EFFECT OF LEPTIN LEP-2548G > A (rs7799039) AND LEPTIN RECEPTOR LEPR 223Q > R (rs1137101) GENE POLYMORPHIC VARIANTS ON THE DEVELOPMENT OF CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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The search for functional single-nucleotide polymorphisms (SNPs) of genes that affect the risk of obesity, type 2 diabetes mellitus, and associated vascular complications development is actively ongoing. The aim of the study: to evaluate the effect of the leptin *LEP-2548G/A* and the leptin receptor *LEPR 223Q/R* gene SNPs on the risk of cardiovascular complications development in patients with type 2 diabetes mellitus in the Eastern Ukrainian population over time.

Materials and methods. Type 2 diabetic (T2D) patients at the initial examination and 10 years later were evaluated. During this time, 5 non-fatal heart attacks and 16 deaths due to cardiovascular disease were registered in the study group (n = 60). At baseline, 60 T2D patients (F/M: 26/34) aged 53.35 ± 1.38 yrs, duration of diabetes 5.33 ± 0.67 yrs, with a HbA1c 7.74 ± 0.19%, body mass index 33.28 ± 0.89 kg/m^2, waist-to-hip ratio 0.99 ± 0.01 were examined. Genotyping was performed by polymerase chain reaction and restriction fragment length polymorphism using appropriate primers (*LEP 2548G/A*: forward: tcccatgagaactattctttttttg; reverse: atatggctccctttgcccgacc; *LEPR 223Q/R*: forward: acctctggttccccaaaag; reverse: tcatcattttagtgcataacttaccc) and endonucleases (HhaI and MspI, respectively). Restriction products were analyzed by electrophoresis in a 2% agarose gel. pUC19 DNA hydrolyzed by MspI endonuclease (MBI Fermentas, Lithuania) was used as a molecular weight marker. Unpaired two-tailed Student's t-test, Mann-Whitney test and χ^2-test were used; probability (P) value of 5% or less was considered statistically significant.

Results. It was determined that SNP *LEP -2548G/A* significantly affects the development of cardiovascular complications in T2D patients in the Eastern Ukrainian population, namely, the *A*-allele is associated with an increased risk of heart failure in women and heart failure and coronary heart disease in men. The presence of a heterozygous genotype for the *LEPR 223Q/R* polymorphism is associated with a lower risk of heart failure development in T2D men in the Eastern Ukrainian population. Minor genotypes, namely, *AA* by the *LEP -2548G/A* polymorphism and *RR* by the *LEPR 223Q/R* polymorphism, significantly increase in the risk of mortality related to cardiovascular events (OR (*AA*) = 21.00; CI 3.75-117.76, P < 0.05; OR (*RR*) = 5.00; CI 1.343–18.62, P < 0.05, respectively).

Conclusions. The functional significance of single-nucleotide polymorphisms *LEP -2548G/A* and *LEPR 223Q/R* in relation to the development of cardiovascular complications in patients with type 2 diabetes mellitus in the Eastern Ukrainian population has been proven. Data on the studied polymorphic variants of the leptin and leptin receptor genes can be used to form risk groups and be taken into account when choosing effective preventive and therapeutic strategies.

Keywords: type 2 diabetes mellitus, cardiovascular complications, leptin, leptin receptor, single nucleotide polymorphisms.