Kulynych R. L., Soloviuk O. A., Soloviuk O. O. Pathophysiological association of expression hormone of adipose tissue omentin-1 and the degree of vascular remodeling of brachyocephalic vessels in persons with obesity and disorders of carbohydrate metabolism. Journal of Education, Health and Sport. 2020;10(10):127-143. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2020.10.10.012
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.10.012
https://zenodo.org/record/4256818

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 12.10.2020. Revised: 16.10.2020. Accepted: 30.10.2020.

PATHOPHYSIOLOGICAL ASSOCIATION OF EXPRESSION HORMONE OF ADIPOSE TISSUE OMENTIN-1 AND THE DEGREE OF VASCULAR REMODELING OF BRACHYOCEPHALIC VESSELS IN PERSONS WITH OBESITY AND DISORDERS OF CARBOHYDRATE METABOLISM

R. L. Kulynych, O. A. Soloviuk, O. O. Soloviuk

State Institution "Zaporozhye Medical Academy of Postgraduate Education of the Ministry of Health of Ukraine", Vintera blvd., Zaporozhye, Ukraine, 69096
ORCID: https://orcid.org/0000-0002-8416-0639
cardiolog1978@gmail.com, alsolovyuk@gmail.com

Abstract

Introduction. The relationship of visceral obesity and excess body weight (EBW) with the development of cardiovascular diseases, type 2 diabetes mellitus (DM) and effect on quality and duration of life determine the relevance of studying this problem.

Objective: to assess omentin-1 metabolism and pathophysiological relationship between its level and the severity of lesions in the intima-media thickness (IMT) of the carotid arteries in type 2 DM in combination with EBW and obesity.

Material and research methods. We examined 98 people with DM, the first group consisted of 64 people with EBW and obesity, second group consisted of 34 people with normal body weight, control group – 28 healthy individuals.

Research results. Evaluation of the correlation matrix showed the presence of a positive rather strong negative connection between IMT, especially the right carotid artery and the level of omentin-1 in the blood (Rs = –0.55; p = 0.002). According to the results of

the regression analysis and the study of the scatter diagram of the obtained data, the functional relationship between IMTright / IMTleft and the serum omentin-1 indicator was reliably approximated by a step-type model (polynomial curve, R = 0.49, R2 = 0.24, normalized R2 = 0.22 at F = 10.59, standard error 0.15, p <0.01)). The columnar bivariate 3D histogram clearly shows the physiological relationship between these indicators and indicates that the largest number of individuals with omentin-1 levels from 5-10 ng / ml had significant disorders of the vascular wall (IMT from 1.0 to 1.2 mm).

Conclusion. Obtained data indicate a statistically significant associative relationship between the dynamics of the predictor of cardiovascular risk – IMT with the degree of impaired expression of omentin-1.

Key words: omentin-1; obesity; type 2 diabetes mellitus; intima-media thickness; cardiovascular risk.

Introduction. The relationship of visceral obesity with the development of cardiovascular disease, type 2 diabetes mellitus (DM), as well as the impact of obesity and excess body weight (EBW) on quality and life expectancy, determine the relevance of the study of this problem [1]. It is well known that adipose tissue regulates glucose homeostasis not through its absorption, but indirectly, by regulation lipid homeostasis. Disruption of the balance of lipid metabolism can lead to systemic dysregulation of carbohydrate metabolism and the formation of insulin resistance [2].

Omentin-1 is an adipokin weighing 38 kDa, which is secreted and produced by stromal vascular cells of visceral adipose tissue. Circulation and expression of the omentin-1 gene in adipose tissue are reduced in obese patients. Omentin-1 is also found in endothelial cells and may play a role in regulating endothelial function. In addition, several clinical studies have shown an association between low omentin-1 levels and coronary heart disease, increased arterial stiffness, and carotid atherosclerosis [3]. Increasing the volume of visceral fat tissue reduces the expression of the omentin-1 gene, and thus serum omentin-1 levels and visceral obesity are negatively correlated. Changes in adipokine levels, leading to endothelial dysfunction, cause the development of atherosclerosis in obesity and EBW. There are convincing data from experimental and clinical studies on the effects of omentin-1 on vascular reactivity and atherogenesis. Experimental studies have shown that omentin-1 causes vasodilation of isolated blood vessels of rats by increasing the activity of endothelial nitric oxide synthase and stimulates ischemia-induced revascularization in mice [4]. Omentin-1

modulates endothelial cell function and revascularization processes. Omentin-1 has been reported to stimulate the Akt-eNOS signaling pathway and promote normalization of endothelial function in response to ischemia in vivo and in vitro. Several clinical studies have also shown an association between low omentin-1 levels and carotid intima-media thickness, carotid artery plaque, and coronary heart disease. In these studies, omentin-1 levels were negatively correlated with the parameters of atherosclerosis. Studies show that aerobic exercise increases serum omentin-1 levels in men with EBW and obesity and cardiovascular risk factors [5].

It is known that changes in the size of the intimo-medial segment of the common carotid artery acts as an early marker of the systemic atherosclerotic process [6]. In the case of an increase in the thickness of the indicator, there is an increase in the risk of atherosclerotic plaque formation several times over the next few years [7]. Thickening of the intima-media is associated with other risk factors for cardiovascular disease (myocardial infarction, stroke, sudden death, smoking, dyslipidemia, hypertension, etc.) [8]. Several studies have shown the association of intima-media thickening with the development of metabolic syndrome and DM [9].

In a study of 60 patients with metabolic syndrome (MS), atherosclerotic lesions of the carotid arteries were assessed by ultrasound, then patients were divided into two subgroups: MS with atherosclerosis (MS+AS) and MS without atherosclerosis (MS-AS) according to the level of intima-media thickness (IMT) of the carotid artery and the presence of plaques [10]. Vascular stiffness, deformation, and elasticity were calculated, and waist circumference and blood pressure were measured in patients. Plasma omentin-1 levels were assessed by ELISA, and insulin resistance index (HOMA-IR) was also determined. The authors investigated the relationship between omentin-1 and IMT, as well as some metabolic markers. It is reported that omentin-1 levels were lower in the MS group than in the control group, and also decreased even more in MS+AS compared to MS-AS. In the correlation analysis, omentin-1 was a negative predictor of IMT, vascular stiffness, waist circumference, body mass index (EBW), systolic blood pressure (SBP), blood glucose and HOMA-IR. Thus, the level of omentin-1 is closely related to MS and may play an important role in the development of atherosclerosis and DB.

Another study prospectively examined the results of a survey of 78 people (average age 46.5 years, 69% men; 59 patients with MS and 19 controls). Subclinically, cardiovascular disease was determined by the presence of carotid artery plaques and / or IMT carotid artery > 0.9 in 2 / 3D ultrasound, left ventricular hypertrophy, or high coronary calcium scoring

(CCS). Plasma levels of adipokines and endothelial cell molecules were measured by Luminex xMAP enzyme-linked immunosorbent assay [11]. The study showed that an increase in sICAM-1, sVCAM-1 and PAI-1 along with a decrease in omentin-1 levels led to a shift in balance toward proinflammatory mediators, indicating subclinical atherosclerosis and altered cardiovascular risk stratification in patients with early stage of MS in traditional assessments.

Therefore, the study of these structural characteristics in patients with DM in combination with EBW and obesity is an extremely important issue.

Objective: to assess the metabolism of omentin-1 and to study the pathophysiological relationship between its level and the severity of lesions of the intimo-medial segment of the carotid arteries in type 2 diabetes mellitus in combination with EBW and obesity.

Material and research methods. We examined 98 people with DM, who were inpatient treatment in the KI "RK Endocrine Dispensary" ZRC. Among the surveyed, the first group consisted of 64 people (34 women and 30 men) with EBW and obesity (body mass index > 25 kg / m^2), average age 56.3 ± 10.23 years, the duration of DM was on average 7.47 ± 5.07 years (with a run-up from the first identified to 28 years). The second group consisted of 34 people (19 women and 15 men) with normal body weight (body mass index ≤ 25 kg / m^2), the average age was 55.6 ± 11.92 years, the duration of DM was 6.5 ± 5.70 years (with a run-up from the first identified to 22 years). As a control, a group of 28 apparently healthy individuals was examined, which was comparable to the first and second groups in terms of gender and age.

Blood sampling for research was performed in the morning on an empty stomach between $8^{\underline{00}}$am and $9^{\underline{00}}$am from the cubital vein. Sterile Vacutainers Systems manufactured by Becton Dickinson and Company were used to take blood samples. Separation gel tubes were used to obtain blood serum. Blood sampling and further processing was performed according to the manufacturer's instructions.

The concentration of omentin-1 was investigated by ELISA by solid-phase enzyme-linked immunosorbent assay using commercial test systems and a kit from Bender MedSystems GmbH (Austria) according to the instructions in vitro. All ELISA techniques were used with full-plate semi-automatic enzyme-linked immunosorbent assay "SUNRISE TS" manufactured by Tecan (Austria). The research was conducted in the central research laboratory of the State Institution "Zaporizhzhya Medical Academy of Postgraduate Education of the Ministry of Health of Ukraine".

The omentin-1 assay kit (OMT-1) uses a competitive enzyme-linked immunosorbent assay technique with monoclonal anti-OMT-1 antibodies and the OMT-1-HRP conjugate. The assay sample and buffer are incubated with the OMT-1-HRP conjugate in the wells of the plate for one hour. After the incubation period, the wells are decanted and washed five times. The wells are then incubated with the substrate for the enzyme HRP. The reaction product of the enzyme-substrate forms a blue complex. Finally, a stop solution is added to stop the reaction, which will later turn yellow. Color intensity is measured spectrophotometrically at 450 nm in a special reader for microplates. The color intensity is inversely proportional to the OMT-1 concentration, as OMT-1 in the samples and the OMT-1-HRP conjugate compete for the binding site of the OMT-1 antibody. Because the number of sites is limited and most sites occupy OMT-1 from the study sample, fewer sites remain for OMT-1-HRP conjugate binding. The plotted standard curve corresponds to the color intensity of the concentration of standards. The concentration of OMT-1 in each sample is interpolated from this standard curve.

Ultrasound of the carotid arteries was performed in the lying position of the patient on the device MyLab50X with a linear sensor of 7 MHz with a slight deviation of the patient's head in the opposite direction. Measurements were performed in B-mode in the longitudinal section along the distal wall of the carotid arteries at a distance of 1.0 to 1.5 cm proximal to the bifurcation of the common carotid artery. Focusing dynamic gain on the depth of the scan was set at the level of the wall far from the sensor. The area of interest in the B-mode increased until the image of the vessel in the minimum format. Carried out synchronization with the R-wave of the electrocardiogram. The calculation was performed on the image, which clearly visualized the 3-layer structure of both the anterior and posterior walls of the carotid artery. On the depicted far wall, one cursor was placed on the border of the artery lumen – intima, the other cursor – on the border of the media adventitia. Measurements were performed in the area of visually the maximum value three times, on different cardiac cycles and the arithmetic mean value was calculated. Reference values of the norm were taken when the IMT is less than 0.9 mm.

The work is a fragment of the research of the Department of Therapy, Clinical Pharmacology and Endocrinology of State Institution "Zaporozhye Medical Academy of Postgraduate Education of the Ministry of Health of Ukraine" - "The course of hypertension in combination with general diseases of the lungs and joints as a manifestation of comorbidity: traditional and additional risk factors". BH.P. 03.23.03-15, № state. registration 0115U000658.

Data are presented as mean and standard error of the mean. Correlation analysis between groups of independent samples using the Spearman correlation coefficient was used to determine the direction and nature of the relationship. The statistical significance of intergroup differences was assessed using the Mann-Whitney method. Statistical analysis was performed using the program "Statistica 6.1" (StatSoft Inc., USA, serial №RGXR412D674002FWC7). For all types of analysis, differences at a significance level of less than 0.05 were considered statistically significant.

Research results. We determined the concentration of omentin-1 in the subjects depending on the presence of EBW. The results show that patients of the first group with type 2 DM and obesity had the lowest levels of omentin-1 – 8.08 [5.04 - 11] ng / ml compared to patients of the second group who were not obese (the difference was 127.48%, $p<0.05$) and especially for relatively healthy people in the control group – 21.08 [11.83 - 48] ng / ml. Overweight and obesity led to a significant decrease in serum omentin-1 in patients of the first group, which, in turn, leads to increased insulin resistance and worsening of type 2 DM, as well as activation of pathogenetic chain mechanisms of cardiovascular damage and a number of concomitant metabolic changes. In addition, a decrease in omentin-1 values leads to increased levels of triglycerides and very-low-density lipoprotein cholesterol. Decreased omentin-1 levels are also accompanied by a decrease in blood levels of adiponectin and high-density lipoprotein cholesterol.

Next, we studied the concentration of omentin-1 metabolism in the subjects depending on the degree of compensation for type 2 DM in patients of different groups. Decompensated type 2 DM in patients with EBW with HbA1c values ≥ 8% was reflected in a steady decrease in omentin-1 levels (7.73 [4.93 - 10.74] ng / ml) in patients of this cohort – 28.29% less than patients with diabetes and EBW in the compensated course of the disease (10.78 [10.41 - 11.33] ng / ml). In relatively healthy subjects of the control group, omentin-1 was 48.86% higher as patients the first group with compensated DM, and 63.33% higher than patients with HbA1c ≥ 8% ($p <0.05$), and mean was 21, 08 [11.83 - 48] ng / ml.

In the second group of patients with type 2 DM without EBW, the peculiarities of diabetes and the quality of glycemic control did not significantly affect the level of omentin-1. With good glycemic control and HbA1c <8% without EBW omentin-1 was 13.66% higher (19.55 [13.75 - 21.88] ng / ml) than with type 2 DM decompensation without EBW and HbA1c ≥ 8% (16,88 [13.61 - 21.95] ng / ml), and compared to the control group was lower by 7.26 and 19.92%, respectively (mean of the control group was 21.08 [11.83 - 48] ng / ml).

The increase in the duration of type 2 DM for more than 5 years in both obese and non-obese patients was manifested by a decrease in omentin-1 levels by 39.24 and 25.95%, respectively ($p<0.05$), and amounted to 4.94 [0.76 - 11.05] and 14.15 [13.78 - 19.5] ng / ml. In the presence of patients with type 2 DM lasting up to 5 years, with EBW and obesity, omentin-1 was determined at the level of 8.13 [5.8 - 11.13] ng / ml (difference with the control group of 61.43%), in the absence of EBW and obesity – 19.11 [13,38 - 22] ng / ml, it was close to the values of healthy people – 21,08 [11,83 - 48] ng / ml (difference 9.35%) ($p <0,05$). In patients with type 2 DM lasting more than 5 years, with EBW and obesity omentin-1 was lower relative to the control group by 76.57%, and in the absence of EBW and obesity – by 32.87% ($p <0.05$). That is, with increasing duration of type 2 DM there is a gradual decrease in omentin-1 values in patients, especially in the group of patients with obesity and EBW.

In our work, we also determined the thickness of the complex of the intima-media segment (IMT) of the brachiocephalic arteries in the subjects depending on different characteristics. At persons of the 1st group the indicator was the maximum both from the right (1,18 [1,03 - 1,3] mm), and the left side (1,15 [1,03 - 1,28] mm) in comparison with indicators of persons of the 2nd group – 0.91 [0.81 - 0.98] and 0.99 [0.9 - 1.05] mm, more by 16.10% ($p <0.05$) and 20, 87% ($p <0.05$), respectively. The difference between the 1st and control groups was 38.82% ($p<0.05$) and 27.78% ($p <0.05$) on the right and left side, respectively. This indicator in the 2nd group on the left side was comparable to the control group (difference 1.11%), and on the right side was 16.47% ($p <0.05$) more compared to almost healthy individuals.

The state of carbohydrate metabolism compensation in individuals with type 2 DM in combination with EBW and obesity had a significant effect on IMT. Thus, in the 1st group, the IMT index under the condition of HbA1c ≥ 8% on the left side was 15.69% ($p<0.05$) more (1.18 [1.06 - 1.28] mm) than with effective compensation carbohydrate metabolism and HbA1c <8% (1.02 [0.96 - 1.28] mm), on the right side the difference was also significant and amounted to 15.38% ($p<0.05$) at IMT values of 1.04 [0.95 - 1.25] mm with HbA1c <8% and 1.2 [1.06 - 1.37] mm with HbA1c ≥ 8% ($p <0.05$).

In group 2, in patients with different levels of glycosylated hemoglobin, the value of IMT on both sides was comparable without statistically significant difference. Thus, on the left side the IMT indicator differed by 5.26% in favor of the group with HbA1c <8%, and on the right side – by 2.06% in favor of the group with decompensation of DM – HbA1c ≥ 8%. IMT on the left side in patients with HbA1c <8% and HbA1c ≥ 8% was 5.56 and 1.12%

higher compared to the control group (p<0.05), and on the right side – by 14.12 and 16.47%, respectively (p <0.05).

In the 1st group, the values of IMT on the right side were higher by 15.18% (p<0.05) with a duration of DM for more than 5 years (1.29 [1.05 - 1.42] mm) than with less history of the disease (1.12 [1.01 - 1.21] mm), on the left side the corresponding difference was 17.59% (p <0.05), the value of IMT in patients with obesity and DM up to 5 years left was 1.08 [1.0 - 1.18] mm, more than 5 years – 1.27 [1.14 - 1.35] mm. Regarding the control group, IMT was higher on the left side by 20.0 and 41.11% (p <0.05) in patients of the 1st group up to 5 years and more than 5 years of type 2 DM, and on the right side – by 31.76 and 51, 76%, respectively (p<0.05).

In the 2nd group, a significant difference in the values of IMT was determined by the case, amounting to 8.33% (p <0.05) between persons with a disease duration of less than 5 years (0.96 [0.87 - 0.99] mm) and more than this term (1.04 [0.97 - 1.07] mm). On the left side, the corresponding difference was 10.34% (p <0.05), the value of IMT in patients without obesity and DM up to 5 years of duration on the left side was 0.87 [0.73 - 0.97] mm, more than 5 years – 0.96 [0.88 - 1.01] mm. Compared with the control group, IMT was lower on the left by 3.33% and higher by 6.67% in patients of group 2 under 5 years and more than 5 years of type 2 DM, and on the right – higher by 12.94 and 22.35% respectively (p <0.05).

In the presence of chronic diabetic complications in persons of the 1st group, the IMT index on the right side was 1.29 [0.95 - 1.34] mm, on the left – 1.26 [0.98 - 1.27] mm. In patients without DM complications IMT on the right was 1.16 [1.03 - 1.3] mm, on the left – 1.14 [1.03 - 1.29] mm. The difference in the indicators of IMT on the left side in patients of the 1st group with complications compared to patients without complications was significant and amounted to 10.5% (p <0.05), on the right side – 11.21% (p <0.05). Regarding the IMT control group, patients of the 1st group were statistically significantly higher on the left side by 26.67 and 40.00% (p <0.05) compared with the group without and with complications, and on the right side by 36.47 and 51.76 % (p <0.05), respectively.

In group 2, the average IMT in people without and with chronic diabetic complications was comparable on both the right and left side, with an intergroup difference of 2.02 and 6.74%, respectively, on the right and left side. Regarding the IMT control group, the patients of the 2nd group had a difference on the left side by -1.11 and 5.56% compared with the group without and with complications, and on the right side – by 16.47 and 18.82% (p <0.05) respectively within the statistical significance.

In order to assess not only the relationship, but also its focus and closeness, a correlation analysis by Spearman and regression analysis was performed. Evaluation of the correlation matrix showed the presence of a positive rather strong negative connection between the IMT (especially the right carotid artery) and the level of blood omentin-1 (Spearman Rank Order Correlations Rs = –0.55; p = 0.002).

The results of regression analysis and the graph of the relationship between serum omentin-1 on the one hand, and IMT-right and IMT-left on the other, are shown in **Fig. 1.** The level of omentin-1 in the blood was considered as an argument (X), with the dependent sign being the values of the IMT of the common carotid artery on both sides.

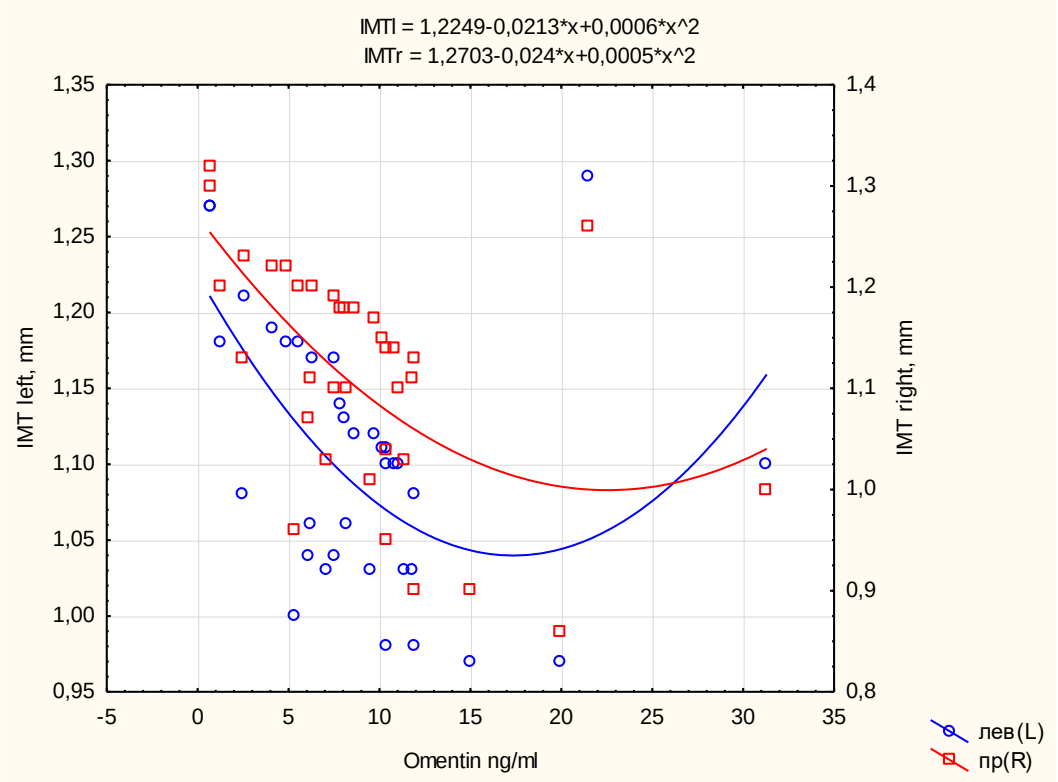

Fig. 1. The results of regression analysis between serum level of omentin-1 and IMT-right, IMT-left

When constructing a functional relationship between IMT-right/ IMT-left and serum omentin-1 index, according to the results of regression analysis and scattering diagram study, it should be noted that the approximation error and the value of the residual variance show high accuracy of the obtained model. Thus, the problem of regression analysis can be considered solved for IMT-right (R = 0.49, R2 = 0.24, normalized R2 = 0.22 at F = 10.59,

standard error 0.15, p <0.01). The recorded, gradually regressive parabola, interdependence shows that more than half of the total variance of the IMT-right trait may be associated with a change in the expression of omentin-1 (as a sign of impaired metabolism of adipose tissue hormones), with the largest increase in function observed in the range from 5 to 13, where in the vast majority of cases (almost 85%) there was a structural and functional remodeling of the arteries and there are atherosclerotic signs of damage to the common carotid artery (IMT more than 1 mm). The obtained data indicate a statistically significant associative relationship between the dynamics of the generally accepted predictor of cardiovascular risk IMT with the degree of expression of adipose tissue hormone in patients with type 2 DM in combination with EBW or obesity.

In **Fig. 2** presents a graphical method of studying the series of distribution of values of the number of persons depending on the severity of vascular remodeling of brachiocephalic arteries and the degree of dysfunction of adipose tissue metabolism (IMT on the right side, as more indicative).

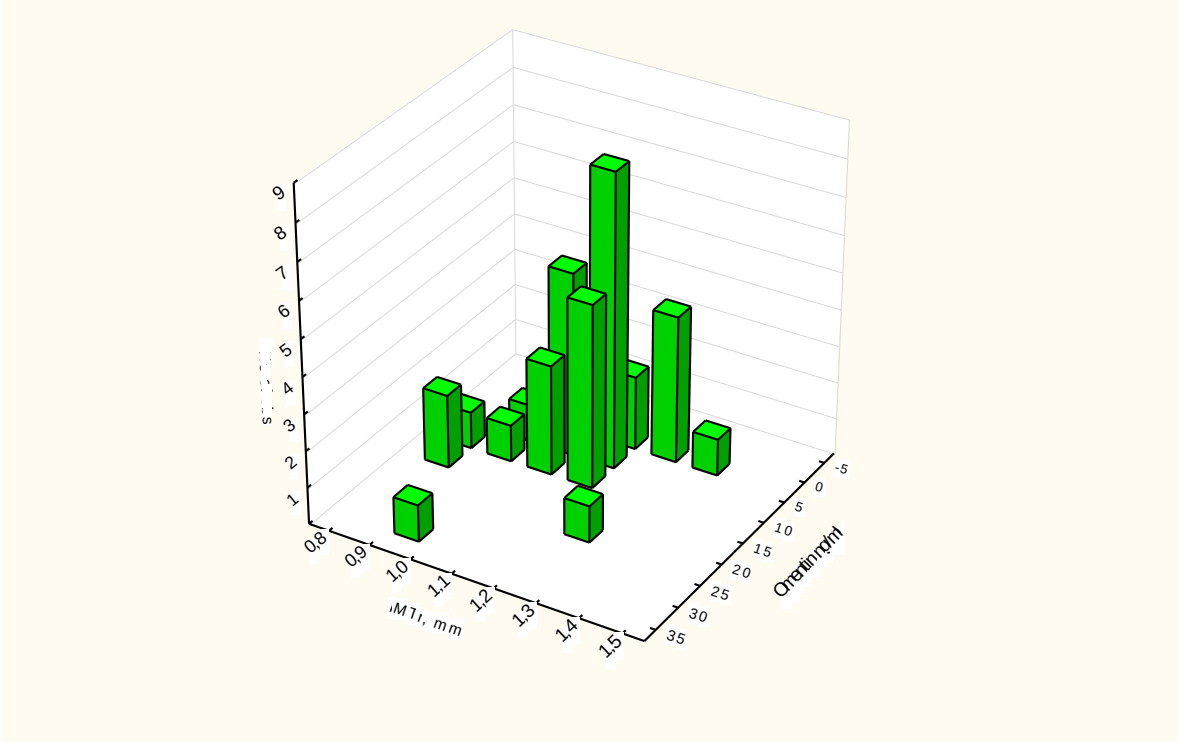

Fig. 2. Bar graph of the distribution of the number of people with type 2 diabetes mellitus in combination with excess body weight depending on the IMT and the expression of omentin-1

The obtained bar bivariate 3D histogram clearly shows the physiological relationship between these indicators and shows that the largest number of individuals with omentin-1

levels from 5-10 ng / ml had significant disorders of the vascular wall (IMT from 1.0 to 1.2 mm).

Discussion. It is now well known that omentin-1 is an important adipokine secreted by visceral adipose tissue. Evidence has shown that compared to EBW and obesity, omentin-1 has a more important effect on the prognosis of DM. Omentin-1 shows its effects as endocrine, paracrine and autocrine regulation [12]. These mechanisms suggest that altered omentin-1 secretion may disrupt glucose homeostasis in the body and subsequently contribute to the development of DM.

It was found that exercise can increase serum omentin-1 in type 2 DM, while in other studies, metformin treatment could reduce serum omentin-1 in type 2 DM [13]. Obviously, aerobic exercise can be used to increase omentin-1 levels in patients with diabetes, while drug interventions have an inhibitory effect. Some studies have reported a decrease in omentin-1 levels in prediabetes [14]. A possible explanation for this phenomenon is that because omentin-1 may increase insulin sensitivity, its decrease may cause impaired glucose homeostasis in patients with prediabetes.

In clinical trials, circulating omentin-1 concentrations were reduced in obese / diabetic individuals. In obesity, the concentration of omentin-1 decreased in plasma and adipose tissue. In addition, it was found that the concentration of omentin-1 was positively correlated with high-density lipoprotein and adiponectin and, conversely, negatively correlated with body mass index and insulin resistance [15].

Notwithstanding all the above, the exact role of omentin-1 in glucose metabolism and its target tissues has yet to be determined; and in relation to the receptors and modes of action by which it signals, the above results suggest new perspectives in early diagnosis, identification of new biomarkers and the provision of new targets for pharmacological intervention.

IMT is an important marker of atherosclerotic vascular disease worldwide. The method is simple, non-invasive and is performed using ultrasound of the arteries in B-mode, and therefore is used quite often in the diagnostic process. IMT is also a reliable predictor of future cerebral and cardiovascular events. Regression of increased carotid artery IMT due to the positive effects of hypolipidemic and antihypertensive drugs has been reported. Despite the strong association between elevated IMT arteries and cardiovascular disease, the question of whether IMT arteries should be measured to detect subclinical progression of atherosclerosis in clinical practice remains unclear [16]. Researchers should consider other methodological aspects, such as determining the parameters and location of plaques, choosing

the measurement site on the artery, and estimating the maximum or minimum IMT. Therefore, ultrasound examination of the artery is an important tool for assessing cardiovascular risk in a clinical setting.

There is significant evidence that IMT has been shown to be useful in predicting accidental vascular events in asymptomatic cardiac patients as well as in patients with severe symptoms, with an increase in IMT by 1 standard deviation associated with an 8% increased risk of myocardial infarction and a 19% increase risk of stroke [17].

However, the added value of IMT measurements in the presence or absence of risk factors in patients included in the Framingham Risk Score is not always clear. These inconsistencies and common measurement problems were the main shortcomings identified in the recommendations of the American College of Cardiologists / American Heart Association in cardiovascular risk assessment as a reason to measure / not measure IMT [18]. For hypertensive patients, caution seems warranted following the recent results of the IMPROVE cohort (Immediate management of patients with ruptured aneurysm: open versus endovascular repair), which showed that the area under the receiver curve or statistics for predicting myocardial infarction and stroke remained virtually unchanged, as IMT was added to the Framingham risk scale [19]. It has been suggested that IMT may be a useful marker for patients at intermediate risk based on the Framingham Risk Score, and although IMPROVE found some statistical evidence of improved reclassification of patients with hypertension, the effect was again negligible (NRI = 5.6%).

A survey of 914 employees between the ages of 21 and 60 (347 women) measured SBP at rest, EBW, and IMT by carotid ultrasound. Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of obesity stratified by weekly PA for abnormally enlarged IMT. Logistic regression analysis showed that those with general obesity (OR = 2.50, 95% CI = 1.60-3.91, P <0.001) or central obesity (OR = 2.08, 95% CI = 1.29-3.40, P = 0.003), significantly higher risk of abnormally elevated IMT even after adjustments for age, sex, smoking, alcohol consumption, resting blood pressure and a history of hypertension, diabetes and hyperlipidemia compared with those who did not have general or central obesity (OR = 1). Multidimensional linear regression showed that age (P <0.001), sex (P = 0.002), hypertension (P = 0.014), smoking (P = 0.054), EBW (P <0.001) and physical activity (P = 0.011) were important determinants of abnormally elevated IMT in this study population [20].

The next cohort of authors measured the average IMT of the common carotid artery and the maximum IMT of the internal carotid artery in 2965 participants in the Framingham

Offspring Study cohort. The results of cardiovascular disease were evaluated during an average follow-up period of 7.2 years [21]. A variety of Cox proportional risk models have been developed for IMT and risk factors. The reclassification of cardiovascular disease was assessed based on an 8-year risk category on the Framingham scale (low, medium or high) after adding IMT values. Risk factors on the Framingham risk scale predicted these events with statistics C 0.748 (95% confidence interval [CI], 0.719-0.776). The adjusted risk ratio for cardiovascular disease with an increase of 1 SD in the average IMT of the common carotid artery was 1.13 (95% CI, 1.02-1.24), with a slight change in the statistics C 0.003 (95% CI from 0.000 to 0.007); the corresponding risk factor for the maximum IMT of the internal carotid artery was 1.21 (95% CI, 1.13-1.29) with a moderate increase in C statistics by 0.009 (95% CI, 0.003-0.016). The index of pure reclassification increased significantly after adding the IMT of the internal carotid artery (7.6%, P <0. 001), but not the IMT of the common carotid artery (0.0%, P = 0.99). In the presence of plaque, which is defined as IMT of the internal carotid artery more than 1.5 mm, the net reclassification index was 7.3% (P = 0.01) with an increase in statistics C by 0.014 (95% CI, From 0.003 to 0.025). The authors concluded that the maximum IMT of the common carotid artery predict cardiovascular events, but only the maximum IMT (and the presence of plaque inside) of the internal carotid artery significantly moderately improves risk classification.

Conclusions:

1. The presence of EBW and obesity in patients with type 2 DM leads to a decrease in the level of the marker of compensation for disturbed metabolism of carbohydrates and lipids, a decrease in insulin resistance – omentin-1 by 127.48% compared to patients with type 2 DM without EBW and obesity. Patients with glycated hemoglobin HbA1c values of more than 8% showed a decrease in omentin-1 values compared with patients with compensated diabetes, the difference was more pronounced in patients with EBW and obesity (28.29%, p <0.05), in the absence of EBW and obesity the difference was 13.66%. An increase in the duration of type 2 diabetes led to depression of the studied marker omentin-1 in obese patients by 39.24% (p<0.05), in the absence of obesity – by 25.95%.

2. The thickness of the complex of the intima-media segment (intima-media thickness (IMT)) of the brachiocephalic arteries in the examined individuals was greater in the presence of EBW by 16.10% (p <0.05) and 20.87% (p <0.05), respectively, on the right and left side. Depending on the degree of compensation for type 2 DM in obese patients, the thickness of the intima-media segment of the brachiocephalic arteries in the examined individuals had the

following difference: with HbA1c ≥ 8% on the left side it was 15.69% (p <0.05) more than HbA1c <8%; on the right side the difference was also significant and amounted to 15.38% (p <0.05).

3. The thickness of the intima-media complex of the carotid arteries in the examined individuals with EBW increased with the duration of type 2 DM over 5 years by 17.59 and 15.18% (p<0.05) on the left and right side, respectively. The difference IMT indices on the left side in patients of group 1 with obesity, type 2 DM and complications compare to patients without complications was significant and amounted to 10.5% (p <0.05), on the right side – 11.21% (p<0.05).

4. Evaluation of the correlation matrix showed the presence of a positive rather strong negative connection between IMT (especially the right carotid artery) and the level of omentin-1 in the blood (Rs = -0.55; p = 0.002). According to the results of the regression analysis and the study of the scatter diagram of the obtained data, the functional relationship between IMTright / IMTleft and the serum omentin-1e indicator was reliably approximated by a step-type model (polynomial curve, R = 0.49, R2 = 0.24, normalized R2 = 0.22 at F = 10.59, standard error 0.15, p <0.01)). The columnar bivariate 3D histogram clearly shows the physiological relationship between these indicators and indicates that the largest number of individuals with omentin-1 levels from 5-10 ng / ml had significant disorders of the vascular wall (IMT from 1.0 to 1.2 mm).

5. Obtained data indicate a statistically significant associative relationship between the dynamics of the generally recognized predictor of cardiovascular risk, IMT, with the degree of impaired expression of the adipose tissue hormone omentin-1 in these patients.

Prospects for further research. Prospects for further research are to study the dynamics of serum omentin-1 levels in patients with metabolic syndrome during therapy with SGLT2 inhibitors.

References

1. Ohashi K, Shibata R, Murohara T, Ouchi N. Role of anti-inflammatory adipokines in obesity-related diseases. Trends Endocrinol Metab. 2014;25:348–355.

2. Ghoorah K, Campbell P, Kent A, Maznyczka A, Kunadian V. Obesity and cardiovascular outcomes: a review. Eur Heart J Acute Cardiovasc Care. 2016;5(1):77–85.

3. Çimen AR, Cerit ET, Iyidir OT, Karakus R, Uyar BB, Toruner FB, Cakir N, Arslan M. Serum omentin-1 levels and endothelial dysfunction in obesity. Acta Endocrinol

(Buchar). 2017 Apr-Jun;13(2):138-143. doi: 10.4183/aeb.2017.138. PMID: 31149164; PMCID: PMC6516446.

4. Pan X, Kaminga AC, Wen SW, Acheampong K, Liu A. Omentin-1 in diabetes mellitus: A systematic review and meta-analysis. PLoS One. 2019 Dec 10;14(12):e0226292. doi: 10.1371/journal.pone.0226292. PMID: 31821362; PMCID: PMC6903756.

5. Du Y, Ji Q, Cai L, Huang F, Lai Y, Liu Y, Yu J, Han B, Zhu E, Zhang J, Zhou Y, Wang Z, Zhao Y. Association between omentin-1 expression in human epicardial adipose tissue and coronary atherosclerosis. Cardiovasc Diabetol. 2016 Jun 28;15:90. doi: 10.1186/s12933-016-0406-5. PMID: 27352781; PMCID: PMC4924240.

6. Varona JF, Ortiz-Regalón R, Sánchez-Vera I, López-Melgar B, García-Durango C, Castellano Vázquez JM, Solís J, Fernández-Friera L, Vidal-Vanaclocha F. Soluble ICAM 1 and VCAM 1 Blood Levels Alert on Subclinical Atherosclerosis in Non Smokers with Asymptomatic Metabolic Syndrome. Arch Med Res. 2019 Feb;50(2):20-28. doi: 10.1016/j.arcmed.2019.05.003. Epub 2019 May 31. PMID: 31349950.

7. Sengul E, Duygulu G, Dindar S, Bunul F. Serum omentin-1, inflammation and carotid atherosclerosis in patients with non-diabetic chronic kidney disease. Ren Fail. 2013 Sep;35(8):1089-93. doi: 10.3109/0886022X.2013.817256. Epub 2013 Jul 25. PMID: 23883412.

8. Yoo HJ, Hwang SY, Hong HC, Choi HY, Yang SJ, Seo JA, Kim SG, Kim NH, Choi KM, Choi DS, Baik SH. Association of circulating omentin-1 level with arterial stiffness and carotid plaque in type 2 diabetes. Cardiovasc Diabetol. 2011 Nov 22;10:103. doi: 10.1186/1475-2840-10-103. PMID: 22108456; PMCID: PMC3235986.

9. Cerit ET, Akturk M, Altinova AE, Tavil Y, Ozkan C, Yayla C, Altay M, Demirtas C, Cakir N. Evaluation of body composition changes, epicardial adipose tissue, and serum omentin-1 levels in overt hypothyroidism. Endocrine. 2015 May;49(1):196-203. doi: 10.1007/s12020-014-0460-2. Epub 2014 Oct 25. PMID: 25344100.

10. Liu R, Wang X, Bu P. Omentin-1 is associated with carotid atherosclerosis in patients with metabolic syndrome. Diabetes Res Clin Pract. 2011 Jul;93(1):21-5. doi: 10.1016/j.diabres.2011.03.001. Epub 2011 Apr 16. PMID: 21497934.

11. Varona JF, Ortiz-Regalón R, Sánchez-Vera I, López-Melgar B, García-Durango C, Castellano Vázquez JM, Solís J, Fernández-Friera L, Vidal-Vanaclocha F. Soluble ICAM 1 and VCAM 1 Blood Levels Alert on Subclinical Atherosclerosis in Non Smokers with Asymptomatic Metabolic Syndrome. Arch Med Res. 2019 Feb;50(2):20-28. doi: 10.1016/j.arcmed.2019.05.003. Epub 2019 May 31. PMID: 31349950.

12. Bohula EA, Scirica BM, Inzucchi SE, McGuire DK, Keech AC, Smith SR, et al. Effect of lorcaserin on prevention and remission of type 2 diabetes in overweight and obese patients (CAMELLIA-TIMI 61): a randomised, placebo-controlled trial. Lancet (London, England). 2018;392(10161):2269–79. Epub 2018/10/09. 10.1016/s0140-6736(18)32328-6.

13. Vedal TSJ, Steen NE, Birkeland KI, Dieset I, Reponen EJ, Laskemoen JF, et al. Adipokine levels are associated with insulin resistance in antipsychotics users independently of EBW. Psychoneuroendocrinology. 2019;103:87–95. Epub 2019/01/20. 10.1016/j.psyneuen.2019.01.001 .

14. Abdelraouf Korany M, Sonbol A, Mohamed Elgouhary S. Omentin-1 and diabetic retinopathy in type 2 diabetic patients. Alexandria Journal of Medicine. 2018;54(4):323–6. 10.1016/j.ajme.2018.04.003

15. Hayashi M, Morioka T, Hatamori M, Kakutani Y, Yamazaki Y, Kurajoh M, et al. Plasma omentin levels are associated with vascular endothelial function in patients with type 2 diabetes at elevated cardiovascular risk. Diabetes Res Clin Pract. 2019;148:160–8. Epub 2019/01/15. 10.1016/j.diabres.2019.01.009.

16. Nezu T, Hosomi N, Aoki S, Matsumoto M. Carotid Intima-Media Thickness for Atherosclerosis. J Atheroscler Thromb. 2016;23(1):18-31. doi: 10.5551/jat.31989. Epub 2015 Oct 13. PMID: 26460381.

17. Bae JH, Kim WS, Lee MS, Kim KS, Park JB, Youn HJ, et al. The changes of individual carotid artery wall layer by aging and carotid intima-media thickness value for high risk. Cardiovasc Ther. 2016;34(6):397–403. doi: 10.1111/1755-5922.12209.

18. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49–73.

19. Bots ML, Groenewegen KA, Anderson TJ, Britton AR, Dekker JM, Engstrom G, et al. Common carotid intima-media thickness measurements do not improve cardiovascular risk prediction in individuals with elevated blood pressure: the USE-IMT collaboration. Hypertension. 2014;63(6):1173–81. doi: 10.1161/HYPERTENSIONAHA.113.02683.

20. Jin Y, Kim D, Cho J, Lee I, Choi K, Kang H. Association between Obesity and Carotid Intima-Media Thickness in Korean Office Workers: The Mediating Effect of Physical

Activity. Biomed Res Int. 2018 Aug 1;2018:4285038. doi: 10.1155/2018/4285038. PMID: 30155478; PMCID: PMC6093045.

21. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med. 2011 Jul 21;365(3):213-21. doi: 10.1056/NEJMoa1012592. PMID: 21774709; PMCID: PMC3153949.