

TECHNOLOGY TRANSFER: INNOVATIVE SOLUTIONS IN MEDICINE, 2020

1. 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].

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 [3]. 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 [4]. Thickening of the intima-media is associated with other risk factors for cardiovascular disease (myocardial infarction, stroke, sudden death, smoking, dyslipidemia, hypertension, etc.) [5]. Several studies have shown the association of intima-media thickening with the development of metabolic syndrome and DM [6]. Therefore, the study of these structural characteristics in patients with DM in combination with EBW and obesity is an extremely important issue.

The aim: 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.

2. Materials and methods

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, No. state. reg-

OMENTIN METABOLISM AND PATHOPHYSIOLOGICAL RELATIONSHIP BETWEEN ITS LEVEL AND THE SEVERITY OF LESIONS IN THE INTIMA-MEDIA THICKNESS OF THE CAROTID ARTERIES IN TYPE 2 DIABETES MELLITUS IN COMBINATION WITH OBESITY

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Abstract: 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.

The aim: 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.

Materials and 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. The concentration of omentin-1 was investigated by ELISA by solid-phase enzyme-linked immunosorbent assay in vitro. 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.

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 ($R_s = -0.55$; $p = 0.002$). 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.

Keywords: omentin-1, obesity, excess body weight, type 2 diabetes mellitus, intima-media thickness.

istration 0115U000658. Totally 98 people with DM were examined, who were inpatient treatment in the KI "RK Endocrine Dispensary" ZRC in 2017–2020. Among the surveyed, the first group consisted of 64 people (34 women and 30 men) with EBW and obesity (body mass index >25 kg/m²), 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/m²), 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.

Authors confirm that the appropriate ethics review and informed consent welfare protocols have been followed and conducted their research in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee for all participants. Informed consent was obtained from all patients included in the study.

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. 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.

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 No. RGXR412D674002FWC7). For all types of analysis, differences at a significance level of less than 0.05 were considered statistically significant.

3. Results

The study 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 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 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 $\geq 8\%$ was reflected in a steady decrease in omentin-1 levels (7.73 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 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 $\geq 8\%$ ($p < 0.05$), and mean was 21 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 ng/ml) than with type 2 DM decompensation without EBW and HbA1c $\geq 8\%$ (16.88 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 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 and 14.15 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 ng/ml (difference with the control group of 61.43 %), in the absence of EBW and obesity – 19.11 ng/ml, it was close to the values of healthy people – 21.08 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 mm), and the left side (1.15 mm) in comparison with indicators of persons of the 2nd group – 0.91 and 0.99 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 $\geq 8\%$ on the left side was 15.69 % ($p < 0.05$) more (1.18 mm) than with effective compensation carbohydrate metabolism and HbA1c $< 8\%$ (1.02 mm), on the right side the difference was also significant and amounted to 15.38 % ($p < 0.05$) at IMT values of 1.04 mm with HbA1c $< 8\%$ and 1.2 mm with HbA1c $\geq 8\%$ ($p < 0.05$). 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 $\geq 8\%$. IMT on the left side in patients with HbA1c $< 8\%$ and HbA1c $\geq 8\%$ 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 mm) than with less history of the disease (1.12 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 mm, more than 5 years – 1.27 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 mm) and more than this term (1.04 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 mm, more than 5 years – 0.96 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 mm, on the left – 1.26 mm. In patients without DM complications IMT on the right was 1.16 mm, on the left – 1.14 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 $R_s = -0.55$; $p = 0.002$).

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 ($R = 0.49$, $R^2 = 0.24$, normalized $R^2 = 0.22$ 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. 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).

4. 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 [7]. 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 [8]. 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 [5]. 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 [9].

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 [10]. 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.

Study limitations. The findings of this study have to be seen in light of some limitations. The first is the lack of previous research studies on the topic and the second limitation concerns the presence of the individual variability of the complex «intima – media carotids» in the same patient from different sides.

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.

5. Conclusions

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. 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 $HbA1c \geq 8$ % 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 % ($p < 0.05$). 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 % ($p < 0.05$).

Conflicts of interest

Neither author has actual or potential conflicts of interest.

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