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Blood adipokins in young people with early ischemic heart disease on the background of abdominal obesity

Aim	To study blood adipokines spectrum in people aged 25–44 years with early ischemic heart disease (IHD), including that associated with abdominal obesity (AO).
Material and methods	A cross-sectional study was performed on a random sample of the population aged 25–44 years in Novosibirsk. 1457 subjects (653 men, 804 women) were evaluated. This study included 123 people divided into four study subgroups: subgroup 1, with IHD associated with AO (n=24); subgroup 2, with IHD and without AO (n=25); subgroup 3, without IHD and with AO (n=44); and subgroup 4, without either IHD or AO (n=30). Concentrations of serum adipokines were measured simultaneously by multiplex assay with a Luminex MAGPIX flow fluorometer and by immune enzyme assay with a MULTISCAN analyzer.
Results	Subjects with early IHD had lower blood concentrations of adipsin and visfatin than subjects without IHD. Subjects with early IHD associated with AO had higher blood concentrations of adipsin, plasminogen activator inhibitor-1, and leptin and lower concentrations of monocyte chemoattractant protein-1 (MCP-1) and visfatin compared to subjects with early IHD and without AO. The multivariate logistic regression analysis showed that lower blood concentrations of MCP-1 were associated with a likelihood of early IHD.
Conclusion	In young people aged 25–44 years, lower blood concentrations of MCP-1 were associated with a likelihood of early IHD, including that associated with AO.

Keywords	Early ischemic heart disease; abdominal obesity; blood adipokines; monocyte chemoattractant protein-1; multiplex analysis
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Introduction

Despite significant advances in the diagnosis and treatment of coronary artery disease (CAD), the number of cardiovascular diseases (CVDs) in young people is steadily increasing worldwide [1]. This is mainly due to the increasing prevalence of CVD risk factors (RFs). In comparison with elderly patients, those with early-onset CAD are more exposed to such RFs as smoking, abdominal obesity (AO), and family history than diabetes mellitus (DM) and arterial hypertension [2–4].

Much attention is currently paid to the concept according to which AO causes a mild chronic systemic inflammatory reaction, resulting from a combination of increased insulin resistance and increased production of inflammation mediators, due to the elevated levels of visceral/abdominal adipocytes [5, 6].

Biomolecules secreted by adipose cells (adipokines) in AO are an important research focus for modern medicine. Adipokines, also being endogenous biologically active mediators of inflammation secreted by visceral adipocytes, not only regulate intercellular and intersystem interactions, but also determine the processes of cell survival, stimulation or suppression of growth, cell differentiation, functional activity, and apoptosis. Adipokines coordinate the immune, endocrine, and nervous systems both under normal conditions and in response to pathological effects [7]. Adipocytokines produced by adipocytes and non-adipose cells (activated macrophages forming giant cells) are a wide range of various biomolecules, such as hormones [adiponectin, resistin, leptin, visfatin), pro-inflammatory cytokines (interleukins (IL) – 1 beta, IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor-alpha (TNF-α)], molecules of the complement system (adipsin), and vascular hemostasis [plasminogen activator inhibitor 1 (PAI-1)], etc [8].

Visceral fat tissue is currently seen as an integral relationship between the development of metabolic disorders

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and CVDs. Numerous studies have shown that adipokine imbalance is highly associated with an increased risk of cardiometabolic diseases and complications [9–11].

Given the effects of visceral obesity on human health in general and CAD in particular, we tested a hypothetic relation between the development of early CAD in the presence of AO and changes in the blood levels of adipokines in this particular population. Specifically, we assumed an increase in the leptin/adiponectin ratio [12], elevated levels of visfatin and MCP-1 according to the recent findings [13, 14].

Aim

To study the spectrum of blood adipokines in patients aged 25–44 years with early-onset CAD, including with AO.

Materials and methods

A cross-sectional population study of a random sample of the Novosibirsk population aged 25–44 years was conducted in the Research Institute for Internal and Preventive Medicine. The study was approved by the Ethics Committee of the Institute. All subjects signed informed consent forms for the examination and processing of personal data. The study included a survey using a set of validated questionnaires, including the Rose Angina Questionnaire (RAQ), anthropometry (height, body weight, waist circumference (WC), and hip circumference (HC) with the calculation of the waist-to-hip ratio, body mass index, history taking, electrocardiogram (ECG) interpreted according to the Minnesota code, ultrasonography, etc. CAD was diagnosed according to the following criteria: large-focal myocardial infarction (MI) on ECG, exertional angina according to the RAG, ischemic changes on ECG without left ventricular hypertrophy, rhythm, and conduction disturbances. AO was established with WC more than 80 cm in female patients and more than 94 cm in male patients.

The study included all patients with CAD from the population sample and a control group comparable in age and sex with a total of 123 people who were divided into four subgroups:

- Group 1 – patients with CAD and with AO (n = 24, 8 male and 16 female);
- Group 2 – patients with CAD without AO (n = 25, 10 male and 15 female);
- Group 3 – patients without CAD and with AO (n = 44, 20 male and 24 female); and
- Group 4 – patients without CAD and without AO (n = 30, 12 male and 18 female).

Detailed characteristics of the study subgroups examined are presented in Table 1.

Blood samples for biochemical analysis were collected from all patients after fasting in the morning, from the median cubital vein, not earlier than 12 hours after the last meal.

The modern multiplex technology of biochemical analysis in medical and biological research allows evaluating blood levels of a large range of cytokines/chemokines, including those little studied in the pathogenesis of CVDs. Therefore, the simultaneous analysis of serum levels of adipokines was performed using a multiplex analysis on a Luminex MAGPIX flow-through fluorometer with two panels (Millipore): HADK1MAG-61-KMILLIPLEXMAP Human Adipokine Magnetic Bead Panel 1, determining such adipokines as adiponectin, adipsin, lipocalin-2, plasminogen activator inhibitor 1 (PAI-1), resistin, and HADK2MAG-61KMIL-LIPLEXMAP Human Adipokine Magnetic Bead Panel 2, determining such adipokines as IL-1 beta, IL-6, IL-8, insulin, leptin, MCP-1, TNF-alpha, and nerve growth factor (NGF). Two more adipokines, visfatin and omentin-1, were estimated in blood serum by immunoassay on a MULTISCAN analyzer using RayBiotech test systems.

The data obtained were statistically processed using SPSS v.17.0. The results are presented as the median and interquartile range (Me [25th percentile, 75th percentile]). The samples were compared using the non-parametric Mann–Whitney U-test, Wilcoxon test, ANOVA with Dunnett's

Table 1. Anthropometric and clinical characteristics of the examined patients

Indicator	Patients without CAD		p	Patients with CAD		p
	Without AO	With AO		Without AO	With AO	
Age, years	35.0 [31.0; 40.3]	37.0 [30.5; 42.0]	0.590	34.5 [31.3; 41.5]	41.0 [36.8; 45.3]	0.042
WC, cm	74.9 [70.5; 76.2]	90.7 [84.0; 98.2]	<0.001	67.2 [66.0; 78.0]	86.1 [83.2; 96.5]	<0.001
BMI, kg/m^2	22.9 [20.8; 25.4]	28.9 [25.6; 33.1]	<0.001	21.5 [19.6; 24.0]	28.7 [26.8; 33.6]	<0.001
HR, bpm	73.5 [64.0; 79.0]	77.0 [68.5; 81.0]	0.024	69.0 [63.0; 82.8]	71.0 [66.3; 80.8]	0.298
AH, %	6.7	18.2	0.159	8.0	37.5	0.017
SBP, mm Hg	118.0 [108.0; 126.8]	118.2 [112.1; 130.0]	0.758	120.5 [109.4; 132.6]	124.8 [111.0; 147.4]	0.190
DBP, mm Hg	77.5 [71.4; 83.4]	80.0 [71.6; 87.5]	0.352	79.7 [66.1; 84.5]	80.5 [72.4; 94.4]	0.250

The data are presented as the median and interquartile range (Me [25th percentile; 75th percentile]) and relative rate (%) for AH.
CAD, coronary artery disease; AO, abdominal obesity; WC, waist circumference; BMI, body mass index; HR, heart rate; AH, arterial hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

multiple comparison test. We performed a logistic regression analysis with the definition of odds ratio (OR) and 95% confidence interval (CI). The differences were statistically significant at $p < 0.05$.

Results

We identified changes in the levels of some adipokines in young people with early CAD compared to those without CAD (Table 2). Patients without CAD demonstrated 1.1 and 1.05 times lower blood levels of adipsin and visfatin, respectively, compared to those without CAD. Moreover, in CAD patients, a trend ($p = 0.05$) toward lower blood levels of MCP-1 (1.3 times) was observed.

Next, we conducted a similar analysis depending on the presence of AO in young people (Table 3). Patients with CAD in the presence of AO had 1.25, 1.3, and 3.3 times higher blood levels of adipsin, PAI-1, and leptin, respectively, and 1.5 and 1.05 times lower levels of MCP-1 and visfatin, respectively, than those with CAD and without AO. Insulin levels were also higher in patients with AO.

Table 2. Serum adipokines in CAD

Adipokine	Patients without CAD (n=74)	Patients with CAD (n=49)	p
Adipsin, ng/mL	6188.52 [5145.15; 8854.56]	5409.43 [4429.71; 7137.06]	0.024
Visfatin, pg/mL	8.74 [7.78; 9.72]	8.32 [7.11; 8.82]	0.027
MCP-1, pg/mL	451.26 [296.33; 639.50]	349.98 [201.38; 575.92]	0.049
Adiponectin, pg/mL	103.16 [49.06; 439.40]	144.50 [57.69; 241.10]	0.833
Resistin, ng/mL	33.06 [25.54; 45.26]	28.93 [22.14; 37.16]	0.194
IL-1 beta, pg/mL	1.58 [0.72; 2.23]	1.47 [0.62; 2.26]	0.711
IL-6, pg/mL	1.73 [1.05; 2.76]	1.76 [1.03; 6.14]	0.280
IL-8, pg/mL	9.54 [6.22; 13.43]	9.10 [5.66; 15.01]	0.715
Insulin, pg/mL	171.95 [72.89; 389.74]	198.74 [107.51; 383.09]	0.715
Leptin, pg/mL	2393.00 [862.12; 4731.50]	1939.50 [808.80; 4671.00]	0.719
PAI-1, ng/mL	58.54 [44.70; 84.29]	55.28 [42.26; 84.60]	0.359
NGF, pg/mL	0.47 [0.32; 0.56]	0.39 [0.31; 0.56]	0.529
TNF-alpha, pg/mL	15.39 [10.78; 20.23]	13.88 [9.36; 19.67]	0.266
Lipocalin-2, ng/mL	204.73 [132.17; 302.82]	167.04 [127.99; 206.25]	0.112
Omentin-1, pg/mL	0.065 [0.034; 0.084]	0.057 [0.041; 0.087]	0.997

The data are presented as the median and interquartile range (Me [25th percentile; 75th percentile]). CAD, coronary artery disease; MCP-1, monocyte chemoattractant protein 1; IL, interleukin; PAI-1, plasminogen activator inhibitor 1; NGF, nerve growth factor; TNF-alpha, tumor necrosis factor-alpha.

Table 3. Adipokine levels in CAD with and without AO

Adipokine	Patients without CAD (n=74)		p	Patients with CAD (n=49)		p
	Without AO (n=30)	With AO (n=44)		Without AO (n=25)	With AO (n=24)	
Adipsin, ng/mL	6099.6 [4820.7; 9945.6]	7416.5 [5708.4; 9956.4]	0.049	4736.6 [3980.3; 6806.3]	5929.7 [4904.7; 7580.3]	0.041
PAI-1, ng/mL	56.37 [42.61; 81.32]	63.88 [52.83; 104.86]	0.049	48.92 [39.75; 68.90]	63.01 [48.89; 89.18]	0.048
Insulin, pg/mL	118.87 [56.57; 212.44]	353.98 [140.73; 449.57]	0.019	154.16 [68.18; 308.37]	315.80 [144.90; 395.92]	0.015
Leptin, pg/mL	867.23 [726.34; 2571.0]	3610.5 [2383.7; 8471.0]	0.001	1300.0 [462.39; 1968.2]	4247.5 [2014.5; 7961.7]	0.001
MCP-1, pg/mL	394.65 [294.39; 510.46]	577.14 [454.75; 711.32]	0.052	375.23 [279.13; 642.85]	250 [162.02; 517.03]	0.101
Visfatin, pg/mL	9.42 [8.0; 9.87]	8.17 [7.47; 8.98]	0.048	8.38 [7.37; 9.02]	7.92 [6.60; 8.58]	0.019
IL-1 beta, pg/mL	1.57 [0.64; 2.18]	1.23 [0.56; 2.2]	0.267	1.56 [0.62; 5.24]	2.1 [0.52; 3.13]	0.662
IL-6, pg/mL	2.34 [1.18; 3.58]	2.26 [1.22; 3.57]	0.362	2.08 [1.05; 7.06]	1.46 [1.02; 4.76]	0.529
IL-8, pg/mL	8.9 [5.78; 12.53]	9.75 [6.99; 15.17]	0.694	8.57 [4.25; 15.29]	9.50 [6.24; 14.96]	0.609
Lipocalin-2, ng/mL	201.82 [141.13; 255.78]	258.95 [111.44; 352.69]	0.243	134.38 [115.12; 243.85]	178.55 [153.52; 205.68]	0.355
Adiponectin, pg/mL	236.25 [69.91; 458.78]	61.95 [22.08; 426.56]	0.419	144.50 [75.43; 400.77]	147.27 [36.98; 191.19]	0.517
Resistin, ng/mL	31.66 [26.77; 40.30]	34.56 [21.30; 48.79]	0.507	25.54 [19.13; 45.17]	30.53 [25.79; 34.88]	0.589
NGF, pg/mL	0.44 [0.39; 0.56]	0.47 [0.31; 0.65]	0.496	0.39 [0.31; 0.54]	0.44 [0.39; 0.58]	0.377
TNF-alpha, pg/mL	15.07 [13.17; 21.45]	17.39 [0.42; 20.47]	0.961	14.52 [9.72; 20.92]	13.83 [8.92;19.67]	0.515
Omentin-1, pg/mL	0.069 [0.049; 0.091]	0.050 [0.033; 0.082]	0.177	0.063 [0.043; 0.093]	0.045 [0.035; 0.082]	0.233

The data are presented as the median and interquartile range (Me [25th percentile; 75th percentile]). CAD, coronary artery disease; AO, abdominal obesity; PAI-1, plasminogen activator inhibitor 1; MCP-1, monocyte chemoattractant protein 1; IL, interleukin; NGF, nerve growth factor; TNF-alpha, tumor necrosis factor-alpha.

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Table 4. Results of logistic regression analysis of the association of adipokines with the risk of CAD

Indicator	Univariate analysis			Multivariate analysis		
	Exp B	95% CI	p	Exp B	95% CI	p
Adipsin	0.999	0.998–1.001	0.062	0.999	0.998–1.001	0.550
PAI-1	0.999	0.997–1.005	0.219	0.999	0.997–1.002	0.634
Insulin	1.001	0.999–1.002	0.365	1.002	0.999–1.004	0.102
Leptin	0.998	0.997–1.001	0.742	0.999	0.998–1.001	0.622
MCP-1	0.998	0.997–1.002	0.122	0.997	0.995–0.999	0.008
Visfatin	1.005	0.970–1.041	0.779	1.001	0.964–1.038	0.980

CAD, coronary artery disease; CI, confidence interval;
PAI-1, plasminogen activator inhibitor 1; MCP-1, monocyte chemoattractant protein 1.

Table 5. Results of logistic regression analysis of the association of adipokines with the risk of CAD with abdominal obesity

Indicator	Univariate analysis			Multivariate analysis		
	Exp B	95% CI	p	Exp B	95% CI	p
Adipsin	0.999	0.998–1.001	0.096	0.999	0.998–1.001	0.109
PAI-1	0.999	0.997–1.001	0.341	1.000	0.998–1.001	0.222
Insulin	1.000	0.997–1.002	0.829	1.003	0.998–1.007	0.174
Leptin	1.000	0.999–1.001	0.934	0.999	0.997–1.002	0.905
MCP-1	0.997	0.995–0.999	0.018	0.995	0.991–0.999	0.006
Visfatin	0.869	0.652–1.159	0.341	0.835	0.612–1.139	0.254

CAD, coronary artery disease; CI, confidence interval;
PAI-1, plasminogen activator inhibitor 1; MCP-1, monocyte chemoattractant protein 1.

The results of an univariate and multivariate logistic regression analysis (age- and sex-adjusted) conducted to investigate the relationship between adipokines and the risk of early CAD in all young people included in the study are presented in Table 4. The univariate regression analysis showed only a trend (p = 0.062) that the risk of developing early CAD is associated with lower blood levels of adipsin (OR 0.999, 95% CI 0.998–1.001). According to the multivariate logistic regression analysis, the risk of developing early CAD was associated with lower blood levels of MCP-1. According to the multivariate logistic regression analysis, the risk of developing early CAD turned out to be associated with lower blood levels of MCP-1 (OR 0.997, 95% CI 0.995–0.999; p=0.008).

The results of the univariate and multivariate logistic regression analysis (age- and sex-adjusted) conducted to reveal the relationship between adipokines and the risk of early CAD in young people with AO are presented in Table 5. It can be seen that the risk of developing early CAD in the presence of AO was associated with lower blood levels of MCP-1.

Thus, we identified lower levels of adipsin and visfatin in all patients with early CAD, and a trend toward lower levels of MCP-1. The division of patients with early CAD into subgroups with and without AO showed that early CAD in the presence of AO was associated with higher levels of adipsin, PAI-1, leptin, insulin, statistically significantly lower levels of visfatin and MCP-1.

Discussion

It should be noted that only some of our findings are consistent with those presented in foreign literature.

For example, adipsin (complement factor D), being a trypsin peptidase, is mainly secreted by adipocytes, monocytes, and macrophages, and catalyzes the limiting stage of the alternative complement pathway. Its pathophysiological role in the development of CVDs is not well understood. Ohtsuki et al. [15] examined 370 patients with coronary atherosclerosis and concluded that serum levels of adipsin were directly associated with the adverse prognosis (death and re-hospitalization) for patients with CAD. Tafere et al. [16] discovered that patients with DM had low blood levels of adipsin and that biomoleconolecer could be used as a new auxiliary biomarker in the diagnosis of insulin resistance and DM. Our data on adipsin, at a first glance, are not entirely consistent with the literature. This can be explained by the fact that, on the one hand, we investigated the younger population. On the other hand, in our study, patients with early CAD in the presence of AO also showed higher insulin levels. It should be noted that adipsin levels decrease in DM when beta-cell insufficiency develops [17].

PAI-1 is a serine protease inhibitor that is inherently involved in the blood clotting process, the violation of which intensifies the processes of atherogenesis. There is a direct relation of PAI-1 blood levels with some CAD RFs, such as obesity, hyperglycemia [18], and metabolic syndrome [19].

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Furthermore, some prospective studies showed a correlation of elevated blood levels of PAI-1 with the risk of developing CAD [20, 21]. Out data on PAI-1 levels are also consistent with the above studies.

Leptin secreted by adipocytes is an important link between obesity and the development of CVDs. The associations between the blood levels of leptin and stroke, chronic heart failure, acute MI, and CAD have been described [22]. The results of the NHANES III study showed that high blood levels of leptin are independently associated with acute MI in male and female patients [23]. In a case-control cohort study, Kappelle et al. [24] showed that the incidence of CVDs was directly associated with the blood levels of leptin and adiponectin and the leptin/adiponectin ratio. According to the authors, the leptin/adiponectin ratio may be the most sensitive marker of CVDs in male patients, compared to individual indicators of blood leptin and adiponectin. We also detected higher levels of leptin in patients with early CAD in the presence of AO.

Our data on visfatin are far from being consistent with other studies. Visfatin secreted by adipocytes is a protein of the acute phase of inflammation that inhibits apoptosis. The results of meta-analysis by Yu et al. [14], which included 15 articles, 1,053 patients with CAD and 714 control subjects, indicate that the blood levels of visfatin in CAD are significantly higher than those in the control subjects. These results suggest that increased blood levels of visfatin may be a marker of CAD risk. Auguet et al. [25] found that the content of visfatin in an unstable carotid plaque was significantly higher than in the atherosclerotic artery wall. Zheng et al. [26] showed that the blood levels of visfatin in patients with CD and with carotid plaques were higher than in patients with DM without plaques. The logistic regression analysis results showed that higher blood levels of visfatin were an independent predictor of the presence of atherosclerotic plaques. All the above data on visfatin are reported by studies in patients over 45 years old. In our study, the blood levels of visfatin are negatively associated with early CAD. This fact may be due to the younger age of subjects (25–44 years), and the association of visfatin with CAD at this age may be slightly different from the literature data. Factors of acute inflammation may not be essential to the development of the disease at such an early age.

Our findings on pro-inflammatory MCP-1 also contradict those obtained in other studies. For example, it is known that MSR-1 is a link between adipocyte-induced inflammation and the development of atherosclerotic processes, due to inducing the migration of macrophages into a developing plaque. Its blood levels are elevated in obese patients, which leads to the recruitment of monocytes from the bone marrow into the tissues through the blood flow [27, 28]. MRD-1 can induce macrophage division in fat tissue implants, and in-vivo MRD-1 deficiency reduces the proliferation of adipose macrophages [29]. While most data confirm the role of MCP-1 in the development of obesity-related pathology, there are some inconsistencies in the literature. For example, Inouye et al. [30] reported no changes in the number of adipose macrophages in obese mice with MSR-1 deficiency caused by a high-fat diet. However, the same authors showed that these mice gained greater body mass and were glucose intolerant. Cranford et al. [31] showed that MSR-1 deficiency could have different effects on metabolic and inflammatory processes depending on the genetic background. The results of our study on MSR-1 are also somewhat inconsistent with the traditional world literature data in relation to this biomolecule. As we have indicated, it might be due to the younger age of subjects (25–44 years), and the associations of MSR-1 with early CAD are less evident. Hypothetically, this can directly depend on the normal hormonal status of the young organism, when sufficient hormone levels restrain the activity of pro-inflammatory chemotactic disorders. Moreover, it may be due to the small number of patients with CAD in our study, but we were limited in this regard by the young age of the subjects.

Conclusion

Summarizing the findings, it should be noted that there are few similar studies of adipokines in early coronary artery disease in young people. We found that lower levels of monocyte chemoattractant protein 1 were associated in young people aged 25 to 44 years with the risk of developing early coronary artery disease, including in the presence of abdominal obesity. However, it is premature to talk about the unconditional practical significance of estimating the blood levels of monocyte chemoattractant protein 1 to assess the risks of early coronary artery disease. Nevertheless, this is a promising direction for further research in studying the development of coronary artery disease, especially early development, in the presence of abdominal obesity.

No conflict of interest is reported.

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