УДК 616-056.257-092:616-018.26:577.175.8.04
https://doi.org/10.20538/1682-0363-2023-4-48-56

Prevalence of some internal diseases depending on the adipokine level in people under 45 years of age

Kashtanova E.V., Polonskaya Ya.V., Shcherbakova L.V., Shramko V.S., Stakhneva E.M., Khudyakova A.D., Sadovski E.V., Denisova D.V., Ragino Yu.I.

Research Institute of Internal and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences
175/1, Bogatkova Str., Novosibirsk, 630089, Russian Federation

ABSTRACT

The aim was to study the prevalence of some common internal diseases in young people of working and childbearing age, depending on the levels of adipokines.

Materials and methods. The study included 1,340 people aged 25–44 years. The levels of leptin, adiponectin, adipsin, lipocalin-2, plasminogen activator inhibitor-1 (PAI-1), and resistin were determined by the multiplex analysis. Low-density lipoprotein hypercholesterolemia (LDL hypercholesterolemia), coronary artery disease (CAD), type 2 diabetes mellitus (T2DM), arterial hypertension (AH), renal dysfunction (RD), and chronic bronchitis (CB) were studied.

Results. With an increase in the level of adiponectin, the prevalence of CAD increased by 8.6 times. The highest quartile of the adipsin level was characterized by an increase in the prevalence of LDL hypercholesterolemia by 12.9%, AH by 3.9%, and RD by 17.9%. The quartiles of lipolkalin-2 showed higher prevalence of LDL hypercholesterolemia, AH, and RD in Q_4 compared to Q_1. The prevalence of CB was associated with a decrease in the level of lipocalin-2 and was higher by 35.9% within Q_1 compared to Q_4. In the quartiles of PAI-1, the prevalence of T2DM and LDL hypercholesterolemia was 2 and 1.5 times higher, respectively, and the prevalence of RD was 2.5 times lower in Q_4 than in Q_1. In quartiles of resistin, the prevalence of LDL hypercholesterolemia, AH, and RD increased by 13–38%, while the prevalence of CB decreased by 20% in Q_4 compared to Q_1. The prevalence of LDL hypercholesterolemia and RD was higher within Q_4 of leptin.

Conclusion. The results indicate the need for further research aimed at studying the molecular mechanisms underlying the effects of adipokines. This will allow to find a combined approach to restoring normal physiological levels of adipokines, which can have a positive effect in the studied internal diseases.

Keywords: internal diseases, adipokines, adiponectin, lipocalin-2, resistin

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Source of financing. The article was written within the state assignment “Epidemiological monitoring of the population’s health and study of molecular genetic and molecular biological mechanisms underlying the development of common internal diseases in Siberia to improve approaches to their diagnosis, prevention, and treatment” (No. 122031700094-5_) and funded by the Russian Science Foundation grant (No. 21-15-00022).

Conformity with the principles of ethics. All patients signed an informed consent to participate in the study and to personal data processing. The study was approved by the local Ethics Committee at the Research Institute of Internal and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences (Protocol No. 16 of 26.11.2019).

For citation: Kashtanova E.V., Polonskaya Ya.V., Shcherbakova L.V., Shramko V.S., Stakhneva E.M., Khudyakova A.D., Sadovski E.V., Denisova D.V., Ragino Yu.I. Prevalence of some internal diseases depending

✉ *Kashtanova Elena V.,* elekastanova@yandex.ru

on the adipokine level in people under 45 years of age. *Bulletin of Siberian Medicine.* 2023;22(4):48–56. https://doi.org/10.20538/1682-0363-2023-4-48-56.

Распространенность некоторых терапевтических заболеваний в зависимости от уровней адипокинов у людей до 45 лет

Каштанова Е.В., Полонская Я.В., Щербакова Л.В., Шрамко В.С., Стахнёва Е.М., Худякова А.Д., Садовский Е.В., Денисова Д.В., Рагино Ю.И.

Научно-исследовательский институт терапии и профилактической медицины (НИИТПМ) – филиал Института цитологии и генетики Сибирского отделения Российской академии наук (ИЦиГ СО РАН) Россия, 630089, г. Новосибирск, ул. Бориса Богаткова, 175/1

РЕЗЮМЕ

Цель – изучить встречаемость некоторых распространенных терапевтических заболеваний у молодых людей трудоспособного и детородного возраста в зависимости от уровней адипокинов.

Материалы и методы. В исследование включено 1 340 человек в возрасте 25–44 лет. Методом мультиплексного анализа определены уровни лептина, адипонектина, адипсина, липокалина-2, ингибитора активатора плазминогена-1 (ИАП-1) и резистина. Изучены: гиперхолестеринемия липопротеинов низкой плотности (гиперХС-ЛНП), ишемическая болезнь сердца (ИБС), сахарный диабет 2-го типа (СД2), артериальная гипертензия (АГ), почечная дисфункция (ПД), хронический бронхит (ХБ).

Результаты. С увеличением уровня адипонектина распространенность определенной ИБС возрастает в 8,6 раз. Самый высокий квартиль уровня адипсина характеризуется увеличением распространенности гиперХС-ЛНП на 12,9%, АГ на 3,9% и ПД на 17,9%. Квартили липолкалина-2 показали более высокую распространенность гиперХС-ЛПН, АГ и ПД в Q_4 по сравнению с Q_1. Распространенность ХБ ассоциирована со снижением уровня липокалина-2 и выше в Q_1 на 35,9%, в сравнении с Q_4. В квартилях ИАП-1 встречаемость СД2 и гиперХС-ЛНП в 2 и 1,5 раза соответственно выше, а ПД в 2,5 раза ниже в Q_4, чем в Q_1. В квартилях резистина на 13–38% увеличивается распространенность гиперХС-ЛНП, АГ, ПД. На 20% снижается распространенность хронического бронхита в Q_4 по сравнению с Q_1. Встречаемость гиперХС-ЛНП и ПД была выше в Q_4 лептина.

Заключение. Результаты свидетельствуют о необходимости дальнейших исследований, направленных на изучение молекулярных механизмов, лежащих в основе эффектов адипокинов, что позволит найти комбинированный подход, направленный на восстановление нормальных физиологических уровней адипокинов. Это может дать положительный эффект при изученных терапевтических заболеваниях.

Ключевые слова: терапевтические заболевания, адипокины, адипонектин, липокалин-2, резистин

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Статья подготовлена в рамках государственного задания «Эпидемиологический мониторинг состояния здоровья населения и изучение молекулярно-генетических и молекулярно-биологических механизмов развития распространенных терапевтических заболеваний в Сибири для совершенствования подходов к их диагностике, профилактике и лечению» (№ 122031700094-5_) и при финансовой поддержке гранта Российского научного фонда (№ 21-15-00022).

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании и обработку персональных данных. Исследование одобрено локальным этическим комитетом НИИТПМ – филиал ИЦиГ СО РАН (протокол № 16 от 26.11.2019).

Для цитирования: Каштанова Е.В., Полонская Я.В., Щербакова Л.В., Шрамко В.С., Стахнёва Е.М., Худякова А.Д., Садовский Е.В., Денисова Д.В., Рагино Ю.И. Распространенность некоторых терапевтических заболеваний в зависимости от уровней адипокинов у людей до 45 лет. *Бюллетень сибирской медицины.* 2023;22(4):48–56. https://doi.org/10.20538/1682-0363-2023-4-48-56.

INTRODUCTION

Adipokines are important circulating biomolecules mediating intertissue interactions throughout the body and thus playing a key role in maintaining endocrine homeostasis. The most studied adipokines are adiponectin, leptin, resistin, monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-6, IL-1ß, and IL-10. Adipokines are involved in various functions and can affect many processes, including energy and appetite modulation, lipid and glucose metabolism, insulin and endothelial cell functions, inflammation, etc. [1].

To date, numerous associations of adipokines with widespread noncommunicable diseases have been identified, including cardiovascular diseases, type 2 diabetes mellitus, hypertension, and others [2, 3], although the functions and molecular mechanisms underlying the effects of adipokines have not been fully elucidated. The aim of this study was to investigate the prevalence of some common internal diseases in young people of working age and childbearing age, depending on adipokine levels.

MATERIALS AND METHODS

The study was conducted on a population sample of residents of Novosibirsk aged 25–44 years, formed in 2013–2017 in Research Institute of Internal and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences (IITPM – Branch of IC&G SB RAS). To build a sample, the database of the Territorial Compulsory Health Insurance Fund for the Novosibirsk Region was used. Using a random number generator, persons of both sexes aged 25–44 years were selected from this database. Throughout this time frame, 1,512 people were examined within a single-stage population screening; their biological material was collected, and a database was compiled.

All patients signed an informed consent to examination and processing of personal data. The study was approved by the local Ethics Committee at IITPM – Branch of IC&G SB RAS (Protocol No. 16 of 26.11.2019). The study included 1,340 people (618 men, 720 women) – all of them were persons whose samples of biological material were housed in the biological collection of the IITPM – Branch of IC&G SB RAS at the time of the study. Two people did not fill out a questionnaire including demographic and social data, but their serum was included in the work.

A clinical examination of patients was carried out at IITPM – Branch of IC&G SB RAS. The survey program included collection of demographic and social data, a survey on smoking habits, two measurements of blood pressure (BP), spirometry, anthropometric measurement (measurement of height, body weight, waist circumference (WC), hip circumference (HC)), functional tests, etc.

The serum content of total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (LDL-C), and glucose was determined by the enzymatic method using the reagent kit manufactured by Thermo Fisher Scientific (Finland) on the Konelab Prime 30i biochemical analyzer (Finland). The concentration of LDL-C was calculated according to the Friedewald equation. Conversion of serum glucose into fasting plasma glucose (FPG) was carried out according to the formula (EAST, 2005): FPG (mmol / l) = –0.137 + 1.047 = serum glucose (mmol / l). The levels of leptin, adiponectin, adipsin, lipocalin-2, plasminogen activator inhibitor-1 (PAI-1), and resistin were determined by the multiplex analysis using the Human Metabolic Hormone Panel V3 (USA) and the Human Adipokine Panel 1 (USA) on the Luminex MAGPIX system (USA). Concentrations were expressed in ng / ml for lipocalin-2, PAI-1, leptin, and resistin and in mcg / ml for adiponectin and adipsin.

Hypercholesterolemia was established at the level of LDL-C > 3.0 mmol / l [4]. The diagnosis of coronary heart disease (CHD) (according to epidemiological criteria - “Definite CHD”) was made in the presence of the following criteria: past large myocardial infarction (ECG), angina pectoris (Rose Angina Questionnaire), ischemic-like ECG changes without left ventricular hypertrophy, rhythm and conduction disturbances (ECG). Type 2 diabetes mellitus was established in the presence of FPG ≥ 7 mmol / l [5]. Arterial hypertension (AH) was observed with an average systolic blood pressure (SBP) greater than 140 mm Hg and / or diastolic blood pressure (DBP) greater than 90 mm Hg, according to the clinical guidelines “Arterial hypertension in adults” approved by the Ministry of Health of Russia in 2020 [6]. The presence of renal dysfunction was recorded at a glomerular filtration rate (GFR) < 90 ml / min / 1.73 cm². The GFR was calculated using the CKD-EPI equation. The diagnosis of chronic bronchitis (CB) was established on the basis of anamnestic data: cough with sputum for 3 months within a year and more often for 2 years or more, no signs of bronchial obstruction [7].

Baseline clinical, anamnestic, and biochemical characteristics of the studied sample are summarized in Table 1.

Table 1

Clinical, anamnestic, and biochemical characteristics of the studied sample, Me [Q_1; Q_4]

Parameter	Value
Age, years	37.08 [31.5; 41.83]
SBP, mm Hg	120.0 [110.5; 130.0]
DBP, mm Hg	78.5 [71.6; 87.0]
BMI	25.23 [22.16; 29.14]
Fasting plasma glucose, mmol / l	5.73 [5.31; 6.04]
TC, mmol / l	4.99 [4.32; 5.68]
HDL-C, mmol / l	1.29 [1.09; 1.50]
LDL-C, mmol / l	3.15 [2.51; 3.76]
TG, mmol / l	0.97 [0.69; 1.44]
Creatinine, mcmol / l	74.0 [67.0; 82.0]
GFR	101.37 [90.36; 110.05]

Note: SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, TC – total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, TG – triglycerides, GFR – glomerular filtration rate

Statistical processing of the results was carried out in the SPSS 20.0 software. Normality of the distribution of variables was checked by the Kolmogorov – Smirnov test. Quantitative variables whose distribution was different from normal were presented as the median and the interquartile range *Me* [Q_1; Q_4]. Categorical variables were presented as relative values (%). The Pearson's $\chi 2$ criterion was used to compare the proportions. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The levels of the studied adipokines are presented in Table 2. In the study sample (n = 1,340), serum concentrations of adiponectin, adipsin, lipocalin-2, PAI-1, resistin, and leptin were measurable in 58, 82, 98, 61, 77, and 98% of samples, respectively, which is associated with obtaining too low levels in some samples, which did not allow to detect the biomarker.

To study the prevalence of internal diseases depending on the blood concentrations of the studied adipokines, the entire population sample was divided into quartiles based on the content of the studied parameters (Table 2).

The prevalence of the studied diseases in the quartiles of adipocytokines is presented in Table 3. The results of the study showed that with an increase in the level of adiponectin, the prevalence of a distinct coronary heart disease increases by 8.6 times.

Table 2

Levels of the studied adipokines in quartiles, *Me* [Q_1; Q_4]

Parameter	Adiponectin,mcg / ml	Adipsin, mcg / ml	Lipocalin-2, g /ml	PAI-1, ng / ml	Resistin, ng / ml	Leptin, ng / ml
Entire sample	37.14 [25.78; 114.47]	11.69 [7.59;14.1]	385.69 [198.36; 1,133.02]	21.66 [13.18; 32.41]	152.84 [25.74; 596.22]	4,524.61 [1,743.14; 8,513.13]
Q_1	16.1 [11.18; 22.31]	4.35 [2.79; 6.04]	125.7 [82.46; 166.44]	9.41 [6.27; 11.10]	13.93 [6.74; 19.57]	959.23 [435.82; 1,299.6]
Q_2	32.15 [28.06; 34.21]	9.75 [8.81; 10.55]	297,.62 [242.92; 343.81]	17.85 [15.95; 19.71]	51.98 [35.13; 101.08]	2,994.16 [2,123.5; 3,793.3]
Q_3	54.19 [41.04; 98.83]	13.03 [12.42; 13.50]	668.27 [503.57; 976.42]	26.25 [23.81; 29.43]	502.83 [414.56; 551.92]	6,280.95 [5,375.41; 7,112.79]

Table 3

Prevalence of the studied diseases in the quartiles of adipocytokines, %

Group	Q_1	Q_4	p
Adiponectin			
Hypercholesterolemia	58.1	59.7	0.940
CHD	0.5	4.3	0.050
T2DM	46.7	36.0	0.867
CB	55.6	66.7	0.529
AH	9.9	8.3	0.312
Renal dysfunction	22.4	22.4	0.276
Adipsin			
Hypercholesterolemia	48.7	61.6	0.009
CHD	1.1	2.3	0.490
T2DM	31.3	35.1	0.968
Bronchitis	50.0	56.9	0.230
AH	5.6	9.5	<0.0001
Renal dysfunction	17.2	35.1	<0.0001
Lipocalin-2			
Hypercholesterolemia	48.1	61.0	0.005
CHD	1.0	1.9	0.516
T2DM	37.5	30.0	0.958
Bronchitis	40.9	5.0	<0.0001
AH	3.7	11.6	0.001
Renal dysfunction	12.2	24.0	<0.0001
PAI-1			
Hypercholesterolemia	44.1	58.9	0.012
CHD	1.0	0.0	0.075
T2DM	30.0	64.3	0.043

Table 3 (continued)

Group	Q_1	Q_4	p
Bronchitis	57.1	56.5	0.564
AH	4.9	5.9	0.696
Renal dysfunction	20.6	8.0	0.010
Resistin			
Hypercholesterolemia	48.0	61.3	0.010
CHD	0.8	3.3	0.180
T2DM	40.0	31.0	0.808
Bronchitis	20.0	0	0.001
AH	1.2	14.1	<0.0001
Renal dysfunction	3.4	41.2	<0.0001
Leptin			
Hypercholesterolemia	50.9	59.5	0.038
CHD	2.2	2.2	0.881
T2DM	18.8	48.1	0.108
Bronchitis	41.7	57.9	0.536
AH	6.4	10.1	0.394
Renal dysfunction	14.0	31.3	<0.0001

Note: CHD – coronary heart disease, T2DM – type 2 diabetes mellitus, CB – chronic bronchitis, AH – arterial hypertension.

The highest quartile of adipsin was characterized by an increase in the prevalence of hypercholesterolemia by 12.9%, AH – by 3.9%, and renal dysfunction – by 17.9%. The analysis of the quartiles of lipocalin-2 showed higher prevalence of hypercholesterolemia, AH, and renal dysfunction in Q_4 compared to Q_1. The prevalence of CB was associated with a decrease in the level of lipocalin-2; it was 35.9% higher in Q_1 compared to Q_4. In the quartiles of PAI-1, the prevalence of T2DM and hypercholesterolemia was 2 and 1.5 times higher, respectively, and the prevalence of renal dysfunction was 2.5 times lower in Q_4 than in Q_1.

When considering the quartiles of resistin, we noted a 13–38% increase in the prevalence of hypercholesterolemia, AH, and renal dysfunction and a 20% decrease in CB in Q_4 compared to Q_1. The analysis of leptin quartiles showed significant changes in the prevalence of only hypercholesterolemia and renal dysfunction. The prevalence of these diseases was higher in Q_4.

DISCUSSION

Adipokines in the human blood serum are found in a wide dynamic range, from pg / ml to mcg / ml. Changes in the expression and secretion of adipokines correlate with such internal diseases as T2DM, AH, CB, and cardiovascular diseases, which pose a serious health problem worldwide.

Adiponectin is secreted mainly by the adipose tissue and exists in cells and plasma in three main forms: a low-molecular-weight trimer, a medium-molecular-weight hexamer, and a high-molecular-weight (HMW) multimer, which is the main bioactive isoform contributing to its insulin-sensitizing and cardiovascular protective effects [8].

Studies show that plasma adiponectin levels decrease in patients with obesity [9], T2DM [10, 11], atherosclerosis [12], and AH [13]. Along with the inverse correlation with the total mass of the adipose tissue, adiponectin secretion is also regulated by the quality of adipose tissue [9]. Metabolically healthy but obese people tend to have higher levels of adiponectin compared to unhealthy people with similar adipose tissue mass [14]. In addition, disorganized formation of adiponectin isoforms may be associated with cardiometabolic disorders. Patients with CHD have a lower proportion of the HMW multimeter as opposed to a higher proportion of the trimeric form. Similarly, only HMW adiponectin form increases after weight loss in obese patients [15]. A number of studies have shown that high levels of adiponectin are associated with adverse cardiovascular and other metabolic outcomes [16–18]. Our study showed that in the quartile with a high adiponectin level, the prevalence of CHD was significantly higher.

Leptin is synthesized mainly by the adipose tissue and in a small amount – by the gastric mucosa. The structure of leptin is similar to that of proinflammatory cytokines, such as IL-6 and granulocyte colony stimulating factor (G-CSF). Leptin mediates its effects by binding to specific receptors (ObR) expressed in the brain and peripheral tissues (nervous tissue, liver, pancreas, heart, and intestines). The main target organ of leptin is the arcuate nucleus of the hypothalamus, which plays an important role in regulating appetite and energy homeostasis. Leptin suppresses food intake and promotes energy expenditure. Regardless of these effects, leptin improves the sensitivity of peripheral tissues (liver and skeletal muscles) to insulin and modulates the function of beta cells in the pancreas. In most cases, people with obesity, despite the high level of leptin circulating in the bloodstream, do not lose weight, which reflects the presence of leptin resistance [19].

It is known that many factors, such as free fatty acids, estrogen, tumor necrosis factor (TNF)α or impaired renal clearance, stimulate leptin secretion [20]. In our study, in the quartile with high leptin levels, the prevalence of renal dysfunction (GFR 90) was 2 times higher than in the quartile with low leptin values. Thus, circulating leptin levels are elevated in

the early stages of chronic kidney disease (CKD) [21] and increase with the progression of the disease [22].

Adipsin, also called complement factor D, is mainly secreted by adipocytes, monocytes, and macrophages. Adipsin maintains adipose tissue homeostasis and increases insulin secretion in response to glucose. Studies show that in the presence of T2DM, there is a decrease in adipsin levels and there is an independent negative relationship between adipsin and HOMA-IR [23]. The works of other authors indicate a direct relationship between obesity, adipose tissue, and adipsin [24]. In our study, the prevalence of T2DM depending on the level of adipsin in Q_1 and Q_4 did not differ.

Adipsin is associated with various pathophysiological processes underlying atherosclerosis, including low-grade inflammation, endothelial dysfunction, and lipid metabolism [25, 26]. The study on the prevalence of AH depending on the level of adipsin revealed a significant increase in the incidence of AH in the quartile with high values of this adipokine. As for the association of adipsin with lipid metabolism disorders, in our study, the incidence of hypercholesterolemia was higher in the quartile with the highest adipsin values. The prevalence of renal dysfunction was 2 times higher in the quartile with the highest adipsin values, which may be associated with the activation of an alternative complement pathway in patients with CHB [27].

Lipocalin-2 is a secreted glycoprotein involved in a wide range of pathophysiological processes and energy metabolism. Some researchers consider lipocalin-2 as a biomarker of cardiometabolic and chronic kidney diseases [28–30], although there are conflicting reports about the use of this molecule as a biomarker for early diagnosis or prognosis of these diseases [31, 32]. In our study, the prevalence of hypercholesterolemia, AH, and renal dysfunction were associated with high levels of lipocalin-2, and the prevalence of CB was associated with a decrease in lipocalin-2.

Resistin is a polypeptide belonging to the family of resistin-like molecules, a group of proteins that initiate inflammatory processes. Resistin in humans is mainly produced by macrophages, granulocytes, monocytes, and bone marrow cells. Resistin levels are elevated in T2DM [33]. High concentrations of resistin are also found in cardiovascular complications. S. Niaz et al. demonstrated a progressive increase in serum resistin levels in patients with AH and CHD compared to the control group [34].

The mechanism underlying the association between resistin levels and AH is still unclear. One of the possible mechanisms may be mediated via TLR4. Resistin is believed to alter the renin – angiotensin pathway and vascular remodeling [35]. Another potential mechanism is that resistin can reduce the expression of endothelial nitric oxide synthase and increase the expression of endothelin-1, as well as its release in human endothelial cells [36]. In our study, the incidence of AH was 11.7 times higher in the quartile with high levels of resistin than in the quartile with its lowest values. The study on the prevalence of CHD among young people did not show a significant difference between quartiles with the highest and lowest resistin values.

Our results regarding the prevalence of renal dysfunction are consistent with the data of a number of studies that show that high concentrations of resistin in CHB are due to a decrease in GFR and, as a consequence, low elimination of resistin through the kidneys [37, 38]. On the other hand, it has been proven that increased concentrations of resistin are associated with a higher risk of renal dysfunction. The mechanism via which resistin can accelerate renal dysfunction is not yet well studied, but the probable reason is that resistin enhances synthesis of proinflammatory cytokines and increases oxidative stress, which, consequently, causes glomerular dysfunction [39].

In our study, the prevalence of CB was high in the quartile with the lowest values of resistin. O. Pérez-Bautista et al. showed that in patients with chronic obstructive pulmonary disease, compared to the control group, the content of C-peptide, ghrelin, glucagon-like peptide-1, and leptin was higher, and the levels of glucagon and resistin were lower [40].

PAI-1, a member of the serine protease inhibitor superfamily, can be produced by various cells, such as platelets, adipocytes, vascular endothelial cells, endometrial cells, and liver cells. PAI-1 is one of the most powerful antifibrinolytic proteins that binds to a tissue plasminogen activator or a urokinase-type plasminogen activator, inhibiting their function and reducing plasmin production. Studies show that in patients with metabolic syndrome and (or) T2DM, plasma concentrations of PAI-1 are elevated, which contributes to the hypofibrinolytic environment [41]. In our study, the prevalence of T2DM was 2 times higher in the quartile with the highest values of PAI-1, compared to the quartile with the lowest values. The study on the prevalence of renal dysfunction (GFR 90) revealed the difference between the first and fourth

quartile of PAI-1. In the quartile with the lowest values of PAI-1, the incidence of renal dysfunction was 2.5 times higher.

CONCLUSION

In this study, we investigated the prevalence of some socially sensitive internal diseases (CHD, AH, T2DM, CB, renal dysfunction) and hypercholesterolemia, a risk factor in young people aged 25–44 years, depending on adipokine levels. The highest prevalence of internal diseases was found for lipocalin-2 and resistin. The prevalence of CB was associated with low values of these adipokines, while hypercholesterolemia, renal dysfunction, and AH were more common at high values of lipocalin-2 and resistin. The incidence of hypercholesterolemia was significantly higher in quartiles with the highest values of all studied adipokines. The prevalence of CHD was associated only with adiponectin levels.

Further studies aimed at investigating the molecular mechanisms underlying the effects of adipokines will allow to find a combined approach to restoring normal physiological levels of adipokines, which can have a positive effect in the studied internal diseases.

REFERENCES

1. Fasshauer M., Blüher M. Adipokines in health and disease. *Trends Pharmacol. Sci*. 2015;36(7):461–470. DOI: 10.1016/j.tips.2015.04.014.
2. Zhao S., Kusminski C.M., Scherer P.E. Adiponectin, leptin and cardiovascular disorders. *Circ. Res*. 2021;128(1):136–149. DOI: 10.1161/CIRCRESAHA.120.314458.
3. Bielecka-Dabrowa A., Bartlomiejczyk M.A., Sakowicz A., Maciejewski M., Banach M. The role of adipokines in the development of arterial stiffness and hypertension. *Angiology.* 2020;71(8):754–761. DOI: 10.1177/0003319720927203.
4. Mach F., Baigent C., Catapano A.L., Koskinas K.C., Casula M., Badimon L. et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *European Heart Journal*. 2020;1(1):111–188. DOI: 10.1093/eurheartj/ehz455.
5. Rydén L., Grant P.J., Anker S.D., Berne C., Cosentino F., Danchin N. et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *European Heart Journal*. 2013;34(39):3035–3087. DOI: 10.1093/eurheartj/eht108.
6. Arterial hypertension in adults. Clinical guidelines 2020. *Russ J Cardiol*. 2020;25(3):3786 (in Russ.). DOI: 10.15829/1560-4071-2020-3-3786.
7. Kokosov A.N. Chronic obstructive bronchitis. *Klinicheskaya Meditsina*. 1999;1:11–16 (in Russ.).
8. Achari A.E., Jain S.K. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int. J. Mol. Sci*. 2017;18:1321. DOI: 10.3390/ijms18061321.
9. Gariballa S., Alkaabi J., Yasin J., Al Essa A. Total adiponectin in overweight and obese subjects and its response to visceral fat loss. *BMC Endocr. Disord*. 2019;19(1):55. DOI: 10.1186/s12902-019-0386-z.
10. Liu C., Feng X., Li Q., Wang Y., Li Q., Hua M. Adiponectin, TNF-α and inflammatory cytokines and risk of type 2 diabetes: A systematic review and meta-analysis. *Cytokine*. 2016;86:100–109. DOI: 10.1016/j.cyto.2016.06.028.
11. Lindberg S., Jensen J.S., Pedersen S.H., Galatius S., Frystyk J., Flyvbjerg A. et al. Low adiponectin levels and increased risk of type 2 diabetes in patients with myocardial infarction. *Diabetes Care*. 2014;37:3003–3008.
12. Kou H., Deng J., Gao D., Song A., Han Z., Wei J. et al. Relationship among adiponectin, insulin resistance and atherosclerosis in non-diabetic hypertensive patients and healthy adults. *Clin. Exp. Hypertens*. 2018;40(7):656–663. DOI: 10.1080/10641963.2018.1425414.
13. Kim D.H., Kim C., Ding E.L., Townsend M.K., Lipsitz L.A. Adiponectin levels and the risk of hypertension: a systematic review and meta-analysis. *Hypertension.* 2013;62(1):27–32. DOI: 10.1161/HYPERTENSIONAHA.113.01453.
14. Doumatey A.P., Bentley A.R., Zhou J., Huang H., Adeyemo A., Rotimi C.N. Paradoxical hyperadiponectinemia is associated with the metabolically healthy obese (MHO) phenotype in African Americans. *J. Endocrinol. Metab*. 2012;2(2):51–65. DOI: 10.4021/jem95W.
15. Kobayashi H., Ouchi N., Kihara S., Walsh K., Kumada M., Abe Y. et al. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. *Circ. Res*. 2004;94(4):27–31. DOI: 10.1161/01.RES.0000119921.86460.37.
16. Woodward L., Akoumianakis I., Antoniades C. Unravelling the adiponectin paradox: Novel roles of adiponectin in the reg-ulation of cardiovascular disease. *Br. J. Pharmacol*. 2017;174:4007–4020. DOI: 10.1111/bph.13619.
17. Wannamethee S.G., Whincup P., Lennon L., Sattar N. Circulating adiponectin levels and mortality in elderly men with and without cardiovascular disease and heart failure. *Arch. Intern. Med.* 2007;167:1510–1517. DOI: 10.1001/archinte.167.14.1510.
18. McEntegart M.B., Awede B., Petrie M.C., Sattar N., Dunn F.G., Macfarlane N.G. et al. Increase in serum adiponectin concentration in patients with heart failure and cachexia: Relationship with leptin, other cytokines, and B-type natriuretic peptide. *Eur. Heart J*. 2007;28:829–835. DOI: 10.1093/eurheartj/ehm033.
21. Dornbush S., Aeddula N.R. Physiology, leptin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021.
19. Khazaei M., Tahergorabi Z. Leptin and its cardiovascular effects: Focus on angiogenesis. *Advanced Biomedical Research*. 2015;4(1):79. DOI: 10.4103/2277-9175.156526.
20. Fried S.K., Ricci M.R., Russell C.D., Laferrère B. Regulation of leptin production in humans. *J. Nutr.* 2000;130(12):3127S–3131S. DOI: 10.1093/jn/130.12.3127S.
21. Katsiki N., Mikhailidis D.P., Banach M. Leptin, cardiovas-

cular diseases and type 2 diabetes mellitus review-article. *Acta Pharmacol. Sin*. 2018;39:1176–1188. DOI: 10.1038/aps.2018.40.
22. Marchelek-Mysliwiec M., Wisniewska M., Nowosiad-Magda M., Safranow K., Kwiatkowska E., Banach B. et al. Association between plasma concentration of klotho protein, osteocalcin, leptin, adiponectin, and bone mineral density in patients with chronic kidney disease. *Horm. Metab. Res*. 2018;50:816–821. DOI: 10.1055/a-0752-4615.
23. Wang J.S., Lee W.J., Lee I.T., Lin S.Y., Lee W.L., Liang K.W. et al. Association between serum adipsin levels and insulin resistance in subjects with various degrees of glucose intolerance. *J. Endocr. Soc*. 2018;3(2):403–410. DOI: 10.1210/js.2018-00359.
24. VasilenkoM.A., Kirienkova E.V., Skuratovskaia D.A., Zatolokin P.A., Litvinova L.S., Mironyuk N.I. The role of adipsin and leptin production in the development of insulin resistance in patients with abdominal obesity. *Doklady Akademii Nauk.* 2017;475(3):336–341 (in Russ.). DOI: 10.7868/S0869565217210228.
25. Hertle E., Arts I.C., van der Kallen C.J., Feskens E.J., Schalkwijk C.G., Stehouwer C.D. et al. The alternative complement pathway is longitudinally associated with adverse cardiovascular outcomes. *Thromb. Haemost*. 2016;115(2):446–457. DOI: 10.1160/TH15-05-0439.
26. Song N.J., Kim S., Jang B.H., Chang S.H., Yun U.J., Park K.M. et al. Molecule-induced complement factor D (adipsin) promotes lipid accumulation and adipocyte differentiation. *PLoS One*. 2016;11(9):e0162228. DOI: 10.1371/journal.pone.0162228.
27. Jalal D., Renner B., Laskowski J., Stites E., Cooper J., Valente K. et al. Endothelial microparticles and systemic complement activation in patients with chronic kidney disease. *J. Am. Heart Assoc*. 2018;7(14):e007818. DOI: 10.1161/JAHA.117.007818.
28. Buonafine M., Martinez-Martinez E., Jaisser F. More than a simple biomarker: the role of NGAL in cardiovascular and renal diseases. *Clin. Sci. (London)*. 2018;132(9):909–923. DOI: 10.1042/CS20171592.
29. Cabedo Martinez A.I., Weinhäupl K., Lee W.K., Wolff N.A., Storch B., Żerko S. et al. Biochemical and structural characterization of the interaction between the siderocalin NGAL/LCN2 (neutrophil gelatinase-associated lipocalin/lipocalin 2) and the N-terminal domain of its endocytic receptor SLC22A17. *J. Biol. Chem.* 2016;291(6):2917–2930. DOI: 10.1074/jbc.M115.685644.
30. Chella Krishnan K., Sabir S., Shum M., Meng Y., Acín-Pérez R., Lang J.M. et al. Sex-specific metabolic functions of adipose lipocalin-2. *Mol. Metab*. 2019;30:30–47. DOI: 10.1016/j.molmet.2019.09.009.
31. Chong J.J.H., Prince R.L., Thompson P.L., Thavapalachandran S., Ooi E., Devine A. et al. Association between plasma neutrophil gelatinase-associated lipocalin and cardiac disease hospitalizations and deaths in older women. *J. Am. Heart Assoc*. 2019;8(1):e011028. DOI: 10.1161/JAHA.118.011028.
32. Cruz D.N., Gaiao S., Maisel A., Ronco C., Devarajan P. Neutrophil Gelatinase-Associated Lipocalin as a Biomarker of Cardiovascular Disease: A Systematic Review. *Clin. Chem. Lab. Med*. 2012;50:1533–1545. DOI: 10.1515/cclm-2012-0307.
33. Wang L.K., Wang H., Wu X.L., Shi L., Yang R.M., Wang Y.C. Relationships among resistin, adiponectin, and leptin and microvascular complications in patients with type 2 diabetes mellitus. *J. Int. Med. Res*. 2020;48(4):300060519870407. DOI: 10.1177/0300060519870407.
34. Niaz S., Latif J., Hussain S. Serum resistin: A possible link between inflammation, hypertension and coronary artery disease. *Pak. J. Med. Sci*. 2019;35(3):641–646. DOI: 10.12669/pjms.35.3.274.
35. Jiang Y., Lu L., Hu Y., Li Q., An C., Yu X. et al. Resistin induces hypertension and insulin resistance in mice via a TLR4-dependent pathway. *Sci. Rep*. 2016;6:22193. DOI: 10.1038/srep22193.
36. Chen C., Jiang J., Lü J.M., Chai H., Wang X., Lin P.H. et al. Resistin decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells. *Am. J. Physiol. Heart Circ. Physiol*. 2010;299(1):H193–201. DOI: 10.1152/ajpheart.00431.2009.
37. Axelsson J., Bergsten A., Qureshi A.R., Heimbürger O., Bárány P., Lönnqvist F. et al. Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance. *Kidney Int*. 2006;69(3):596–604. DOI: 10.1038/sj.ki.5000089.
38. Dan S., Aditya P., Banerjee P., Bal C., Roy H., Banerjee I. Effect of chronic kidney disease on serum resistin level. *Niger J. Clin. Pract*. 2014;17(6):735–738. DOI: 10.4103/1119-3077.144387.
39. Liu G., Deng Y., Sun L., Ye X., Yao P., Hu Y. et al. Elevated plasma tumor necrosis factor-α receptor 2 and resistin are associated with increased incidence of kidney function decline in Chinese adults. *Endocrine*. 2016;52(3):541–549. DOI: 10.1007/s12020-015-0807-3.
40. Pérez-Bautista O., Montaño M., Pérez-Padilla R., Zúñiga-Ramos J., Camacho-Priego M., Barrientos-Gutiérrez T. et al. Women with COPD by biomass show different serum profile of adipokines, incretins, and peptide hormones than smokers. *Respir. Res*. 2018;19(1):239. DOI: 10.1186/s12931-018-0943-4.
41. Vecchiola A., García K., González-Gómez L.M., Tapia-Castillo A., Artigas R., Baudrand R. et al. Plasminogen activator inhibitor-1 and adiponectin are associated with metabolic syndrome components. *Am. J. Hypertens*. 2022;35(4):311–318. DOI: 10.1093/ajh/hpab138.

Authors' contribution

Kashtanova E.V., Polonskaya Ya.V., Stakhneva E.M. – conception and design of the study, interpretation of the research data. Shcherbakova L.V. – statistical processing and analysis of the data, editing of the article. Shramko V.S. – carrying out of biochemical studies, analysis and interpretation of the research data. Sadovski E.V. – compilation of the database, analysis and interpretation of the research data. Khudyakova A.M., Denisova D.V. – analysis and interpretation of the research data. Ragino Yu.I. – final approval of the manuscript for publication.

Authors' information

Kashtanova Elena V. – Dr. Sci. (Biology), Associate Professor, Head of the Laboratory for Clinical, Biochemical and Hormonal Studies of Internal Diseases, Research Institute of Therapy and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, elekastanova@yandex.ru, http://orcid.org/0000-0003-2268-4186

Polonskaya Yana V. – Dr. Sci. (Biology), Senior Researcher, Laboratory for Clinical, Biochemical and Hormonal Studies of Internal Diseases, Research Institute of Therapy and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, yana-polonskaya@yandex.ru, http://orcid.org/0000-0002-3538-0280

Shcherbakova Lilia V. – Senior Researcher, Laboratory for Clinical, Population and Preventive Research of Internal and Endocrine Diseases, Research Institute of Therapy and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, 9584792@mail.ru, http://orcid.org/0000-0001-9270-9188

Shramko Victoria S. – Cand. Sci. (Med.), Researcher, Laboratory for Clinical, Biochemical and Hormonal Studies of Internal Diseases, Research Institute of Therapy and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, nosova@211.ru, http://orcid.org/0000-0002-0436-2549

Stakhneva Ekaterina M. – Cand. Sci. (Biology), Senior Researcher, Laboratory for Clinical, Biochemical and Hormonal Studies of Internal Diseases, Research Institute of Therapy and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, stahneva@yandex.ru, http://orcid.org/0000-0003-0484-6540

Khudyakova Alyona D. – Head of the Laboratory for Genetic and Environmental Determinants of the Human Life Cycle, Research Institute of Therapy and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, alene.elene@gmail.com, http://orcid.org/0000–0001–7875–1566

Sadovski Evgeny V. – Junior Researcher, Laboratory for Clinical, Biochemical and Hormonal Studies of Internal Diseases, Research Institute of Therapy and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, stinger000@mail.ru, http://orcid.org/0000-0001-7350-534X

Denisova Diana V. – Dr. Sci. (Med.), Principal Researcher, Laboratory for Preventive Medicine, Research Institute of Therapy and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, denisovadiana@gmail.com, http://orcid.org/0000–0002–2470–2133

Ragino Yulia I. – Dr. Sci. (Med.), Corresponding Member of the Russian Academy of Sciences, Head of Research Institute of Therapy and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, ragino@mail.ru, http://orcid.org/0000-0002-4936-8362

(✉) **Kashtanova Elena V.,** elekastanova@yandex.ru

Received 18.08.2023;
approved after peer review 11.09.2023;
accepted 14.09.2023