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ANALYSIS OF ASSOCIATIONS OF CANDIDATE GENES POLYMORPHISM WITH THE DEVELOPMENT OF KNEE OSTEOARTHRITIS IN OBESE PATIENTS

DOI 10.25789/YMJ.2023.83.17

УДК 616.728.3-007.248

Background. Knee Osteoarthritis (OA) is a chronic disease with multifactorial pathogenesis. Risk factors for developing knee OA include age, genetic predisposition, and obesity. The share of genetic factors in the development of the disease accounts for up to 50 %. Despite the obvious association between obesity and knee OA, studies that reveal the role of genetic factors in the development of the disease in the interaction with obesity or overweight are extremely limited. **The aim of the study:** To study the association of candidate genes polymorphic loci *GDF5* (rs143384), *NFAT5* (rs6499244), *WWP2* (rs34195470), *SBNO1* (rs1060105, rs56116847) with the development of knee OA in patients with obesity. **Materials and methods**. The sample for the study included 322 obese individuals: 255 patients with OA of the knee and 67 people in the control group. Genotyping of DNA samples from all study participants was performed using standard real-time PCR on CFX96 amplifier (USA). Associations of genetic markers with knee OA in obese patients were assessed using the odds ratio and 95 % confidence interval. **Results.** Analysis of the associations of the studied polymorphic loci with the development of knee OA in obese patients revealed significant differences only for the *GDF5* (rs143384) gene polymorphism. It was established that the frequency of the G/G genotype rs143384 in obese knee OA patients was 14.12 %, which is 1.8 times less compared to the control (25.36 %, p = 0.043, OR = 0.48). **Conclusions.** The modifying role of obesity on the nature of the rs143384 polymorphic marker *GDF5* gene associations with the developing knee OA in the population of the Russia Central Chernozem Region was shown. The G/G genotype rs143384 was found to be a protective factor in the development of knee OA in obese patients.

Keywords: knee osteoarthritis, *GDF5*, candidate genes, obesity.

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Introduction. Knee Osteoarthritis (OA) is a chronic joint disease that is accompanied by progressive softening and destruction of cartilage, the growth of new cartilage and bone material at the articular margins, as well as the formation of areas of sclerosis and cysts in the subchondral bone [2]. Knee OA or gonarthrosis is widespread due to an increase in life expectancy of the population, as well as an increase in obesity [16]. According to S. Safiri et al. (2020) the prevalence of OA of the knee and hip joints worldwide is 3754.2 per 100 thousand population [10]. The social and economic importance of OA is high. Hip and knee OA ranks 11th in terms of disability in the world and 38th in terms of the number of years lived with disability [24].

Knee OA is a chronic disease with multifactorial pathogenesis [1, 16]. The leading risk factors for the development of knee OA are age, genetic predisposition, and obesity [16]. In obese individuals, the risk of developing OA is three times higher than in individuals with normal weight [6]. It is known that in patients with knee OA, who are obese or

overweight, progression of the disease is more often observed. The role of obesity in the pathogenesis of gonarthrosis is reduced not only to an excessive load on the joint, but also to the secretion of many biologically active substances by the adipose tissue itself, for example, adipokines, which have various negative effects on the joint [21]. Thus, adipokines enhance catabolic processes in cartilage tissue and increase the synthesis of pro-inflammatory mediators (IL-1β, IL-6, TNF-α, etc.) in joint tissues [21].

Osteoarthritis and obesity result from the interaction of many genetic and environmental factors [7, 23], and these diseases share common pathophysiological mechanisms. The share of the genetic determinant in the development of osteoarthritis is up to 50% [25]. It should be noted that, despite numerous data indicating a significant relationship between obesity and the development/progression of knee OA, genetic studies that reveal the role of individual single nucleotide polymorphisms (SNPs) in the development of the disease when interacting with obesity or overweight are limited, which determines the relevance of further research in this direction.

The aim of the study: to study the association of candidate genes polymorphic loci *GDF5* (rs143384), *NFAT5* (rs6499244), *WWP2* (rs34195470), *SBNO1* (rs1060105, rs56116847) with the development of knee OA in patients with obesity.

Material and methods. The sample for the study included 322 obese individuals: 255 patients with knee OA and 67 people in the control group. Body mass index (BMI) was calculated by the standard method as the ratio of body weight (kg) to the square of height (m). According to WHO, obesity was determined in individuals with a BMI ≥ 30 kg/m^2. The sample for the study was formed on the basis of the City Hospital No 2 of Belgorod.

The inclusion criteria for the group of patients were as follows: a) diagnosed primary knee OA, b) age at least 40 years, c) 2-4 radiological stages of the disease according to the Kellgren-Lawrence classification, d) the presence of pain in the knee joint according to the visual analog scale of more than 40 points, e) the presence of voluntary informed consent to the study. The control group included individuals without any pathology of the musculoskeletal system (examined during preventive examinations).

Criteria for exclusion from the study groups: a) non-European origin, residence and / or birth outside the Central Chernozem region of Russia, b) the presence of severe forms of diseases of the cardiovascular, endocrine systems, renal and hepatic pathology, oncology, history of joint injuries, congenital malformations of the musculoskeletal system.

In each patient, the radiological stage of the disease was determined according to the Kellgren-Lawrence scale: 98 (38.43 %) patients had the 2nd radiological stage of the disease, 114 (44.71%) patients had the 3rd stage, 43 (16.86 %) patients had the 4th stage of OA of the knee joint. All study participants underwent peripheral venous blood sampling (≈ 4–5 ml) and DNA was isolated using the standard phenol-chloroform method.

For this study, five single nucleotide polymorphisms of candidate genes (rs1060105 and rs56116847 of the *SBNO1* gene on chromosome 12, rs34195470 of the *WWP2* gene and rs6499244 of the *NFAT5* gene of chromosome 16, rs143384 of the *GDF5* gene of chromosome 20) were selected, which showed significant associations for the genome- wide level ($p \leq 5 \times 10^{-08}$) with knee OA in samples of European origin [5, 8, 14-15, 19], which have a pronounced functional significance and have a minor allele frequency of at least 5%. The selection of candidate gene polymorphisms was performed from the genome-wide research catalog (GWAS) (https://www.ebi.ac.uk/gwas/). The functional significance of the studied SNPs was assessed using modern databases of functional genomics – online resources HaploReg (v4.2) and GTExPortal [3].

Genotyping of DNA samples from all participants in the study was performed using standard real-time PCR on a CFX96 amplifier, including positive and negative controls.

Separately, in the group of patients with knee OA and in the control, an assessment was made of the correspondence between the observed distribution of genotypes of the studied SNPs and the theoretically expected distribution according to the Hardy–Weinberg pattern. Deviations were considered statistically significant at $P_{HWE} \leq 0.05$. Comparative analysis of the frequencies of alleles and genotypes of the studied polymorphic loci between the group of patients and the control group was performed in 2 x 2 contingency tables using the χ^2 test with Yates' correction for continuity. The association of genetic markers with knee OA was assessed using odds ratio (OR) and 95% CI (95% confidence interval for OR). $P < 0.05$ was taken as a statistically significant level.

Results and discussion. The studied groups of patients with knee OA and controls with obesity did not differ in sex and age composition, as well as height ($p > 0.05$) (Table 1). However, patients with OA of the knee had a higher BMI compared to the control group ($p = 0.0001$).

Table 1

Characteristics of patients with osteoarthritis and the control group with obesity

Index		OA patients with obesity [n = 255]	Control group with obesity [n = 67]	*p*
Men, n [%]		86 [33.73]	26 [38.80]	0.53
Women, n [%]		169 [66.27]	41 [61.20]	
Average age, years	Me [Q25 – Q75]	53.0 [50.0 – 56.0]	54.0 [50.0 – 58.0]	0.12
	Min/Max	40.0/68.0	42.0/70.0	
	M [σ]	52.55 [5.48]	53.54 [6.15]	
Height, cm	Me [Q25 – Q75]	167.0 [162.0 – 173.0]	165.0 [160.0 – 173.0]	0.20
	Min/Max	156.0/193.0	156.0/180.0	
	M [σ]	167.89 [7.23]	166.78 [7.67]	
BMI, kg/m^2	Me [Q25 – Q75]	33.87 [31.60 – 36.73]	31.92 [31.10 – 34.34]	**0.0001**
	Min/Max	30.00/47.05	30.04/38.67	
	M [σ]	34.50 [3.50]	32.72 [2.32]	

Примечание. Me – медиана; Q25-Q75 – интерквартильный размах – 25-й и 75-й процентили; Min/Max – минимальное/максимальное значения; M – среднее значение; σ – стандартное отклонение; *p* – уровень статистической значимости.

It was found that for the distribution of genotypes over all polymorphic loci of candidate genes *GDF5* (rs143384), *NFAT5* (rs6499244), *WWP2* (rs34195470), *SBNO1* (rs1060105, rs56116847) in the group of patients with knee OA, as well as in the control group, the Hardy-Weinberg pattern (P_{HWE} > 0.05) (Table 2).

In a comparative analysis of the frequencies of alleles and genotypes of the studied polymorphic loci of candidate genes between the group of patients and controls, significant differences were established only for the rs143384 gene *GDF5*. It was found that the frequency of the G/G genotype rs143384 of the *GDF5* gene in the control group was 1.8 times higher than in the group of patients (p = 0.043) (Table 2).

In our work, it was found that the G/G genotype rs143384 of the *GDF5* gene is a protective factor in the development of knee OA (OR = 0.48). To date, according to five published genome-wide studies, the rs143384 *GDF5* polymorphism has been associated with knee OA [5, 8, 14-15, 19]. Three studies [5, 15, 19] showed that allelic variant A of this polymorphic locus is a risk factor for the development of knee OA (OR = 1.07 – 1.10). In a genome-wide study by U. Styrkarsdottir et al. (2019) established an association of the allelic variant G rs143384 of the *GDF5* gene with gonarthrosis in a sample of European origin (OR = 0.91) [14]. Similar results were obtained in the largest GWAS meta-analysis to date of C. Henkel et al. (2023) (a sample of about 700 thousand individuals with OA and a control group was studied), which also showed the association of the G allele of this polymorphism with idiopathic knee OA in Caucasians (OR = 0.94) [8]. Thus, we can note that our results on the protective role of the G/G rs143384 genotype of the *GDF5* gene in the development of knee OA in obese patients are fully consistent with the data presented in independent sources on this issue.

A number of genome-wide studies have revealed a relationship between the studied *GDF5* gene polymorphism and weight and various anthropometric parameters that may be related to overweight and obesity [4, 9, 13]. The allelic variant G rs143384 of the *GDF5* gene is associated with a lower distribution of adipose tissue in the body in women (β = -0.044, p = 1 x 10^{-40}) [9], waist-to-hip ratio adjusted for BMI (β = -0.035, p = 3 x 10^{-28}) [13]. At the same time, in GWAS S. Sakaue et al. (2021) the G allele rs143384 is associated with an increase in body weight in Europeans and Asians (β = 0.028, p = 3 x 10^{-57}) [4].

Table 2

Distribution of frequencies of alleles and genotypes of the studied polymorphic loci of candidate genes in patients and in the control group with obesity

Polymorphism	Allele, genotype	OA patients with obesity n [%]	Control group with obesity n [%]	OR [95% Cl]	p
rs1060105	C	401 [78.63]	110 [82.09]	0.80 [0.48–1.34]	0.447
	T	109 [21.37]	24 [17.91]	1.25 [0.75–2.10]	
	C/C	157 [61.57]	46 [68.66]	0.73 [0.40–1.35]	0.355
	C/T	87 [34.12]	18 [26.87]	1.41 [0.75–2.69]	0.328
	T/T	11 [4.31]	3 [4.47]	0.96 [0.24–4.49]	1.000
	H_o/H_e [P_{HWE}]	0.341/0.336 [1.000]	0.269/0.294 [0.422]	-	-
rs56116847	G	334 [65.49]	83 [61.94]	1.17 [0.77–1.76]	0.507
	A	176 [34.51]	51 [38.06]	0.86 [0.57–1.30]	
	G/G	116 [45.49]	24 [35.82]	1.50 [0.83–2.71]	0.200
	A/G	102 [40.00]	35 [52.24]	0.61 [0.34–1.08]	0.096
	A/A	37 [14.51]	8 [11.94]	1.25 [0.52–3.09]	0.733
	H_o/H_e [P_{HWE}]	0.400/0.452 [0.072]	0.522/0.472 [0.447]	-	-
rs6499244	T	279 [54.71]	81 [60.45]	0.79 [0.53–1.19]	0.275
	A	231 [45.29]	53 [39.55]	1.27 [0.84–1.90]	
	T/T	73 [28.63]	26 [38.81]	0.63 [0.34–1.15]	0.145
	A/T	133 [52.16]	29 [43.28]	1.43 [0.80–2.55]	0.249
	A/A	49 [19.21]	12 [17.91]	1.09 [0.52–2.33]	0.947
	H_o/H_e [P_{HWE}]	0.522/0.496 [0.449]	0.433/0.478 [0.448]	-	-
rs34195470	G	278 [54.51]	75 [55.97]	0.94 [0.63–1.41]	0.839
	A	232 [45.49]	59 [44.03]	1.06 [0.71–1.58]	
	G/G	74 [29.02]	19 [28.36]	1.03 [0.55–1.96]	1.000
	A/G	130 [50.98]	37 [55.22]	0.84 [0.47–1.50]	0.630
	A/A	51 [20.00]	11 [16.42]	1.27 [0.59–2.78]	0.626
	H_o/H_e [P_{HWE}]	0.510/0.496 [0.706]	0.552/0.493 [0.457]	-	-
rs143384	A	302 [59.22]	72 [53.73]	1.25 [0.84–1.87]	0.296
	G	208 [40.78]	62 [46.27]	0.80 [0.54–1.19]	
	A/A	83 [32.55]	22 [32.85]	0.98 [0.54–1.82]	1.000
	G/A	136 [53.33]	28 [41.79]	1.59 [0.89–2.84]	0.123
	G/G	36 [14.12]	17 [25.36]	0.48 [0.24–0.98]	**0.043**
	H_o/H_e [P_{HWE}]	0.533/0.483 [0.096]	0.418/0.497 [0.220]	-	-

Примечание. H_o/H_e – наблюдаемая/ожидаемая гетерозиготность, P_{HWE} – уровень значимости отклонения от закона Харди – Вайнберга.

Growth differentiation factor 5 (GDF5) is a morphogenetic protein of cartilage origin and a member of the TGFβ superfamily, which plays an important role in skeletal formation [18]. C. M. Coleman et al. (2013) note that overexpression of *GDF5* in human mesenchymal stem cells leads to increased chondrogenesis *in vitro* [11]. In the work of K. Kania et al. (2020) revealed a high expression

of *GDF5* in cartilage during recovery after unilateral destabilization of the medial meniscus in mice [20]. E. Hinoi et al. (2013) observed an increase in *GDF5* gene expression in brown adipose tissue in obese mice [12]. Experimental studies in mice have shown that systemic overexpression of *GDF5* in adipocytes reduces non-alcoholic fatty liver disease induced by a high-fat diet [22]

The associations of rs143384 of the *GDF5* gene with knee OA may be based on the pronounced regulatory effects of polymorphism in the human body, which we established in silico (data from the HaploReg (v4.2) online resource): it is located in an evolutionarily conservative region, in the region of histones that mark active H3K9ac promoters in adipose tissue (adipose nuclei, cultured adipocyte cells derived from mesenchymal stem cells), in the region of histones, marking active enhancers of H3K27ac in fatty nuclei, in the area of hypersensitivity to type I DNase in 16 tissues and the region of one Ascl2 DNA regulatory motif. It is also known that rs143384 *GDF5* is associated with the level of expression of 21 genes in more than 30 different tissues and organs (data from the GTExPortal online resource), including those involved in the pathogenesis of gonarthrosis (adipose tissue, thyroid gland, etc.). It should be noted that 6 of these 21 genes (*CPNE1, EDEM2, GDF5, PROCR, RPL36P4, UQCC1*) are expressed in subcutaneous and visceral adipose tissue. Also, the G allelic variant of the rs143384 locus is associated with high expression of two genes *GDF5* and *RPL36P4* in adipose tissue (β = -0.14 – -0.34 for the opposite A allele).

Thus, we can note the important role of the *GDF5* gene in the formation and development of the skeleton, as well as its participation in the processes occurring in adipose tissue, which ultimately can determine the relationship between the G/G genotype rs143384 of the *GDF5* gene and knee OA in obese patients.

Conclusion. Our study shows the modifying role of obesity on the nature of associations of the rs143384 polymorphic marker of the growth differentiation factor 5 gene with the development of knee OA in the population of the Central Chernozem Region of Russia. It has been established that the G/G genotype rs143384 of the *GDF5* gene is a protective factor in the development of knee OA in obese patients.

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