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Study Of Allelic and Genotypic Variants of The C60t Polymorphic Locus of The Superoxide Dismutase (SOD) Gene in The Development of The Cardiovascular Form of Diabetic Autonomic Neuropathy in Patients with Type 2 Diabetes

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ABSTRACT

Diabetic autonomic (vegetative) neuropathy (DAN) is a severe and quite common complication of diabetes mellitus (DM), which is often overlooked or diagnosed late, remaining an underestimated target in therapeutic practice [1, 6]. DAN can manifest in clinically obvious or subclinical forms in patients within two years after diagnosis. The detection rate ranges from 20% to 40%, and with disease duration of more than 10 years, it exceeds 65%. DAN is recognized as an independent risk factor that reduces both quality of life and life expectancy by 2-10 times and is associated with an increased likelihood of further complications [8]. Diabetes mellitus is a leading cause of chronic autonomic neuropathies. The prevalence of autonomic disorders depends on the type of diabetes, being 54% for type 1 and 73% for type 2. The most unfavorable prognosis is associated with cardiac diabetic autonomic neuropathy, with mortality within five to ten years ranging from 27% to 56%. According to the metabolic theory of DAN pathogenesis, chronic hyperglycemia is the primary cause of the disorder, which activates the non-enzymatic glycosylation of nerve fiber sheath proteins and increases the activity of the polyol pathway of glucose metabolism. This leads to structural and functional damage to axons, segmental demyelination, and degeneration, accompanied by impaired axonal transport and slowed nerve conduction. The activation of lipid peroxidation causes damage to mitochondrial and neuronal membranes, leading to subsequent neuron death [4]. The primary markers are superoxide dismutases. The multifactorial nature of diabetic polyneuropathy (DPN) pathogenesis is now unquestionable [3]. Chronic hyperglycemia is the triggering factor for DPN development. Under hyperglycemic conditions, transmembrane glucose transport into endothelial and nerve tissue cells is activated, increasing its intracellular concentration and activating the polyol glucose utilization pathway [2]. Other significant pathogenic mechanisms of DPN include the increased production of superoxide anion radicals, formation of reactive oxygen species, development of oxidative stress, blockade of the hexosamine glucose utilization pathway, formation and accumulation of advanced glycation end products in nerve fibers, and endoneurial blood flow deficiency [7, 9]. Oxidative stress, caused by the excessive formation of free radicals against the backdrop of insufficient activity of the endogenous antioxidant system, is responsible for glucose metabolism disruption [10, 11]. Prolonged impairment of glucose metabolism is one of the main pathogenic mechanisms of DPN development [2].

Objective: The aim of this study was to investigate the role of the C60T gene polymorphism of SOD2 in the development of the cardiovascular form of diabetic autonomic neuropathy (DAN) in patients with type 2 diabetes.

Materials and Methods: The study included 135 patients with type 2 diabetes, with an average age of 56.3 ± 2.3 years and a disease duration of 5.6 ± 1.2 years, who were receiving outpatient treatment at three clinics of the Tashkent Medical Academy. Among them, 69 were women with an average age of 52.3 ± 3.4 years, and 66 were men with an average age of 54.3 ± 2.6 years. The control group consisted of 81 individuals with an average age of 53.6 ± 2.4 years. All patients were tested for fasting blood glucose, postprandial blood glucose (2 hours after eating), and glycated hemoglobin. As a glucose-lowering medication, 88 patients received DPP-4 inhibitors and biguanides, while 47 patients received combined therapy with basal insulin. Individuals who had experienced acute cardiovascular complications were excluded from the study. To diagnose cardiovascular form diabetic autonomic neuropathy (DAN-CV) in patients with type 2 diabetes, Holter monitoring was performed. Based on Holter monitoring parameters, the patients were divided into two groups: those with DAN-CV (+) and those without DAN-CV (-). All patients underwent genetic testing for the C60T polymorphism of the SOD2 gene at the Department of Molecular Genetics of the Republican Specialized Scientific-Practical Medical Center.

Results: In patients with type 2 diabetes, the fasting blood glucose level was 7.6 ± 2.3 mmol/L, and the postprandial blood glucose level (2 hours after eating) was 9.6 ± 1.4 mmol/L. The average glycated hemoglobin level was 9.2 ± 1.2%. According to the results of Holter monitoring and standard cardiovascular tests, 82 patients (60.7%) were diagnosed with DAN-CV (+), while 53 patients (39.2%) were diagnosed with DAN-CV (-). To evaluate the role of the C60T polymorphism of the SOD2

gene in the etiopathogenesis of DAN-CV in patients with type 2 diabetes, we conducted a comparative association study in a sample of patients and conditionally healthy individuals of Uzbek nationality. According to literature sources, the presence of the unfavorable allele of SOD2 (C60T) leads to the destabilization of the α-helical region, which disrupts the transport of the enzyme from the cytoplasm to the mitochondria, resulting in reduced antioxidant activity [5]. Our results also support these findings, as we established an associative link between the functionally weakened T/T genotype of the C60T locus of the SOD2 gene and the risk of developing DAN-CV in patients with type 2 diabetes.

The results of detection and the frequency of allelic and genotypic variants of the C60T locus of the SOD2 gene in the main group and subgroups of patients with type 2 diabetes, with and without DAN-CV, as well as in the control group, are presented in Tables 8, 9, and 10.

1. INTRODUCTION

Table 8: Frequency Distribution of Alleles and Genotypes of the C60T Polymorphism in the SOD2 Gene in Patient and Control Groups

N	Group Frequency	Allele Frequency				Genotype Distribution					
		C		T		C/C		C/T		T/T	
		n	%	n	%	n	%	n	%	n	%
1	Main Group (n=135)	259	95.9	11	4.1	125	92.6	9	6.7	1	0.7
2	DAN+(n=82)	155	94.5	9	5.5	74	90.2	7	8.5	1	1.2
3	DAN-(n=53)	104	98.1	2	1,9	51	96.2	2	3.8	0	0
4	Control Group (n=81)	159	98.1	3	1.8	78	96.3	3	3.7	0	0

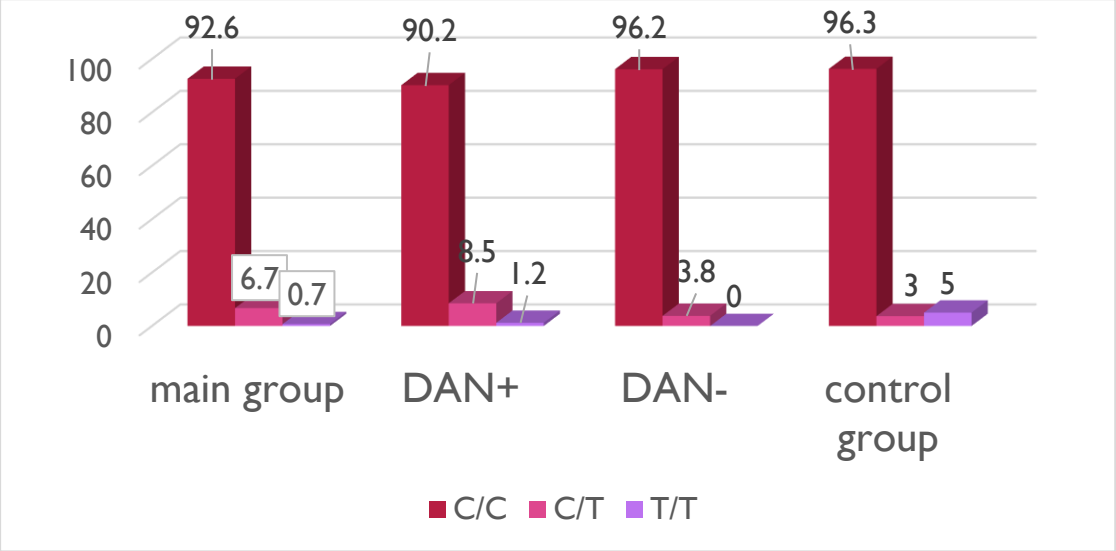

Figure 4: Frequency of Genotypes of the C60T Polymorphism in the SOD2 Gene in Patient and Control Groups

The allelic variants 60C and 60T in the main group of patients and the control group were identified with frequencies of 95.9% and 4.1% versus 98.1% and 1.8%, respectively. Although statistical analysis showed no significant difference in the frequency of the unfavorable 60T allele (4.1% versus 1.8%; χ^2=1.6; p=0.3), it was established that this allelic variant of the SOD2 enzyme might have a potential role in the pathogenesis of this condition (OR=2.3; 95% CI: 0.64 - 7.93).

Table 9: Frequency Distribution of Genotypes and Alleles of the C60T Polymorphism in the SOD2 Gene in Groups of Patients with Type 2 Diabetes and the Control Group

Alleles and Genotypes	Number of Examined Alleles and Genotypes				χ2	p	OR	95%CI
	Main group		Control group					
	n	%	n	%				
C	259	95.9	159	98.1	1.6	0.3	0.4	0.13 - 1.57
T	11	4.1	3	1.9	1.6	0.3	2.3	0.64 - 7.93
C/C	125	92.6	78	96.3	1.2	0.3	0.5	0.13 - 1.76
C/T	9	6.7	3	3.7	0.8	0.4	1.9	0.5 - 6.94
T/T	1	0.7	0	0.0	0.2	0.7	-	-

The proportion of carriers of the C/C, C/T, and T/T genotypic variants in the studied groups of patients and controls was 92.6%, 6.7%, and 0.7%, compared to 96.3%, 3.7%, and 0.0%, respectively. As seen, the concentration of heterozygous/homozygous genotypes C/T and T/T slightly increased in the clinical group of patients compared to the control group (6.7% vs. 3.7% and 0.7% vs. 0.0%, respectively). Statistical analysis showed that carrying the heterozygous genotype did not significantly increase the odds of developing the pathology by 1.9 times (χ^2=0.8; p=0.3; OR=1.9; 95% CI: 0.5 - 6.94).The frequency of the dominant C/C genotype, associated with a high concentration of manganese superoxide dismutase among patients, was also not significantly lower than in the control group, reaching a 5% level of significance (92.6% vs. 96.3%, respectively, with χ^2=1.2; p=0.3; OR=0.5; 95% CI: 0.13 - 1.76). As shown in the table, the rare homozygous T/T genotype was not found in the control group.

Dividing the main group into subgroups (with and without cardiovascular form of diabetic autonomic neuropathy, DAN) and calculating the frequency of allelic and genotypic variants of this polymorphism allowed for a more accurate assessment of the association of this locus with a specific form of the pathology. It was found that this unfavorable allelic variant, associated with a low concentration of manganese superoxide dismutase, might be involved in the pathogenesis of the cardiovascular form of DAN in patients with type 2 diabetes (Tables 10 and 11).

A comparative analysis of the distribution of C60T alleles in the SOD2 gene showed a threefold increase in the proportion of the rare 60T allele among patients compared to the control group (5.5% vs. 1.9%, respectively). As seen in Table 11, among patients with type 2 diabetes, the likelihood of developing the cardiovascular form of DAN when carrying this mutant allelic variant was OR=3.1. Since the lower boundary of the values after adjusting for the 95% confidence interval (95% CI) was slightly below 1 (95% CI: 0.87 - 10.89), it can be stated that the risk association of developing the cardiovascular form of DAN with carrying unfavorable variants of this polymorphism is significant but at a level of tendency (χ^2=3.0, p=0.1).

Inverted differences were observed in the comparative analysis of the distribution of the ancestral C/C and unfavorable C/T and T/T genotypes of the C60T polymorphism in the SOD2 gene among this subgroup of patients and controls. There was a decrease in the proportion of the dominant homozygous C/C genotype and an increase in the concentration of the unfavorable C/T and T/T genotypes among patients compared to the population sample (Table 10).

Table 10. Distribution of Genotype and Allele Frequencies of the C60T Polymorphism in the SOD2 Gene in Subgroups of Type 2 Diabetes Patients with Cardiovascular Form of Diabetic Autonomic Neuropathy (DAN) and Control Group

Alleles and Genotypes	Number of Alleles and Genotypes Examined				χ2	p	OR	95%CI
	DAN+		Control group					
	n	%	n	%				
C	155	94.5	159	98.1	3.0	0.1	0.3	0.09 - 1.15
T	9	5.5	3	1.9	3.0	0.1	3.1	0.87 - 10.89
C/C	74	90.2	78	96.3	2.4	0.2	0.4	0.1 - 1.33

C/T	7	8.5	3	3.7	1.7	0.2	2.4	0.63 - 9.38
T/T	1	1.2	0	0.0	0.9	0.3	-	-

The protective genotype C/C, which provides genetic protection against various free radicals and toxins, was found in 90.2% of patients and 96.3% of healthy donors (χ^2=2.4; p=0.2; OR=0.4; 95% CI: 0.1 - 1.33). Since the difference between patient and control groups reached only a borderline significance level and did not achieve the declared level of statistical tendency, the protective effect of this genotype on the development of the cardiovascular form of diabetic autonomic neuropathy (DAN) in type 2 diabetes patients appears weak. The frequency of the heterozygous genotype C/T among type 2 diabetes patients was slightly higher than in the control group (8.5% vs. 3.7%, respectively; χ^2=1.7; p=0.2). The relative risk of developing the cardiovascular form of DAN for carriers of this genotype was OR=2.4 (95% CI: 0.63 - 9.38). The statistically insignificant differences between the groups may be related to the low frequency of the unfavorable allele 60T in the population.The frequency of the mutant homozygous genotype T/T among patients was slightly higher than in the control group (1.2% vs. 0.0%, respectively), but this genotype showed a non-significant association with the development of cardiovascular DAN. The T/T genotype was not found in the control group.

A similar pattern was observed in the comparative analysis of allele and genotype distribution of this locus in subgroups with and without cardiovascular DAN among type 2 diabetes patients (Table 11).

The protective allele 60C, which provides genetic stability to the antioxidant system, was present in 98.1% of patients without complications compared to 94.5% in the subgroup with cardiovascular DAN. The calculated odds ratio for developing this pathology was less than 1, i.e., OR=0.3 (χ^2=2.1; p=0.2).

There is a tendency towards an increased frequency of the unfavorable allele 60T and genotype C/T in type 2 diabetes patients with cardiovascular DAN compared to the subgroup without complications (5.5% and 8.5% vs. 1.9% and 3.8%, respectively). According to the odds ratio, patients with type 2 diabetes show a weak tendency for increased genetic risk of developing cardiovascular DAN, more than 2.4 times higher for carriers of the unfavorable genotype variant (OR=2.4, χ^2=1.2; p=0.3).

Table 11. Distribution of Genotype and Allele Frequencies of the C60T Polymorphism in the SOD2 Gene in Subgroups of Type 2 Diabetes Patients with and without Cardiovascular Form of Diabetic Autonomic Neuropathy (DAN)

Alleles and Genotypes	Number of Examined Alleles and Genotypes				χ2	p	OR	95%CI
	DAN+		DAN-					
	n	%	n	%				
C	155	94.5	104	98.1	2.1	0.2	0.3	0.08 - 1.46
T	9	5.5	2	1.9	2.1	0.2	3.0	0.69 - 13.29
C/C	74	90.2	51	96.2	1.7	0.2	0.4	0.08 - 1.68
C/T	7	8.5	2	3.8	1.2	0.3	2.4	0.5 - 11.42
T/T	1	0.7	0	0.0	0.7	0.7	-	-

2. SUMMARY AND CONCLUSION

The results obtained indicate that patients with type 2 diabetes exhibited a tendency towards a higher frequency of cardiovascular form of diabetic autonomic neuropathy (DAN) when carrying the unfavorable allele variant of the C60T polymorphism in the SOD2 gene, which is associated with low manganese superoxide dismutase enzyme concentration. Notably, among all examined patients and controls, a very low frequency of the heterozygous genotype and the absence of any carriers of the recessive homozygous genotype of the T58C and C60T polymorphisms in the SOD2 gene were observed. This also confirms the need for further research to strengthen the findings related to these polymorphic loci in the SOD2 gene.

3. CONCLUSION

In patients with type 2 diabetes, Holter monitoring identified 60.7% with cardiovascular form of DAN (+). The unfavorable allele variant of the C60T polymorphism in the SOD2 gene leads to the development of cardiovascular diabetic autonomic neuropathy in type 2 diabetes patients.

REFERENCES

[1] Andrzej Bissinger, "Cardiac Autonomic Neuropathy: Why Should Cardiologists Care about That?", J Diabetes Res. 2017; 2017: 5374176. Published online 2017 Oct 29. doi: 10.1155/2017/5374176

[2] Brownlee M., "The pathobiology of diabetic complications. A unifying mechanism.", Diabetes. 2005. 54, 6. 1615-1625.

[3] Kasznicki J., "Advances in the diagnosis and management of diabetic distal symmetric polyneuropathy.", Arch Med Sci. 2014. 10, 2. 345-354.

[4] Ghelani Hardik, Razmovski-Naumovski Valentina, Rajeswara Rao Pragada, Srinivas Nammi, "(R)-α-Lipoic acid inhibits fructose-induced myoglobin fructation and the formation of advanced glycation end products (AGEs) in vitro", BMC Complement. 2018 Jan 15;18(1):13. doi: 10.1186/s12906-017-2076-6.

[5] Rosenblum JS, Gilula NB, Lerner RA, "On signal sequence polymorphisms and diseases of distribution.", Proceedings of the National Academy of Sciences of the United States of America. 1996 Apr;93(9):4471-4473. DOI: 10.1073/pnas.93.9.4471. PMID: 8633092; PMCID: PMC39562.

[6] Rodica Pop-Busui, Andrew J M Boulton, Eva L Feldman, Vera Bril, Roy Freeman, Rayaz A Malik, Jay M Sosenko, Dan Ziegler, "Diabetes Care", 2017 Jan; 40 (1):136-154. doi: 10.2337/dc16-2042. Diabetes Care: A Position Statement by the American Diabetes Association.

[7] Tesfaye S, Boulton AJM, Dyck PJ et al., "Diabetic Neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments on behalf of the Toronto Diabetic Neuropathy Expert Group.", Diabetes Care. 2010. 33. 2285-2293.

[8] Vinik Aaron I, Tomris Erbas, "Diabetic autonomic neuropathy", Handb Clin Neurol. 2013:117:279-94. doi: 10.1016/B978-0-444-53491-0.00022-5.

[9] Strokov I.A., Strokov K.I., Afonina Zh.A., "Pathogenetic therapy of diabetic polyneuropathy.", Lечащий врач. 2008. 3. 10-14.

[10] Strokov I.A., Golovacheva V.A., Fokina A.S., "Effectiveness of alpha-lipoic acid preparations in diabetic polyneuropathy.", Эффективная фармакотерапия. 3. 38-46.

[11] Khramlin V.N., Chazova T.E., "Clinical experience with Berlition in diabetic peripheral polyneuropathy.", Сахарный диабет. 2001. 4. 46-50.