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Markers of visceral obesity dysfunction and association with cardiovascular risk

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The aim of the study was to evaluate apelin-12 in obese patients in relation to the imdices of visceral obesity.

Methods. A total of 167 individuals aged 40-70 years without diagnosed cardiovascular diseases (CVD) were studied. All patients were divided according to the degree of obesity: group 1 with excessive body weight consisted of 27 individuals, group 2 with class 1 obesity — 108 individuals, group 3 with class 2 obesity — 32 individuals. The control group consisted of 27 healthy subjects. Cardiovascular risk (CVR) was assessed using the SCORE-2 scale. The examination included assessment of anthropometric parameters; determination of lipids, glucose, apelin-12 in blood serum; echocardiography; assessment of body composition by bioimpedance analysis. To evaluate the state of lipid metabolism, we also used special highly specific indices such as: Kahn's lipid accumulation products (LAP); Amato's visceral obesity index (VOI), fatty liver index (FLI) and hepatic steatosis index (HSI).

Results. The study of apelin-12 levels with the parameters of visceral adipose tissue (VAT) dysfunction depending on CVR showed correlations, which allows to predict the progression of visceral obesity by using additional markers. Assessment of such markers as apelin-12 for prediction of lipid metabolism disorders progression, VAT dysfunction together with assessment of estimated VAT indices (VOI, % of adipose tissue, visceral fat level according to bioimpedance analysis, FLI, HSI, epicardial adipose

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tissue thickness) can be included in the algorithm of patient examination for assessment of VAT dysfunction and CVR prevention.

Conclusion. Apelin-12 can be used to assess and predict the progression of lipid metabolism disorders, VAT dysfunction, and together with the assessment of estimated VAT indices (VOI, % adipose tissue, visceral fat level according to bioimpedance analysis, HSI and FLI) may be included in the algorithm of patient examination to assess VAT dysfunction and to prevent CVR.

Keywords: obesity, visceral obesity, biomarkers, apelin-12, cardiovascular diseases.

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Introduction

Obesity has gained the status of a non-infectious pandemic in the XXI century. The associated metabolic disorders are becoming one of the major risk factors (RF) for the development and progression of cardiovascular diseases (CVD). The greatest risk of CVD is associated with visceral obesity and its characteristic metabolic shifts (insulin resistance (IR), hyperglycemia, dyslipidemia, imbalance of adipokines and inflammatory markers). Visceral obesity is associated with an increased risk of carbohydrate and lipid metabolism disorders development, as well as with cardiovascular complications [1]. Currently, many adipokines are known: leptin, adiponectin, apelin, etc. An increase in the concentration of apelin in obesity and its association specifically with the visceral type of adipose tissue distribution has been noted [2]. Thus, a number of authors indicate that the increase in the degree of abdominal obesity (AO) is accompanied by a statistically significant increase in plasma apelin levels [3]. Apelin is positively correlated with waist circumference (WC) and the ratio of WC to hip circumference (HC).

Foreign authors note an increase in the level of apelin in obesity in combination with hyperinsulinemia [4]. In this regard, prediction and early detection of cardiometabolic disorders is an urgent task of modern medicine, the solution of which can be achieved by clinical methods, functional diagnostics, as well as by methods of non-invasive laboratory diagnostics. Currently, there are a number of anthropometric and instrumental methods for quantitative assessment of adipose tissue. However, not all of them fully reflect the degree of visceral obesity and cardiovascular risk (CVR). According to several authors, serum levels of apelin were higher in obese subjects compared to controls, with concentrations of the biomarker positively correlated with body mass index (BMI), cholesterol, insulin, fasting glucose, and IR, with apelin being a more sensitive biomarker of visceral adipose tissue (VAT) dysfunction than adiponectin and leptin [5]. The search for new reliable biomarkers and diagnostic methods for visceral obesity is an important task in the prevention of cardiometabolic complications.

The aim of the study was to evaluate apelin-12 in obese patients in relation to indicators of visceral obesity.

Methods

A total of 167 overweight and obese individuals with first and second classes of obesity, aged 40–70 years, without previously diagnosed CVD were studied. The mean age was 49.3±12.1 years. 42 patients (25%) were men and 125 patients (75%) were female.

The scientific research was conducted within the innovation project № IL-402104184: "Creation of mobile application of personal health card and development of individual wellness program for prevention of cardiovascular diseases at the level of primary health care" in the Central Consultative and Diagnostic Polyclinic №1, the Main Medical Department Under the Administration of the President of the Republic of Uzbekistan. The study was performed on an outpatient basis.

Exclusion criteria were: unstable angina or previous myocardial infarction, chronic coronary heart disease (CHD), chronic heart failure; clinically evident atherosclerosis with hemodynamically significant stenosis of the main arteries, etc., musculoskeletal problems significantly limiting walking; uncontrolled angina pectoris or arterial hypertension, heart rate greater than 120 beats/min, other significant diseas-

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es, the course of which may worsen due to functional impairment.

The control group consisted of 27 healthy individuals with low CVR according to SCORE-2 and normal body weight. All patients were distributed depending on the class of obesity: group 1 with excessive body weight consisted of 27 individuals with body mass index (BMI) = 29.3±1.4 kg/m^2 (women — 22, men — 5), group 2 with class 1 obesity consisted of 108 individuals with BMI = 34.9±1.3 kg/m^2 (women — 78, men — 30), group 2 with class 2 obesity — 32 individuals with BMI = 39.2±2.4 kg/m^2 (women — 25, men — 7).

CVR was assessed according to SCORE-2: 82 subjects were with low and moderate CVR, 49 subjects — with high CVR, 36 subjects — with very high CVR without coronary CVD. The examination included assessment of anthropometric parameters such as body mass (BM), height, WC and HC, BMI (BMI = kg/height, m2), WC/HC ratio. Clinical and laboratory parameters such as blood pressure, serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), calculated by formula non-HDL-C (TC — LDL-C), serum glucose, serum apelin-12 were also determined. Echocardiography (EchoCG) with determination of cardiac structural and geometric parameters such as left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD), and epicardial adipose tissue thickness (EATT) by coronary sulcus (CS) was performed [1, 4]. Apelin-12 levels in blood serum were determined by enzyme immunoassay method with "Apelin-12 (Human, Rat, Mouse, Bovine) EIA Kit" reagent kit from Phoenix Pharmaceuticals (USA) [6]. Body composition was assessed by bioimpedance analysis: determination of the percentage of visceral and total adipose tissue. To assess the state of lipid metabolism, we also used the following indices [7]:

The lipid accumulation product (LAP) was calculated by Kahn,

$$LAP = (WC\ (cm) - 65) \times TG;$$

Visceral obesity index (VOI) was calculated by Amato:

— in males:

$$VOI = (WC/39.68 + 1.88 \times BMI) \times (TG/1.03) \times (1.31/HDL - C);$$

— in females:

$$VOI = (WC/36.58 + 1.89 \times BMI) \times (TG/0.81) \times (1.52/HDL\text{-}C).$$

The VOI of 1.93 is considered normal, 1.94–2.32 indicates mild adipose tissue dysfunction, 2.32–3.25 — moderate adipose tissue dysfunction, VAI >3.25 — high adipose tissue dysfunction;

Fatty liver index

$$(FLI) = -3{,}5856 + (0{,}0141 \times age) + (0{,}4711 \times DM) + (4{,}4373 \times WC/height \times 100).$$

It the diabetes is present, then DM — 1, else — 0;

Hepatic steatosis index (HSI) = 8× ALT/AST+BMI (+2 in case of type 2 DM, +2 if female). HSI values>36.0 indicate the presence of hepatic steatosis in the patient with a sensitivity of 93.1 %, specificity of 92.4 % with an AUROC accuracy of 0.812.

Statistical analysis

Statistical processing of the results was carried out by "Excel 2019" program. Quantitative data were described by descriptive statistics and are presented as mean ± standard deviation (median and range are given in parentheses for data with non-normal distribution type). Qualitative data are presented as absolute and relative frequencies. Comparisons between groups were performed using analysis of variance (ANOVA), including its non-parametric variant (ranked ANOVA) for non-normal data distribution. To assess the intragroup dynamics under the condition of normal distribution of data and equality of dispersions we used paired Student's t-test with the Levene and Welch modifications. Wilcoxon signed-rank test was used in case of other types of distribution. The dynamics of change in proportions within the group was assessed using the McNemar test. The Cochran-Armitage test for linear trend was used to assess the tendency of proportions changes. Correlations were assesed by the Spearman's rank correlation coefficient. The level of statistical significance was $p < 0.05$.

Results

While assessing the anthropometric parameters we evaluated BM, height, WC and HC with their ratio, BMI, as well as additional data from bioimpedance analysis of body composition: determination of the percentage of visceral and total adipose tissue, biochemical markers of lipid metabolism disorders, glucose, apelin-12, calculated indices of visceral obesity. These parameters are shown in Table 1.

Significant differences in anthropometric parameters were observed in high-risk and very high-risk individuals compared to the control group. There was an increase in WC/HC ratio, BMI in overweight and obese individuals, respectively, compared to the con-

Table 1. **VAT dysfunction indices, parameters of fat and lipid metabolism in groups depending on the class of obesity**

№	Parameters	Control (n=27)	Overweight (n=27)	Class 1 obesity (n=108)	Class 2 obesity (n=32)
1	Age, years	32.6±6.9	54±9.8	59.3±6.8	45.5±4.3
2	CVR according to SCORE-2	1.25±1.1	5.5±7.1	10.5±8.7	11.5±7.8
3	BM, kg	63.4±7.7	88.7±9.0*	103.2±13.8*	119.1±15.2*
4	WC, cm	76.7±5.9	99.6±9.2*	109.9±10.5*	118±12.2*
5	HC, cm	93.7±5.8	111.8±7.2*	120.9±7.5*	127.4±9.1*
6	WC/HC	0.82±0.08	0.90±0.07*	0.91±0.08*	0.93±0.1*
7	BMI	22.8±2.3	29.3±1.4*	34.9±1.3*	39.2±2.4*
8	Adipose tissue, %	26.4±7.9	40.16±8.01*	43.4±8.1*	45.8±5.6*
9	Visceral (abdominal) fat	5.11±1.8	11.7±3.1*	14.5±4.2*	17.3±4.1*
10	TC, mmol/l	4.8±0.8	5.2±0.8	5.32±0.8*	5.75±0.8*
11	TG, mmol/l	1.2±0.9	1.69±1.01	1.81±1.0*	2.1±1.2*
12	LDL-C, mmol/l	2.5±0.8	3.26±0.9	3.41±0.9*	3.6±0.9*
13	HDL-C, mmol/l	1.04±0.2	0.9±0.3	1.0±0.3	1.01±0.3*
14	Non-HDL-C, mmol/l	2.4±0.8	2.8±0.8	3.52±0.8*	4.51±0.82*
15	ALT, u/l	15.6±5.6	17.9±6.07	16.7±6.3	16.6±5.8
16	AST, u/l	17.2±6.6	16.05±6.06	16.9±6.5	17±5.5
17	CRP, mg/l	1.8±0.7	3.5±1.5*	4.8±2.1*	5.2±1.8*
18	LAP	70.5±8.2	72.6±9.1	76.3±8.5	82.6±9.5*
19	VOI	2.7±0.32	3.5±0.3*	4.5±0.4*	5.3±0.5*
20	FLI	–0.568±0.1	–0.497±0.15*	–0.395±0.09*	–0.387±0.09*
21	HSI	32.0±4.5	36.8±5.3	47.3±4.3*	50.3±6.0*
21	Apelin-12, pg/ml	0.79**±0**.4	3.18±0.55*	7.09±2.9*	19.49±8.1*
22	EchoCG EATT in CS, mm	2.8**±0**.9	5.18±1.55*	7.09±2.9*	9.5±4.3*

Note. * — significant differences, p<0.05.

trol group; the direct correlation of BMI in groups 1, 2, 3 with CVR according to SCORE-2 was revealed (r=0.68, 0.65 and r=0.76, respectively). Obesity and overweight are among the leading causes of CVD and significantly increase the pathophysiological effects of CVR factors [1].

Indices highly specific for CVR and mortality, such as LAP according to Kahn; VOI according to Amato, HIS were used [7].

According to the results of our study, we found a correlation between WC/HC ratio and visceral fat index according to bioimpedance analysis of body composition with a correlation coefficient of r=0.74. LAP index values highly correlated with BMI. The Spearman rank correlation coefficient between LAP index values and BMI was 0.73 in men (p<0.05) and 0.77 in women (p<0.05) [7].

When comparing the functional indices of obesity, significant differences were found. LAP in the class 2 obesity group was 17% (p<0.05) higher compared to the control (p<0.05). VOI in the groups with excess body weight, class 1 obesity, and class 2 obesity was 25.7% (p<0.05), 42% (p<0.05) and 51% (p<0.05) higher compared to the control. Increased VOI and LAP indicated VAT dysfunction and excessive visceral fat accumulation. There was a significant increase in % of adipose tissue and visceral fat levels in all groups; even the indices in the overweight group were 23.3% (p<0.05) and 57.2% (p<0.05) higher, respectively, compared to controls, which may be an indicator of visceral obesity in groups even with normal BM. More significant and reliable increase in % of adipose tissue and visceral fat according to bioimpedance analysis of body composition was found in obese groups: 29% (p<0.05) and 65.5% (p<0.05) in class 1 obesity, 32.7% (p<0.05) and 71% (p<0.05) in class 2 obesity, compared to control group.

When comparing the functional indices of VAT, reliable differences were found: increase of HSI in groups 1, 2 and 3 by 11.7%, 31% (p<0.05) and 35% (p<0.05), respectively, compared to the control group. HSI values >36.0 indicate the presence of hepatic steatosis in the patient with a sensitivity of 93.1%, specificity of 92.4% and AUROC accuracy of 0.812 [8]. There was a significant increase in HSI in overweight, class 1 obesity and class 2 obesity groups by 15% (p<0.05), 44.8% (p<0.05) and 47.8% (p<0.05), respectively, compared to control.

AO was detected by WC/HC ratio in 69% of subjects; in 96% of subjects by BMI, % of adipose tissue

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and by visceral fat, which are reliable indicators of impaired lipid metabolism and independent CVD RF.

According to the results of our study, there was a significant increase in the level of TC, LDL-C, non-HDL-C, TG in groups with class 1 and 2 obesity. There was a direct correlation between BMI and non-HDL-C and LDL-C (r=0.86 and r=0.76, p<0.05). Thus, we can assess the dysfunction of lipid metabolism in all groups: in overweight and obese subjects with high CVR without CVD and with CVD, and in overweight, obese and normal BM.

The results showed a significant increase in EATT in overweight, class 1 obesity, and class 2 obesity groups by 85% (p<0.05), 150% (p<0.05), and 239% (p<0.05), respectively, compared to control. There was a correlation of EATT with the level of CVR according to SCORE-2 and BMI with correlation coefficients of r=0.82 and r=0.70, respectively (p<0.05). Increased EATT is associated with high CVR as well as with IR. With EATT of more than 9.5 mm, IR becomes significantly more frequent.

Analysis of apelin-12 as an early predictor of adipose tissue dysfunction in overweight, class 1 obesity and class 2 obesity groups showed a significant increase of 75% (p<0.05), 88.8% (p<0.05) and 95.9% (p<0.05), respectively, compared to control. There was a high correlation between apelin-12 and BMI, visceral fat level, CVR according to SCORE-2, and EATT with correlation coefficients of r=0.80, r=0.86, r=0.70, and r=0.40, respectively (p<0.05).

Thus, the analysis of VAT dysfunction indices showed an increase in VOI, visceral fat level by bioimpedance analysis, HSI and FLI, EATT with increasing degree of obesity. The revealed results showed that such a marker as apelin-12 can be used to assess and predict the progression of lipid metabolism disorders, VAT dysfunction, and it can be included together with the assessment of estimated VAT, EATT indices in the algorithm of examination of overweight patients and individuals with high CVR [9, 10].

Discussion

One of the more recent methods to assess abdominal adipose tissue status is VOI, a marker of VAT dysfunction. In many studies, elevated indices of VAT dysfunction such as VOI, visceral fat level by bioimpedance analysis, HSI, and HSI have been associated with high cardiometabolic risk, both in the general population and in patients without metabolic disorders [9]. Epicardial adipose tissue is now known to be a marker of visceral obesity and increased CVR. In turn, the association between obesity and CVD is determined by both the degree of obesity and the distribution of adipose tissue. EATT, like any other adipose tissue, serves as an active hormone-producing system (expressing adipokines, chemokines, tumor necrosis factor-α, interleukin-1 and interleukin-6, free fatty acids, angiotensin II, etc.) involved in inflammatory processes in the vascular wall, development of metabolic disorders, thrombosis and atherogenesis [10]. The result of our study showed a significant increase in EATT in groups with overweight, class 1 and class 2. The increase in EATT is associated with IR. With EATT of more than 9.5 mm, IR becomes significantly more frequent. According to the data of Drapkina et al., it is possible to diagnose IR with high accuracy when the EATT is from 2.7 to 4.5 mm and the diastolic function parameter E/A is less than 0.8.

The production of adipokines and the activity of their signaling pathways are altered in obesity, which plays an important role in the relationship between obesity, IR, and increased CVR. We investigated the role of apelin-12 as a biomarker of VAT dysfunction and increased CVR, which is also consistent with previous studies. Currently, apelin is being actively studied as a predictor of obesity complications in different age-sex groups [11].

Visceral obesity is not chosen by chance as the main criterion for the diagnosis of metabolic syndrome (MS). It is a powerful RF of metabolic disorders and contributes to the development of IR and compensatory hyperinsulinemia. Abdominal fat has some characteristics that lead towards the formation of IR, while subcutaneous fat accumulation — does not, and may even be protective against MS [5]. In addition, an increase in EATT is associated with signs of vascular wall remodeling, endothelial dysfunction, impaired lipid metabolism, and impaired left ventricular (LV) diastolic function [9]. A close correlation between the amount of epicardial fat and CHD was also found (r=0.3). EATT less than 7 mm predisposes to the development of subclinical atherosclerosis, while more than 7 mm — to the development of CHD. According to some authors, EATT correlates with myocardial hypertrophy and LV diastolic function [10].

Abdominal fat is hormonally active. VAT is known to produce many different bioactive substances naned adipokines. Adipokines play an important role in the

formation of IR. Apelin adipokine is poorly studied. It has been observed that its level increases in obesity and is directly related to the visceral type of adipose tissue distribution. Plasma apelin concentration has been found to rise significantly with increasing degree of AO and directly correlated with WC and WC/HC ratio [3]. High levels of apelin have also been reported in obesity associated with hyperinsulinemia. The work of researchers investigating the relationship between plasma apelin concentrations and cardiac remodeling in AO patients is of particular interest. It was shown that the concentration of apelin in obese patients was higher than in the control group of healthy people, and the levels of the marker negatively correlated with structural changes of the heart, which may indicate the importance of apelin as a factor with cardioprotective properties [9, 11].

Conclusion

The results indicate VAT dysfunction and excessive visceral fat accumulation in high and very high risk patients with both obese, overweight and normal BM. The established correlations make it possible to predict the intensification of visceral obesity with additional markers that are simple, easily reproducible and inexpensive, and may find wide application in daily clinical practice. Such a marker as apelin-12 can be used to assess and predict the progression of lipid metabolism disorders, VAT dysfunction, and can be included together with the assessment of estimated VAT indices (VOI, % of adipose tissue, visceral fat level by bioimpedance analysis, HSI and FLI) in the algorithm of patient examination to assess VAT dysfunction and prevent CVR.

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