulin resistance. In addition to medications, physical activity and medical nutrition therapy (MNT) are indispensable elements to ensure success in the treatment of both types of diabetes.[18]

Medical Nutrition Therapy affects the prevention of diabetes, the treatment of existing diabetes, and the prevention and treatment of the complications related to diabetes. In studies, the HbA1c levels have been shown to decrease by 1-2% with personalized nutrition therapy, considering the metabolic status and food preferences of an adult with diabetes.[19,20]

The mean age of the patients in this study was 55.88±12.23 years, while it ranged from 22 to 75. While this supports the prevalence of T2DM at the age of 30 and above, the youngest age being 22 brings the thought into mind as such "could it be MODY diabetes seen in the youth (age < 25) and progressing like adult-onset diabetes?" One of the most important factors in the emergence of T2DM is an increase in body weight, namely, a BMI ratio ≥ 25 [21-23]. The mean BMI value of the patients in this study was 30.14±5.91 kg/m^2, and a BMI ≥ 30 is considered as 1st-degree obesity in the literature.[21-25] Our study supports that the risk of DM increases followed by the BMI value increases. Some studies on diabetes show that as the duration of diabetes increases, adherence to the disease decreases, which is similar to our study.[24] This has suggested that over the years, individuals may be tired of following certain rules or unable to adopt a lifestyle change related to the disease. The HbA1c value in patients with DM is a parameter that shows at what level the mean FBS has ranged in the last 3 months.[24,26] If the HbA1c mean value of an individual is high, the individual is expected to have high FBS values.[21,25,26] The results of our study were evaluated in accordance with the literature. In many studies comparing the HbA1c values and the biochemical markers of patients with T2DM, the LDL cholesterol, ALT, Hematocrit, Creatinine, Uric acid, and Triglyceride levels have been reported to increase in parallel with the increase in HbA1c value.[21, 27, 28] In our study, LDL cholesterol, ALT, Hematocrit, and Creatinine values were found to increase minimally with an increase in the HbA1c values of patients, in line with the literature. However, there was no difference found between the groups. A significant difference was found only in the rate of increase in triglyceride levels of the patients (P< 0.001). One of the main components of treatment for a patient with diabetes is MNT and individuals' adoption to lifestyle changes.[21] In some studies, the nutrition knowledge levels of diabetic patients were compared with HbA1c values and the HbA1c values were reported to increase as the level of nutrition knowledge decreased.[29,30] According to the results of the ASHN applied to patients in this study, as the HbA1c value increases, the nutritional knowledge level decreases (P=0.004). The HbA1c levels of patients were determined to decrease as the scores of information on nutrition, emotion for nutrition and positive nutrition increased from the sub-dimensions of the scale. The score of the malnutrition sub-dimension of the scale was found to increase in parallel with the increase in HbA1c value. Our results are consistent with the literature.

Glucokinase, an enzyme encoded by the *GCK* gene, is the principal glucose phosphorylation and is expressed in the liver and pancreatic islets. It plays an important role in the regulation of insulin secretion in response to increased glucose levels in the latter tissue.[31] Mutations in this gene are associated with MODY2, a monogenic type of diabetes, while common variants such as rs1799884 and rs4607517 are consistently associated with T2DM and fasting glucose levels.[31,32] Caro-Gomez et al. (2017) reported that the rs179884 and rs4607517 gene variants in the *GCK* gene were significantly associated with higher fasting glucose levels.[33] In our study, there were no differences observed when the anthropometric or biochemical values of individuals with wild-type GG, heterozygous GA and mutant AA genotypes were compared. However, participants with a *GCK* mutation (rs4607517) had higher values of FBS and HbA1c than those without, while these results were insignificant. Furthermore, genotype and allele

frequencies were found to be similar between the control group and T2DM patients in our study. Both the similarity of different genotype ratios between control and patient groups and the absence of difference between HbA1c values of patients with wild type (GG), heterozygous (GA) and mutant (AA) genotypes indicate that this variant by itself is not effective for the development of T2DM in this study. In addition to making evaluations among different populations and with a larger number of patients, other loci, effective in the development of T2DM, should also be evaluated. Although a lot of progress has been made with recent genetic discoveries for T2DM risk, its genetic prediction is still unclear. While large-scale GWAS meta-analyses are designed to obtain the results of pure genetic effects, variants modified by important environmental and lifestyle factors are likely to remain unidentified. Future efforts to characterize the role of other epigenetic modifications as well as Gene-Environment interactions can be expected to fill this gap in diabetes research.[34,35]

In the study of Matsha et al.,[36] 1321 people were found to have GG genotype, 28 patients GA and 12 patients AA. No difference was observed between genotypes in terms of related parameters. However, those with GA and AA genotypes have been reported to have a slightly higher glycemic index, although not at a statistically significant level, compared to the GG genotype. The number of individuals identified as heterozygous and mutant in our study was higher compared to their study. Identification of the high number of heterozygous and mutant individuals even in the control group has been seen to be due to the percentage differences in the single nucleotide polymorphism between the populations. For example, while the percentage of GA genotype was 0.9% in the study of Matsha et al.,[36] it was found to be 13.5% in our study, a very high rate compared to their result. Also, while the number of AA mutant individuals was reported as 0.1% in their study, it was 1.5% in our study.

Beside all these studies, different polymorphism studies continue to be conducted on blood pressure, obesity and diabetes.[37]

DM disease treatment plan includes medical, MNT and lifestyle changes. It is extremely important for the patient to comply with the treatment plan both to improve the quality of life and prevent complications that may occur due to the disease in the future. In this study, nutrition has been determined to have a very important role in the treatment of patients with T2DM. Because individuals who do not have adequate knowledge about MNT and/or do not show the necessary care and attention to MNT have been found to have higher biochemical markers that pave the way to complications of DM than the values they should be. Furthermore, it is noteworthy that almost all of the patients with T2DM in this study were obese, which indicates the necessity for some new measures to raise awareness of society about healthy nutrition. Although there are studies related to the effect of rs4607517 polymorphism in the GCK gene on the development of T2D, the fact that the frequency of polymorphism of the patient group in our study is similar to the control group makes it necessary for the variant to be screened in larger patient populations.

CONCLUSION

Although there are studies related to the effect of rs4607517 polymorphism in the GCK gene on the development of T2DM, the fact that the frequency of polymorphism of the patient group in our study was similar to the control group makes it necessary for the variant to be screened in larger patient populations. The majority of patients with T2DM were found to have high levels of HbA1c, LDL cholesterol, and triglycerides, inadequate level of nutrition knowledge and were obese.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGMENTS

This study was supported by the Afyonkarahisar Health Sciences University Scientific Research Projects Commission with a project numbered 20.GENEL.015. The authors declare no conflicts of interest.

FUNDING SOURCES

None.

REFERENCES

1. Li C, Sadraie B, Steckhan N, Kessler C, Stange R, Jeitler M, Michalsen A. Effects of A One-week Fasting Therapy in Patients with Type-2 Diabetes Mellitus and Metabolic Syndrome - A Randomized Controlled Explorative Study. Exp Clin Endocrinol Diabetes. 2017; 125(9):618-624. doi: 10.1055/s-0043-101700.
2. Freemantle N, Mauricio D, Giaccari A, at al. Real-world outcomes of treatment with insulin glargine 300 U/mL versus standard-of-care in people with uncontrolled type 2 diabetes mellitus. Curr Med Res Opin. 2020; 36(4):571-581. doi: 10.1080/03007995. 2019. 1708287.
3. Saeedi P, Salpea P, Karuranga S, et al.. Mortality attributable to diabetes in 20–79 years old adults, 2019 estimates: results from the International Diabetes Federation Diabetes Atlas. Diabetes Research and Clinical Practice. 2020;162.
4. World Health Organization. Diabetes. [on-line]. Available at https://www.who.int/health-topics/diabetes #tab=tab_1Accessed 10.06.2021.
5. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and Its

Complications: Report of a WHO Consultation. Part 1, Diagnosis and Classification of Diabetes Mellitus. World Health Organization Department of Non communicable Disease Surveillance. 1999

6. Knowler WC, Crandall JP, Chiasson JL, Nathan DM., at al.. Prevention Of Type 2 Diabetes.Diabetes in America. 3rd edition. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018 Aug. CHAPTER 38.
7. Purnell JQ. Feingold KR, Anawalt B., at al. Definitions, Classification, and Epidemiology of Obesity. Endotext [Internet]. South Dartmouth (MA): MDText.com, 2018: Inc.; 2000.
8. Postic C, Shiota M, Magnuson MA. Cell-specific roles of glucokinase in glucose homeostasis. Recent Prog Horm Res. 2001;56:195–217. doi: 10.1210/rp.56.1.195.
9. Matschinsky FM. Regulation of pancreatic beta-cell glucokinase: from basics to therapeutics. Diabetes 2002;1(Suppl. 3):S394-S404
10. Matschinsky FM, Glaser B, Magnuson MA. Pancreatic beta-cell glucokinase: closing the gap between theoretical concepts and experimental realities. Diabetes. 1998;47:307–315. doi: 10.2337/diabetes. 47.3.307.
11. Hussain K. Mutations in pancreatic β-cell glucokinase as a cause of hyperinsulinaemic hypoglycaemia and neonatal diabetes mellitus. Rev Endocr Metab Disord. 2010;11:179 183. doi: 10.1007/s11154-010-9147-z.
12. Aleem S, Iqbal R, Shar T, at al. Complications of Diabetes: An Insight into Genetic Polymorphism and Role of Insulin.Recent Pat Inflamm Allergy Drug Discov. 2018;12(1):78-86. doi: 10.2174/1872213X 12666180717165331.
13. Wędrychowicz A, Tobór E, Wilk M, at al. Phenotype Heterogeneity in Glucokinase-Maturity-Onset Diabetes of the Young (GCK-MODY) Patients.J Clin Res Pediatr Endocrinol. 2017;1;9(3):246-252. doi: 10.4274/jcrpe.4461.
14. Voevoda MI, Ivanova AA, Shakhtshneider EV, at al. Molecular genetics of maturity-onset diabetes of the young. 2016; 88(4):117-124. doi: 10.17116/ terarkh 2016884117-124.
15. Tekkurşun Demir, G, Cicioğlu, Hİ Sağlıklı Beslenmeye İlişkin Tutum Ölçeği (SBİTÖ): Geçerlik ve Güvenirlik Çalışması (Attitude Scale for Healthy Nutrition (ASHN): Validity and Reliability Study). Gaziantep Üniversitesi Spor Bilimleri Dergisi, 2019, 4(2), 256-274. DOI: 10.31680/gaunjss.559462
16. International Diabetes Federation. IDF Diabetes Atlas, 7 ed. Brussels, Belgium: International Diabetes Federation, 2015.
17. Dinçağ, N. Sürekli glukoz izleme sistemi-diabette kendi kendine izleme, IV. Uluslararası beslenme ve diyetetik kongresi özet kitabı, 2008, 144- 145.
18. Satman İ., Ömer B, Tütüncü Y., Kalaca S., Gedik S., Dinccag N., Karsidag K., Genc S., Telci A., Canbaz B., Turker F., Yımaz T., Cakir B, Tuomilehto J., Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013; 28:169–180. DOI 10.1007/s10654-013-9771-5.
19. Satman, İ., Tip 2 Diyabet Epidemiyolojisi. Ed: İmamoğlu Ş. ve Ark. Editors. Geçmişten geleceğe diyabetes mellitus, 1. Baskı, BAYT Bilimsel Araştırmalar Basın Yayın ve Tanıtım Ltd. Şti, Ankara, s.35-43, 2015.
20. İmamoğlu, Ş., Ersoy, C.Ö., Gürdal, B.Ş.:Diabetes mellitus 2009 Multidisipliner Yaklaşımla Tanı, Tedavi Ve İzlem, Diabetes Mellitusta Tıbbi Beslenme Tedavisi, 3. baskı, Deomed Medikal Yayıncılık, s.115-121, 2009.
21. Türkiye Endokrinoloji ve Metabolizma Derneği Yayınları. Diabetes mellitus ve komplikasyonlarının tanı, tedavi ve izlem kılavuzu 2020. TEMD Diabetes Mellitus Çalışma ve Eğitim Grubu tarafından hazırlanmıştır. ANKARA, 2020; ISBN: 978-605-4011-40-7.
22. Saeedi P, Salpea P, Karuranga S, et al. Mortality attributable to diabetes in 20–79 years old adults, 2019 estimates: results from the International Diabetes Federation Diabetes Atlas. Diabetes Research and Clinical Practice. 2020;162, 108086
23. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. 2007, Diabetes Care, 30(Supplement_1).
24. Goyal R, Jialal I. Diabetes Mellitus Type 2. 2020, Nov 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–.
25. Sapra A, Bhandari P. Diabetes Mellitus. Feb 23. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–.
26. Weiss M, Steiner DF, Philipson LH., at al. Insulin Biosynthesis, Secretion, Structure, and Structure-Activity Relationships. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc 2000; 2000–.
27. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. Nutrition. 2012;28(10):1016-21. doi: 10.1016/ j.nut.2012.01.016.
28. Bonakdaran S, Kharaqani B.. Association of serum uric acid and metabolic syndrome in type 2 diabetes.Curr Diabetes Rev. 2014;10(2):113-7. doi: 10.2174/

157339981066614022816093 8.

29. Calle MC, Fernandez ML. Inflammation and type 2 diabetes.Diabetes Metab. 2018; 38(3):183-91. doi: 10.1016/j.diabet.2011.11.006.
30. Palacios T, Vitetta L, Coulson S, Madigan CD, Denyer GS, Caterson ID. The effect of a novel probiotic on metabolic biomarkers in adults with prediabetes and recently diagnosed type 2 diabetes mellitus: study protocol for a randomized controlled trial.Trials. 2017; 9;18(1):7. doi: 10.1186/s13063-016-1762-x.
31. Gloyn, AL., Tribble, N.D., van de Bunt, M., Barrett, A., Johnson, P.R.V., Glucokinase (GCK) and other susceptibility genes for beta-cell dysfunction: the candidate approach. Biochem. Soc. Trans. 2008;36:306–311. https://doi.org/10.1042/BST0360306.
32. Dimas, AS., Lagou, V., Barker, A. et al.. Impact of type 2 diabetes susceptibility variants on quantitative glycemic traits reveals mechanistic heterogeneity. Diabetes 2014;63, 2158–2171.https://doi.org/10.2337/db13-0949.
33. Caro-Gomez, MA., Naranjo-González, A., Parra-Marín, M.V., et al. Insulin resistance and β-cell function in Colombian mestizo and Embera-Chamí populations and their relation with adiposity degree. Endocrinol. Diabetes Nutr. 2017; 64, 211–220.
34. Franks, PW.; Pearson, E.; Florez, J.C. Gene-environment and gene-treatment interactions in type 2 diabetes: Progress, pitfalls, and prospects. Diabetes Care 2013, 36, 1413–1421.
35. Ling, C.; Groop, L. Epigenetics: A molecular link between environmental factors and type 2 diabetes. Diabetes 2009, 58, 2718–2725.
36. Matsha TE, Raghubeer S, Tshivhase AM. Incidence of HNF1A and GCK MODY Variants in a South African Population The Application of Clinical Genetics 2020:13 209–219.
37. Repchuk Y, Sydorchuk LP, Sydorchuk AR, et al. Linkage of blood pressure, obesity and diabetes mellitus with angiotensinogen gene (AGT 704T>C/rs699) polymorphism in hypertensive patients. Bratisl Lek Listy. 2021;122(10):715-720. doi: 10.4149/BLL_2021_114. PMID: 34570572.