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THE EFFECT OF OBESITY ON SEXUAL DIMORPHISM OF IRISIN LEVELS

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The aim of this study is to conduct a comparative analysis of average irisin levels between female and male (with normal weight and obese) to assess sexual dimorphism. Circulating levels of irisin in the blood of 279 Yakuts (185 female, 94 male, average age 19.8 ± 2.03 years) were determined. A comparative analysis of irisin levels between male and female in three BMI groups (underweight, normal weight, overweight/obesity) was carried out. The average level of irisin in the blood plasma in female was 8.33 ± 2.74 mcg/mL, and in male 7.76 ± 1.86 mcg/mL. Sexual dimorphism (p = 0.02) was detected in Yakuts with normal weight, where the level of irisin was higher in women (8.42 = 2.92 mcg/mL) compared to men (7.51 = 1.61 mcg/mL). Conducted a comparative analysis of irisin levels between male and female based on global data, were including this analysis are 2132 people. The age of the participants ranged from 18 to 61 years old. The meta-analysis was carried out for two different BMI groups: the first group included people with normal weight (18.5-24.9 kg/m^2), the second group included people with varying degrees of obesity (>30 kg/m^2). Comparative analysis of irisin levels in a large sample revealed statistically significant sexual dimorphism, where irisin levels were also higher in female compared to male, only in a sample of obese people (p = 0.02), in a sample of people with normal weight, no sexual differences were found (p = 0.09). Thus, the influence of obesity on sexual dimorphism was revealed.

Keywords: irisin, obesity, adipose tissue, Yakut population.

Introduction. During the previous decade, adipose tissue and skeletal muscles were recognized as endocrine organs secreting hormones adipokines and myokines, respectively. It is believed that there is a certain relationship between muscles and adipose tissue [24], which may be crucial for the regulation of body weight and metabolism, but specific metabolic pathways and mediators remain unclear [12]. Irisin is a short-lived myokine and is produced by proteolytic cleavage of fibronectin type III domain-containing protein (FNDC5) in response to the activation of gamma coactivator 1 of the alpha receptor activated by the proliferator peroxisome (PGC-1 α) [1]. Although irisin is primarily known as a myokine, it can also be an adipomyokine, since it is produced in adipocytes [1]. There are several factors known to affect the levels of irisin circulating in the blood, such as physical activity and diseases such as obesity and type 2 diabetes mellitus (DM2).

Irisin is mainly produced by skeletal muscles during aerobic exercises (running, swimming and treadmill workouts) [19-23, 33]. With intense physical exertion, an increase in the concentration of irisin occurs after 30-60 minutes [23], but after 90 minutes of training, irisin levels no longer increase [2]. In addition, prolonged training leads to a general decrease in the level of circulating irisin, so athletes have rather low levels compared to people who lead a sedentary lifestyle [5].

On the other hand, irisin can be produced by adipocytes, and numerous studies show that the levels of irisin circulating in the blood are significantly higher in obesity and in a prediabetic state [13, 15, 16, 18, 25, 31]. It is believed that in obesity and in a prediabetic state, irisin may be involved in general cycles of compensatory mechanisms, in which the recorded increased amount of irisin is explained by its increased secretion in an attempt to increase energy consumption due to browning of white adipose tissue or other, as yet unidentified effects in skeletal muscles [4, 23, 28]. Sesti et al., [27] suggested that in obesity, an increased level of irisin is an adaptive mechanism for preserving beta cells from overload, and can compensate for impaired insulin sensitivity. However, in T2D, irisin levels begin to decrease over time and become significantly lower in the decompensation stage than in people without diabetes [4, 14, 34]. This pattern is probably related to the dysfunction of β-cells, due to the depletion of their adaptive abilities to insulin resistance [3, 9].

Sexual dimorphism of irisin levels remains an open question, as there are many contradictory results. Some studies do not find differences in irisin levels between male and female [4, 5, 10-13,

21, 34]. However, in some studies, the authors observed a slight sexual dimorphism, where female had elevated levels of irisin, unlike male [2, 6-8, 30, 32].

In this regard, the purpose of this study is to conduct a comparative analysis of average irisin levels between female and male (normal weight and obesity) to assess sexual dimorphism.

Materials and research methods. *Sample.* The research sample comprised 279 people: 185 females and 94 males (with a mean age of 19.8±2.03 years). They presented no health issues at the time of the study and had completed a questionnaire in which they specified their sex, ethnicity, and age. All participants gave written informed consent for participation in the study. This study was approved by the local Biomedical Ethics Committee at the Yakut Scientific Center of Complex Medical Problems, Siberian Branch of the Russian Academy Scientific of Medical Sciences, Yakutsk, Russia (Yakutsk, Protocol No. 16, and 13 December 2014).

Anthropometric measurements. Anthropometric parameters (body weight in kilograms, height in centimeters) were measured for all participants by standardized methods. Body mass index (BMI) was calculated by dividing body mass by the square of the body height. The sample was divided into three groups by BMI [29]: underweight (≤18.49 kg/m^2), normal weight (18.5–24.99 kg/m^2), and overweight/obese (≥25 kg/m^2).

Irisin levels test. Fasting plasma irisin levels (mcg/mL) were determined with the human irisin sandwich enzyme-linked immunoassay (ELISA) "Irisin ELISA BioVendor" (BioVendor – Laboratorni medicina A.S., Czech Republic). The concentration of irisin in the samples was measured at the wavelength of 450 nm on a VICTOR X5 Multilabel Plate Reader (Perkin Elmer Inc., Waltham, MA, USA).

Search criteria for publications for comparative analysis. For this analysis, they carried the main search for suitable studies out in the electronic databases PubMed-Medline. The following search strings were used: "irisin AND obesity OR body mass index OR BMI AND sex differences". The last search was carried out on 04/06/2022. Details of each study included were collected in a pre-designed form. Thus, data were collected: first author, publication date, serum or plasma, age of participants, unit of measurement (mcg/mL or ng/mL), manufacturer of the ELISA kit, study location, sample size, irisin levels (mean average ± standard deviation). Comparative analysis was performed using The RevMan 5.3 software (The Cochrane Collaboration, UK). The difference in blood irisin levels between female and male was assessed using the total inverse variance. Heterogeneity was assessed using the Q-test based on the χ-square analysis and the I^2 test ($p<0.10$ denoted significance). The criteria for inclusion of studies in this analysis were as follows: studies should have been controlled, cross-sectional, prospective or clinical, studies should have studied serum/plasma levels of irisin in male and female aged 18 years and older with normal weight (18.5-24.9 kg/m^2) and/or obesity (>30 kg/m^2). The exclusion criteria were as follows: studies with participants under the age of 18, studies with sick individuals, in vivo and in vitro studies, review publications, studies on laboratory animals, lack of sufficient information on irisin concentrations, lack of BMI data, duplicate study.

Literature search and relevant research. A literature search in electronic databases revealed 622 publications. After applying different filters (sample age, and unit of measurement of irisin in the blood) 325 articles were excluded. The full texts of 297 articles were reviewed, and this resulted in the exclusion of 292 articles. As a result, 5 publications [4, 8, 10, 17, 34] met the inclusion criteria and were included in the final analysis (Figure 1).

Statistical analysis. The obtained data were analyzed using Statistica 13.5, a statistical software program (TIBCO Software Inc., Palo Alto, CA, USA). Values of $p \leq 0.05$ were considered statistically significant. Quantitative results are reported as the mean ± standard deviation. The Kolmogorov–Smirnov test was performed to test the normal distribution and homogeneity of the data was examined. The association of BMI with irisin levels was assessed with the correlation analysis. Comparative analysis of the three BMI groups between males and females was performed with the Mann–Whitney U test for the underweight and overweight/obese groups and with the Student's t-test for the individuals with normal weight.

Results and discussion. The plasma irisin concentration was 8.33 ± 2.74 mcg/mL in females and 7.76 ± 1.86 mcg/mL in males. Table 1 presents characteristics

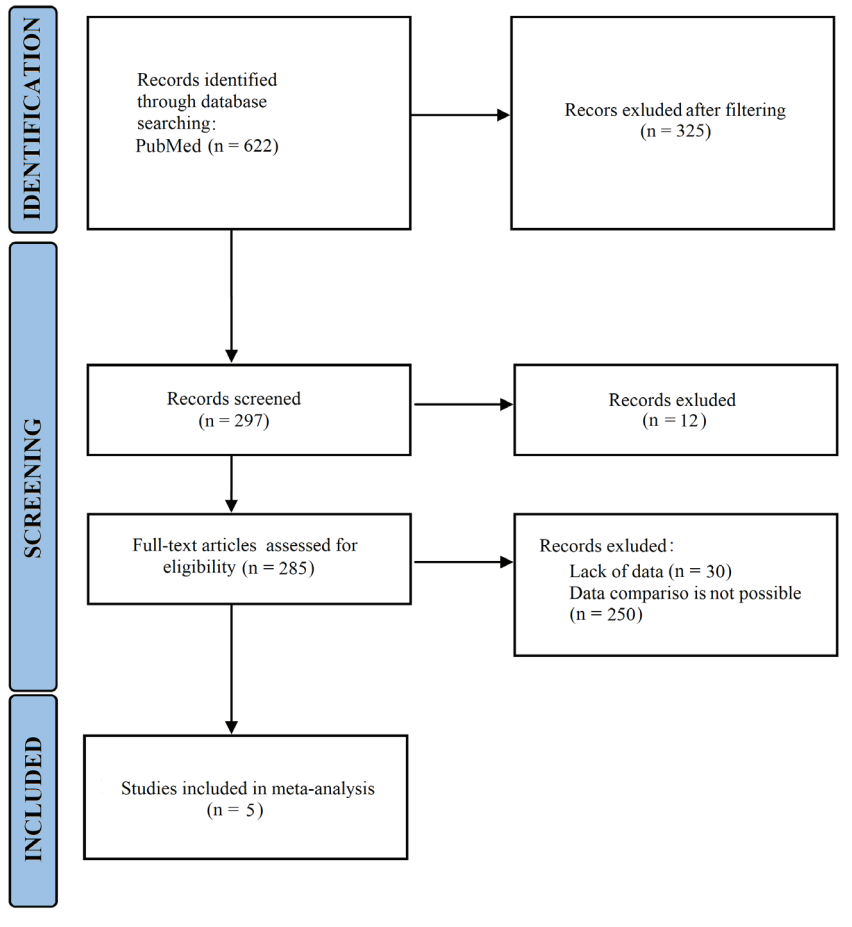

Fig. 1. Block diagram of the selection of publications for comparative analysis.
Note: Representation of the process by which relevant studies were retrieved from databases, selected, or excluded (PRISMA) [35]

of the sample (n = 279), stratified by BMI into three groups – underweight, normal weight and overweight/obese. Men showed significantly higher indicators of weight and height than women (p=0.01) in all three groups. Males with a normal weight displayed a significantly higher BMI than females (p = 0.03). The level of circulating irisin in the "normal weight" group was significantly higher in women (8.42 ± 2.92 mcg/mL) compared to men (7.51 ± 1.61 mcg/mL; p=0.02).

To verify the insignificant sexual dimorphism found by us in irisin levels, we conducted a comparative analysis using literature data. A total of 2132 individuals were included in the comparative analysis, the sample sizes varied from 7 to 537 in individual studies. All the studies were published between 2014 and 2022. The age of the participants ranged from 18 to 61 years. The meta-analysis was carried out for two different BMI groups: the first group included people with normal weight (18.5-24.9 kg/m^2), the second group included people with varying degrees of obesity (>30 kg/m^2). Detailed characteristics of these studies are given in Table 2.

Comparative analysis of normal weight individuals showed that there is a tendency of elevated irisin levels in women (p=0.09) (Figure 2A), heterogeneity in this group was average (I^2=53%). Stronger (p=0.02) sex differences were found in the group of people with obesity of 1 and 2 degrees, where the average levels of irisin were significantly higher in women than in men, the degree of heterogeneity was also average (I^2=54%) (Figure 2B).

The results obtained in an expanded sample of individuals with normal weight probably indicate the presence of minor sexual dimorphism in irisin levels at normal weight. With obesity of varying severity, this sexual dimorphism deepens, which indicates the role of irisin as an adipomyokine, since it is the adipokines secreted by adipose tissue that have a clear sexual dimorphism. For example, women, unlike men, have higher levels of adiponectin, leptin and visfatin [26]. The sexual dimorphism we found in irisin levels in Yakuts with normal weight may be associated with a high content of adipose tissue at normal BMI, but this requires further research.

Conclusion: In the Yakut population, among the group of people with normal weight, sexual differences in irisin levels were found, in female irisin was significantly higher (8.42±2.92 mcg/ml) compared with male (7.51±1.61 mcg/ml; p=0.02). The analysis of irisin levels in 2132 people revealed statistically sig-

Table 1

Characteristics of study subjects by BMI and sex

Characteristics	Underweight (n = 36)		p[1]	Normal Weight (n = 214)		p[2]	Overweight/Obese (n = 29)		p[1]
	F (n = 25)	M (n = 11)		F (n = 144)	M (n = 70)		F (n = 16)	M (n = 13)	
Weight (kg)	44.88 ± 3.71	50.45 ± 3.42	**0.01**	55.53 ± 5.8	66.19 ± 7.44	**0.01**	72.75 ± 11.13	81.46 ± 8.3	**0.01**
Height (cm)	160.24 ± 5.14	170.36 ± 5.89	**0.01**	160.92 ± 6.03	173.33 ± 5.98	**0.01**	162.19 ± 4.96	174.69 ± 6.64	**0.01**
BMI (kg/m2)	17.45 ± 0.73	17.39 ± 0.91	0.868	21.42 ± 1.62	22 ± 1.89	**0.03**	27.56 ± 2.88	26.64 ± 1.49	0.539
Irisin (mcg/mL)	7.88 ± 1.96	8.52 ± 2.64	0.904	**8.42 ± 2.92**	**7.51 ± 1.61**	**0.02**	8.27 ± 1.96	8.48 ± 2.16	0.965

Note: [1] Mann–Whitney U test; [2] Student's t-test; F–females; M–males. Data represent the mean±std.dev.

Table 2

Characteristics of publications included in the comparative analysis

№	Authors of the article and year of publication	Serum or plasma	Age, years	Unit of measurement	ELISA kit	Country	n	Female, mcg/mL	n	Male, mcg/mL
GROUP I										
1	This work	Plasma	19-30	mcg/mL	BioVendor, Czech Republic	Russia	142	8.43±2.94	60	7.65±1.66
2	Jameel et al., 2014 [34]	Plasma	34-39	mcg/mL	AdipoGenen, Switzerland	Australia	21	6.6±1.83	28	7.1±2.12
3	Oelmann et al., 2016 [10]	Plasma	40-61	mcg/mL	AdipoGenen, Switzerland	Germany	537	1.97±1.19	430	1.89±1.12
4	Choi et al., 2019 [4]	Serum	51-66	mcg/mL	BioVendor, Czech Republic	S.Korea	187	4.6±3.8	213	4.2±2.3
Всего							**N=887**		**N=731**	
GROUP II										
5	D'Amuri et al., 2022 [8]	Plasma	37.2 ± 9.1	mcg/mL	AdipoGenen, Switzerland	Italy	7	6.48 ±1.96	9	4.76 ±1.25
6	Klangjareonchai et al., 2014 [17]	Serum	58-64	mcg/mL	AdipoGenen, Switzerland	Thailand	73	3.08+1.03	25	2.67±0.6
7	Choi et al., 2019 [4]	Serum	51-66	mcg/mL	BioVendor, Czech Republic	Germany	200	4.4 ±2	200	4.3 ±1.8
Total							**N=280**		**N=234**	

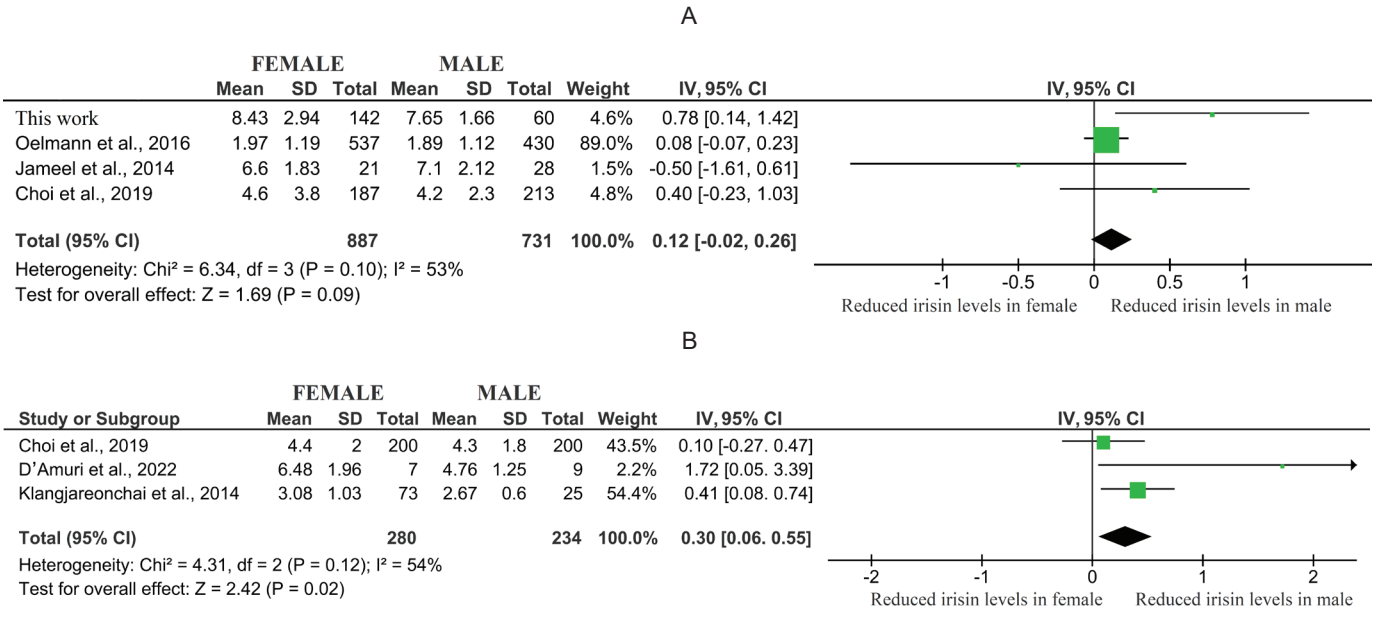

Fig. 2. Comparative analysis of average irisin levels between female and male. Note: A – group I, B – group II.

nificant sexual dimorphism: irisin levels were higher in women compared to men, in a sample of obese individuals (p=0.02). No sexual differences were found in the sample of persons with normal weight (p=0.09). Thus, it was revealed that sexual dimorphism in irisin levels manifests itself with obesity.

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THE ROLE OF HUMORAL IMMUNITY IN THE COMPLEX DIAGNOSIS OF DESTRUCTIVE FORMS OF ACUTE CHOLECYSTITIS

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The incidence of acute cholecystitis, to date, remains at the same level and amounts to 1.6 cases per 100,000 people. Mortality in this pathology ranges from 4 to 26%. There is no doubt that changes occur in any pathology, both in the local and in the general link of immunity, acute cholecystitis is no exception. The most significant deviations are observed in humoral immunity. Based on this, these criteria can be used to improve the diagnosis of acute destructive cholecystitis. The aim. To evaluate changes in the humoral link of immunity in patients with acute destructive cholecystitis. Materials and methods: A single-stage study of 105 patients with various clinical and morphological variants of acute calculous cholecystitis (acute catarrhal cholecystitis (n=35); acute phlegmonous cholecystitis (n=35); acute gangrenous cholecystitis (n=35)), comparable in age, gender and concomitant pathology and time of surgical intervention, was conducted. When patients were admitted to the hospital with suspected acute cholecystitis, the activity of the following immunogram parameters was determined in the first 2 hours: IgA, IgG, IgM and total immunoglobulin. Statistical processing of the obtained results was carried out using the SPSS Statistics 10.0 program in compliance with the principles of statistical analysis adopted for research in biology and medicine. The results. As a result of the study, an increase in the level of IgA in a subgroup of patients with acute gangrenous cholecystitis (subgroup № 3) to 139.5 IU/ml was found, which is 1,3 times higher than the reference level (p<0,05), 1.1 times less (p<0,05) than the values of the clinical comparison group, and 1.1 times higher (p≤0.05) values obtained in subgroups with catarrhal (subgroup № 1) and phlegmonous (subgroup № 2) acute cholecystitis. It was revealed that the concentration of IgG in subgroup № 3 reaches 196,6 IU/ml, which exceeds the indicators in other groups, relative to the norm values by 1,4 times (p≤0,05), comparison group by 1,4 times (p≤0,05), subgroup № 1 by 1,6 times (p≤0,05), subgroup № 2 1,2 times (p≤0,05). In the subgroup with acute gangrenous cholecystitis, it was found that the concentration of IgM is 190,4 IU/ml, which is higher than in other groups: the clinical comparison group by 1,6 times (p≤0,05), subgroup № 1 by 1,5 times (p≤0,05), subgroup № 2 by 1,2 times (p≤0,05). Conclusions. The study found that in destructive forms of acute cholecystitis, an increase in IgG was recorded by 1,6 times in comparison with the group of patients with non-destructive cholecystitis (p<0,05), as well as IgM by 1,3 times in comparison with the group of patients with non-destructive cholecystitis.

Keywords: cholelithiasis, acute cholecystitis, prognosis, destructive forms, cholelithiasis, diagnosis, humoral immunity, IgA, IgM, IgG.

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Acute cholecystitis still remains an important and still unresolved issue of emergency surgery. The continuing high incidence of this nosology (1,6 cases per 100 thousand) and postoperative mortality (0,9-1%) explain the need to search for new prognostic criteria that will increase the sensitivity and specificity of known and publicly available diagnostic methods for acute destructive cholecystitis [9].

Undoubtedly, changes in local and general immunity accompany the pathology of the organs of the hepato-pancreato-duodenal zone, affecting the cellular and humoral link [1,2,3]. At the same time, a number of both domestic and foreign authors indicate that in patients with calculous cholecystitis, which is accompanied by stagnation and thickening of bile, there is an increase in the concentration of immunoglobulins [2, 5]. In her study, N.M. Kozlova points out that the pathology of the biliary system is characterized by an increase in all classes of immunoglobulins [4]. The liver serves as the main source of utilization of serum IgA, which is captured by hepatocytes and secreted into bile, which explains the increase in this immunoglobulin in bile "sludge" [6,8,10]. In the works of L.G. Levkoeva, G.A. Eliseeva, devoted to the study of the level of CEC in blood plasma in patients with chronic cholecystitis, no significant changes were found [6]. At the same time, there are no data in the literature that reliably show changes in humoral immunity in acute destructive cholecystitis.