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PREDICTION OF PROGRESSION OF ATHEROSCLEROSIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND CHRONIC PANCREATITIS

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Abstract

The aim of the research was to study the relationship between the level of vaspin and the thickness of the intima-media of the carotid artery (CIMT), parameters of carbohydrate and lipid metabolism, functional state of the pancreas, markers of inflammation, and to create a mathematical model for the progression of atherosclerosis in patients with type 2 diabetes mellitus (DM-2) and chronic pancreatitis (CP).

Materials and methods: Serum vaspin level in 114 people with DM-2 or CP and a combination of these diseases were obtained. The parameters of lipid and carbohydrate metabolism, inflammation and functional status of pancreas were studied. CIMT was measured by means of B-mode ultrasonography. The obtained data were processed by the methods of non-parametric statistics to study the dependence of the parameters on the group, questions of the statistical significance of differences between two unrelated groups, the tightness of the relationship between the analyzed parameters.

Results: A statistically significant ($p < 0.05$) increase in serum vaspin levels in patients with DM-2 compared with other studied groups was obtained. A reliable correlation between vaspin, carbohydrate metabolism and CIMT was obtained, and it appeared to be dependent on the presence of comorbid pathology. The value of vaspin/tumor necrosis factor-α (TNF-α), starting from which CIMT increase is considered present, was calculated.

Conclusions: Undertaken study confirmed the positive connection of vaspin with insulin resistance markers, but also demonstrated that serum vaspin levels is positively associated with CIMT. A mathematical model for predicting the progression of atherosclerosis in patients with the studied pathology was developed. It was demonstrated that the Vaspin/TNF-α ratio can be used as a marker of early atherosclerotic lesion of vascular wall, indicating the role of vaspin in atherogenesis.

Keywords: type 2 diabetes mellitus, atherosclerosis, carotid intima media thickness, vaspin, adipocytokines.

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1. Introduction

Due to a modern approach to treatment of type 2 diabetes mellitus (DM-2), it is easier to achieve disease compensation nowadays. However, even when blood glucose level is under control, risk of cardiovascular events (CVE) remains in individuals with DM. One of the reasons for occurrence of CVE is the presence of comorbid diseases in DM-2 and a number of other factors, namely: impaired lipid metabolism, inflammatory process, irregular blood glucose level control, which leads to increased time of blood glucose level being beyond the target range. Chronic pancreatitis (CP) is one of the most common comorbid diseases in DM-2. The incidence of DM-2 in CP is 40–60 % depending on the grade of pancreatic injury [1]. In patients with DM-2, atherosclerotic changes develop not only faster, but also earlier, while reducing their lifetime [2].

Impairment of glycemic homeostasis has a direct effect on the development of atherosclerosis, which is a prognostic parameter for the development of ischemic ailments [3] and CVE [4]. A well-known marker of atherogenesis is measurement of carotid intima-media thickness (CIMT), used to detect asymptomatic and subclinical manifestations of atherosclerotic changes, as it is a reliable marker of CVE [5]. There are attempts in the available literature to study the onset of diabetes-associated atherosclerosis by evaluating the inflammation process as a factor in atherogenesis using biomarkers of inflammation [6]. Such inflammation markers include adipokines which have protective properties [7] and produced by adipose tissue and like apelin [8] and vaspin [9].

One of the recently studied adipokines is vaspin. The obtained data allowed to position vaspin as a sensitizer to insulin with anti-inflammatory effect [10]. In vascular smooth muscle cells, vaspin inhibits activation of NF-κB/protein kinase C and inhibits expression of intercellular adhesion molecule, induced by tumor necrosis factor-α (TNF-α), which leads to protection of endothelial cells by suppressing inflammation [11, 12].

In the available literature, we have found no studies of connection between serum vaspin levels and atherosclerosis in patients with isolated DM-2 and DM-2 combined with CP.

The aim of our study was to determine the serum vaspin level in patients with isolated DM-2 and DM-2 combined with CP, to evaluate the connection of vaspin level with the carotid intima-media thickness (CIMT), parameters of carbohydrate and lipid metabolism, functional status of pancreas, markers of inflammation and to create a mathematical model of progression of atherosclerosis in patients with the studied pathology.

2. Materials and methods

From the January of 2018 till January 2019 year 114 patients (including 42 men), aged 42 to 69 years old with a median of 56 years with the diagnosis of DM-2, CP and combination of these pathologies, who had no history of cardiovascular events and were treated in the Gastroenterology Department and Endocrinology Department of Communal Non-Commercial Kharkiv Region Council «Regional Clinical Hospital» were enrolled in the study. Patients were divided into 3 groups: group 1 included $n = 31$ (27.2 %) patients with isolated DM-2; group 2 included $n = 23$ (20.2 %) patients with isolated CP, and group 3 included $n = 60$ (52.6 %) patients with CP and DM-2 combined. Diagnosis of DM was established based on the local guidelines of management DM (based on the recommendations of the European Association for the Study of Diabetes). The diagnosis of CP was established based on the local and United European Gastroenterology guidelines for the diagnosis and therapy of CP (dated 2017). The control group consisted of 20 age-matched healthy individuals (including 10 males).

All patients were informed of the study procedure; they signed a written consent.

The study was approved by the Bioethics Committee of Kharkiv National Medical University (Report No. 6 of 04th October 2017) in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Search for the studied indicators that could be the biochemical markers of growth of CIMT and be sensitive to differentiation of patients was determined as a basis for the achievement of the defined purpose. Therefore, values of compensation of carbohydrate metabolism were determined: fasting plasma glucose level (FPGL) by glucose oxidant method, glycated hemoglobin (HbA1c) by immunoinhibition method, immunoreactive insulin (IRI) by ELISA method, and Homeostasis model assessment of insulin resistance (HOMA-IR index) were calculated. The indicators of lipid metabolism by total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and high-density lipoproteins (HDL) were assessed by enzymatic method. The functional state of pancreas was determined by the content of α-amylase in blood by enzymatic colorimetric method and fecal elastase-1 by ELISA method. Inflammatory status was evaluated quantitatively by C-reactive protein (CRP) level by immunoturbidimetry method. Determination of adipocytokine content, vaspin and TNF-α (as a well-studied serum inflammation marker), was performed by immunoenzyme method using RayBiotech (USA) systems. The body mass index of the patients in each group was calculated by the following formula: body weight (kg)/height (m^2).

The evaluation of CIMT by ultrasound scanning was performed in the proximal and distal segments of the common carotid artery (CCA). Measurements of CIMT were performed in B-mode, in the longitudinal section of the artery 1–1.5 cm proximal to bifurcation on the posterior wall of the artery. A three-time measurement of CIMT was performed, with the mean value determined on each side; then the mean value for the right and left CCA was calculated. An atherosclerotic plaque was considered the focal structure that protrudes into the vessel lumen by 0.5 mm or 50 % more than the value of CIMT of the adjacent sections of the artery, or an increase in CIMT for more than 1.3 mm. The normal value of CIMT conformed to the recommendations of the European Society of Hypertension (ESH) and European Society of Cardiologists (ESC) dated 2013 year and was equal to 0.9 mm.

The obtained data were processed using Statistica Basic Academic 13 for Windows En. Quantitative indicators are given in the form of median (Me) and interquartile range (LQ – lower quartile, UQ – upper quartile). The Kolmogorov-Smirnov test was used to check the correspondence of distribution of quantitative indicators to normal law, since the law of distribution of numerical indicators was different from normal. Because the law of distribution of numerical indices was different from the normal, non-parametric statistics were used: the Kruskall-Wallis test (KWT) and the Mann-Whitney U-test (MWT). Non-parametric Spearman's correlation coefficients (r), which was considered statistically significant at $p < 0.05$, were calculated to determine the existence of functional correlation between parameters.

3. Results

The main results of the study are presented in **Table 1**. All criteria studied had statistically significant group dependence (KWT, $p < 0.05$).

Table 1

Indicators of carbohydrate and lipid metabolism, inflammatory process, functional status of pancreas and adipocytokine levels and CIMT in the examined patients (Me (LQ – UQ))

Parameter	Group 1: DM ($n = 31$)	Group 2: CP ($n = 23$)	Group 3: CP+DM-2 ($n = 60$)	Control group ($n = 20$)
Duration of DM-2 (years)	9.02 [3–13]	–	9.61 ± 2.13	–
BMI (kg/m^2)	28.18 [24–33]	27.53 [24–31]	30.66 [28–34]	25.68 [21–23]
IRI (μIU/mL)	20.31 (10.96–25.3)$^{*)**)}$	13.93 (10.27–15.4)$^{****)}$	22.53 (13.95–30.45)$^{*)}$	11.07 (8.61–13.46)
FPGL (mmol/L)	8.18 (6.40–9.70)$^{*)**)}$	5.40 (5.7–5.0)$^{*)****)}$	8.57 (6.5–10.1)$^{*)}$	4.75 (4.5–5.0)
HbA1c (%)	7.23 (6.58–7.89)$^{*)**)}$	5.45 (4.74–5.89)$^{****)}$	7.49 (6.12–8.72)$^{*)}$	5.39 (5.32–5.46)
HOMA-IR index (μIU/mL)* (mmol/L)	6.55 (3.90–8.99)$^{*)**)***)}$	2.66 (1.86–2.66)$^{*)***)}$	8.38 (4.69–10.71)$^{*)}$	2.39 (1.83–2.96)
TC (mmol/L)	6.12 (5.28–7.16)$^{*)**)***)}$	5.09 (4.56–5.59)$^{*)**)***)}$	6.40 (5.34–7.11)$^{*)**)***)}$	4.7 (4.25–5.48)
TG (mmol/L)	2.35 (1.73–3.05)$^{*)**)}$	1.79 (1.45–1.97)$^{*)****)}$	2.58 (1.98–3.09)$^{*)}$	1.26 (1.12–1.51)
LDL cholesterol (mmol/L)	3.40 (2.53–4.42)$^{*)**)}$	2.87 (2.28–3.61)$^{*)****)}$	3.39 (2.60–3.95)$^{*)}$	2.17 (1.95–2.29)
VLDL cholesterol (mmol/L)	0.99 (0.63–1.22)$^{**)***)}$	0.7 (0.53–0.83)$^{*)***)}$	1.28 (0.94–1.57)$^{*)}$	0.57 (0.44–0.71)
CRP (mg/L)	1.33 (0.0–2.0)$^{*)**)***)}$	3.1 (1.5–6.0)$^{*)****)}$	6.73 (1.19–11.92)$^{*)}$	0.12 (0.0–0.23)
α-amylase (g/g*L)	29.1 (26.39–32)$^{*)**)***)}$	52.36 (41.6–61.1)$^{*)****)}$	32.64 (29.15–35.40)$^{*)}$	24.71 (19.7–28.6)
Elastase-1 (μg/g)	292.4 (271.1–302.2)7$^{*)**)***)}$	167.8 (133.9–201.7)$^{*)****)}$	137.51 (131.55–142.2)$^{*)}$	348.96 (289–381)
CIMT (mm)	1.02 (0.75–1.24)	0.79 (0.68–0.93)	1.21 (0.84–1.33)	0.71 (0.64–0.81)
Number of patients with plaques	17/54.8 %	6/26 %	41/68.3 %	0
Vaspin (pg/mL)	3.47 (3.16–3.76)$^{*)**)***)}$	2.73 (2.56–2.96)$^{*)****)}$	1.78 (1.49–1.69)$^{*)}$	2.42 (2.36–2.47)
TNF-α (pg/mL)	6.87 (5.64–8.14)$^{*)**)***)}$	7.83 (7.06–7.99)$^{*)****)}$	9.79 (8.77–10.22)$^{*)}$	4.20 (3.94–4.47)

Note: the difference is statistically significant ($p < 0.05$) when comparing indicators: * – probable when comparing identical parameters in control patients; ** – probable when comparing identical parameters between the groups 1 and 2; *** – probable when comparing identical parameters between the groups 1 and 3; **** – probable when comparing identical parameters between the groups 2 and 3

In our study, there was a statistically significant deterioration in carbohydrate metabolism in case of DM-2 and CP combined, compared with isolated DM-2 (**Table 1**). When studying the state of lipid metabolism in patients with DM-2, CP and with their combination, signs of hyperlipidemia were observed: namely, a typical atherogenic dyslipidemia prevailed – hypertriglyceridemia, decreased HDL cholesterol, hypercholesterolemia, increased LDL and VLDL cholesterol, which progressed with increase of insulin resistance.

There was an increase in serum vaspin level in patients with isolated DM-2 (3.47 pg/mL) compared with the control group (2.42 pg/mL) and the group with combined pathology (1.78 pg/mL); the difference was statistically significant (MWT, $p < 0.05$) between the groups. TNF-α values tended to increase in the presence of chronic pancreatitis. A statistically significant correlation between vaspin and DM-2 duration in group 1 ($r = –0.35$, $p < 0.05$) and group 3 ($r = –0.44$, $p < 0.05$), and between vaspin and major atherogenic factors of carbohydrate metabolism was obtained: FPGL ($r = 0.62$, $p < 0.05$ – group 1; $r = –0.61$, $p < 0.05$ – group 3), IRI ($r = 0.6$, $p < 0.05$ – group 1; $r = –0.67$, $p < 0.05$ – group 3); HOMA-IR index ($r = 0.45$, $p < 0.05$ – group 1; $r = –0.5$, $p < 0.05$ – group 3); HbA1c ($r = 0.56$, $p < 0.05$ – group 1; $r = –0.6$, $p < 0.05$ – group 3). In turn, the correlation between TNF-α and carbohydrate metabolism was as follows: FPGL ($r = 0.35$, $p < 0.05$ – group 1; $r = 0.43$, $p < 0.01$ – group 3); HbA1c ($r = 0.32$, $p < 0.05$ – group 1; $r = 0.37$, $p < 0.05$ – group 3); IRI ($r = 0.52$, $p < 0.005$ – group 1; $r = 0.56$, $p < 0.05$ – group 3); HOMA-IR index ($r = 0.51$, $p < 0.05$ – group 1; $r = 0.51$, $p < 0.05$ – group 3).

Our study found a statistically significant positive correlation between serum vaspin and TG levels in patients with DM-2 ($r = 0.31$, $p = 0.04$); in patients with DM-2 combined with CP ($r = –0.43$, $p < 0.05$) and between serum vaspin and LDL in group 3 ($r = –0.35$, $p < 0.05$). No statistically significant correlation was found between serum vaspin level and total cholesterol, HDL in all studied groups. Correlation between vaspin and the inflammation marker, C-reactive protein, had the following tendency: in group 1 ($r = 0.35$, $p < 0.05$), in group 2 ($r = 0.57$, $p < 0.05$); in group 3 ($r = –0.41$, $p < 0.05$); Vaspin have correlation with functional state of the pancreas – α-amylase only in group 3 ($r = 0.3$, $p < 0.05$).

In all groups a statistically significant correlation was found between vaspin and TNF-α which had a multidirectional trend ($r = 0.53$, $p < 0.05$ – group 1; $r = 0.71$, $p < 0.05$ – group 2; $r = –0.63$, $p < 0.05$ – group 3). A negative correlation was noted in patients with DM-2 combined with CP – the level of vaspin decreases under the influence of TNF-α activation.

In our study, we found no reliable connection between vaspin, BMI and patient's age.

When assessing the CIMT, it was noted that in patients with isolated DM-2, CIMT was statistically significant higher compared to the control group (1.02 ± 0.12 mm vs 0.71 ± 0.05 mm; MWT, $p < 0.05$). CIMT in patients with CP tended to increase, but it was not reliable compared to the control group (0.79 ± 0.13 mm vs 0.71 ± 0.05 mm; MWT, $p < 0.05$). Comparison of CIMT of group 3 patients with group 1 patients and control group patients showed a statistically significant increase in CIMT (1.21 ± 0.16 mm vs 0.71 ± 0.05 mm; MWT, $p < 0.05$) and (1.02 ± 0.12 mm vs 1.21 ± 0.16 mm; MWT, $p < 0.05$).

During assessing the correlation of CIMT with adipocytokines in the study groups, correlation between CIMT and vaspin – in group 1 ($r = 0.37$, $p = 0.019$) and group 3 ($r = –0.45$, $p < 0.05$), and correlation between CIMT and TNF-α – in group 1 ($r = 0.34$, $p = 0.029$) and group 3 ($r = 0.5$, $p < 0.05$) – was noted.

Correlation of CIMT with the marker of inflammatory process – CRP, was noted in group 1 ($r = 0.3$, $p < 0.01$), and in group 3 ($r = 0.41$, $p < 0.01$). It was found that progression of inflammatory process may lead to an increase in CIMT and increase the progression of atherosclerotic lesions. At the same time, the parameters of pancreatic dysfunction (alpha-amylase, elastase-1) in patients with CP did not affect the CIMT.

We obtained a significant correlation between vaspin and the presence of atherosclerotic plaque in group 1 ($r = 0.42$, $p = 0.007$), and in group 3 ($r = –0.6$, $p < 0.001$).

One of the goals of our study was to create a mathematical model of atherosclerosis progression. To create a model for predicting the progression of atherosclerosis, patients were divided into a relative norm group (1) and a pathology group (0) to study parameters that may

be biochemical markers of CIMT increase and that may be sensitive at that division. The pathology group was considered a combined group consisting of patients with DM-2, patients with CP and patients with comorbid condition. The primary task was to find indicators that would divide norms and pathologies at a statistically significant level. Among the directly studied parameters, it was found that the desired parameters are peculiar to the ratio of vaspin and TNF-α ($p < 0.01$), **Fig. 1**.

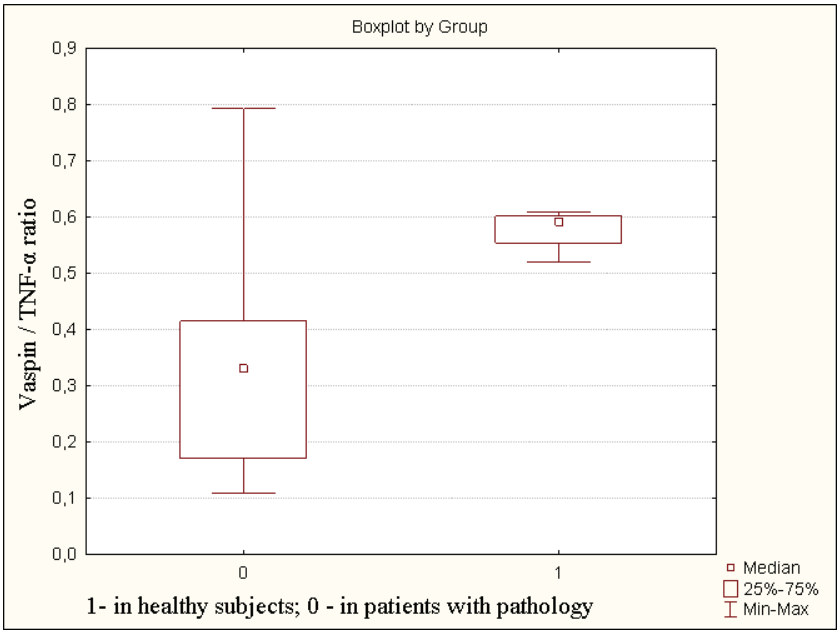

Fig. 1. Box plot of vaspin/TNF-α ratio in healthy subjects (1) and in patients with pathology (0)

As can be seen from the figure, the normal range of vaspin/TNF-α (median) was 0.59 pg/mL with the most typical value range (interquartile range, (IR) of 0.53–0.6 pg/mL. For patients in the pathology group, the corresponding values were as follows: median – 0.32 pg/mL, IR = 0.18–0.41 pg/mL. Considering the fact that the minimum value of the indicator in healthy subjects was 0.51 pg/mL (**Fig. 1**, right box plot), and the vast majority of patients had vaspin/TNF-α ratio values below 0.41 pg/mL (**Fig. 1**, left box plot), it is reasonable to accept the value of 0.5 pg/mL as a level that divides patients into healthy and sick patients.

An undoubtedly interesting property of vaspin/TNF-α ratio was its correlation with the CIMT in patients with pathology: Spearman's correlation coefficient was $R = -0.236$, $p = 0.009$. It shall be noted that there was no correlation between vaspin/TNF-α ratio and CIMT under normal conditions.

Fig. 2 shows the scatterplot, regression line, and regression equation of dependence of CIMT on vaspin/TNF-α ratio in patients with comorbid pathology and underlying DM-2.

As can be seen, the calculated equation for estimating CIMT based on vaspin/TNF-α ratio is as follows:

$$\text{CIMT} = 1.1695 - 0.3082 \times (\text{vaspin/TNF-}\alpha). \quad (1)$$

If we insert the vaspin/TNF-α ratio value = 0.5 pg/mL, which was chosen as the separation level in the previous statement, into the equation (1), we will obtain:

$$\text{CIMT} = 1.1695 - 0.3082 \times 0.5 = 1.015. \quad (2)$$

1.015 mm, obtained in equation (2), is very close to the 0.9 mm level, starting from which CIMT increase is assumed, which confirms the adequacy of the considerations above.

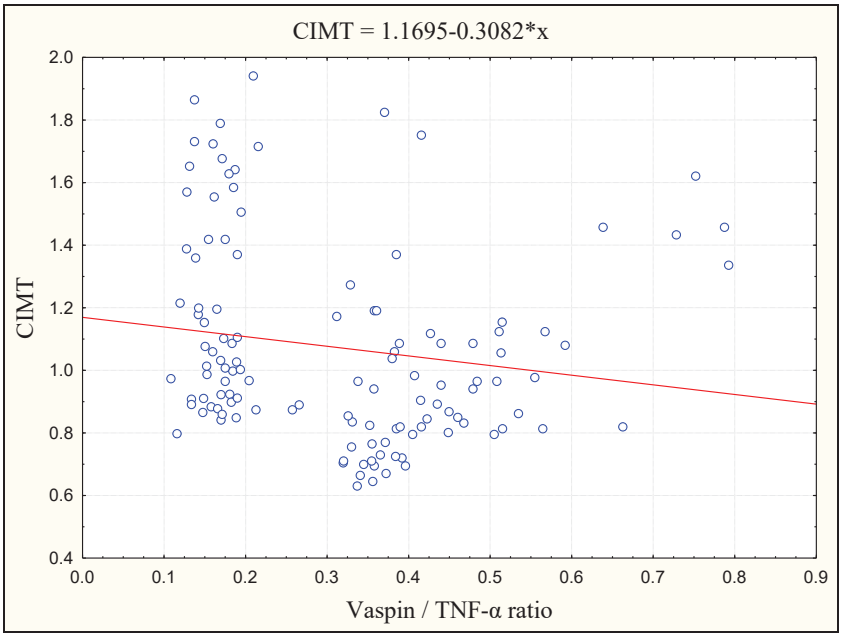

Fig. 2. Scatterplot, regression line and regression equation in pathology patients

4. Discussion

The present study was carried out to investigate the relationship between level of vaspin in the serum of the blood and the CIMT, parameters of carbohydrate and lipid metabolism, functional state of the pancreas, markers of inflammation in patients with isolated DM-2, isolated CP and a combination CP and DM-2, also to create a mathematical model for the progression of atherosclerosis for patients with a combination of these diseases.

Our results demonstrated significantly higher serum vaspin levels in patients with isolated DM-2 (3.47 pg/mL) compared with the control group (2.42 pg/mL) and the group with combined pathology (1.78 pg/mL). In our study, we do not have correlation between vaspin and patient's age, which is different from results performed by Yang L. [13] and Feng R. et al. [14] studies who found positive correlation between serum vaspin level and age in healthy volunteers, but not in patients with DM-2. Serum vaspin showed significant correlations with markers that accelerate atherogenic process namely: FPGL, IRI, HOMA-IR, $HbA1_c$ level, DM-2 duration, TG and LDL. It is useful to note that correlations between vaspin and parameters mentioned above are multidirectional and depend on individual compensatory capabilities. Our results confirm the results research by Domaa et al. [15], who found a statistically significant correlation between serum vaspin level, LDL, and TG in patients with DM-2. The study by Sato et al and Feng R. [16, 17] as well as our research, found no significant correlation between serum vaspin level and total cholesterol.

As vaspin also had a significant correlation with TNF-α, which is a marker of inflammatory process, it is important to note that vaspin may exhibit anti-inflammatory properties and we believe that it may manifest itself at the initial stages of inflammation. That is, we can assume the anti-inflammatory property of vaspin, which suppresses the effect of TNF-α. Apparently, reduced vaspin levels in the group with combined pathology could be caused by an increase in proinflammatory cytokines and CRP. The result may indicate vaspin involvement in inflammation and carbohydrate metabolism. This suggests that the mechanisms of action of adipocytokines deepen and affect the studied parameters, which confirms that vaspin has a positive effect on insulin resistance in DM-2, and a higher concentration of vaspin in patients with DM-2 may be associated with a compensatory response to poor insulin sensitivity. Petersen M. et al. [12] also reported that blood serum TNF-α concentration may increase with increasing insulin concentration. We noted that TNF-α values tended to increase in the presence of CP with the highest level in the 3rd group. Carbohydrate parameters namely: FPGL, HbA1c, IRI, HOMA-IR index had a positive correlation with TNF-α with the most pronounced relationship in 3rd group.

The correlation of CIMT, vaspin and TNF-α was obtained in 1st and 3rd groups and were multidirectional as well. These again confirms the multidirectional action of vaspin and TNF-α. We found a significant correlation between vaspin and the presence of atherosclerotic plaque in 1st and 3rd group as well as Dimova R et al [18] and Kobat. et al. [19] showed that serum vaspin concentrations were significantly lower in patients with carotid stenosis who had an ischemic event, compared with patients without it – that is, the more recent was the ischemic event, the lower was the level of vaspin. Some studies also showed that serum vaspin levels were significantly lower in subjects with ischemic heart disease (IHD), and low concentrations of vaspin correlated with IHD severity [20]. In our study, the serum vaspin level was significantly higher in patients with DM-2 without an atherosclerotic plaque compared with the control group patients, but significantly lower in patients with DM-2 with an atherosclerotic plaque than in patients without it. Thus, vaspin levels may be associated with the progression of an atherosclerotic plaque at the early stages.

The hypervaspinemia – is a compensatory response to antagonize the action of other well known (TNF-α) or still unknown proinflammatory adipokines that are take place in states of insulin resistance. Therefore, this up-regulation may be a defensive mechanism against not only insulin resistance but atherogenesis process as well.

Creation of mathematical model of atherosclerosis progression have shed light on the potential association of serum vaspin and TNF-α level. It was found in our study that the vaspin/TNF-α ratio below 0.5 pg/mL is a prognostically unfavorable factor in terms of the progression of atherosclerosis, obtained ratio is a consequence of the pro-atherogenic properties of TNF-α and compensatory efforts of vaspin.

Considering the above, we can assume that the influence of vaspin on atherogenesis is achieved in several ways: by suppressing the development of oxidative stress and inflammation by influencing the TNF-α-stimulated NF-κB pathway and inhibiting endothelial cell apoptosis by means of PI3K-Akt; by inhibiting formation of macrophage cells, as well as migration and proliferation of vascular smooth muscle cells and increasing the amount of collagen – thereby, vaspin promotes the stabilization of atherogenic plaque by increasing collagen and reducing the macrophage/cell ratio in smooth muscle vessels.

Study limitations. Due to the limited number of patients involved in the study and small number of observations in each of the studied groups, we can assume that obtained results may slight differ with increasing the number of observations, as well as presence of concomitant diseases in the studied patients can influent on the results like cardiovascular events in the anamnesis (which was the exclusion criterion in our study).

Difficult to exclude some confounding effects, including the effects of disease itself and drugs treatment. Lack of enrolling of newly diagnosed DM-2 patients, different duration of DM-2 and different management of DM-2 for each patient may include a possible source of study limitations.

Prospects for further research. It is useful to conduct further research to study a relationship between vaspin level and the thickness of the carotid intima-media in patients with a history of cardiovascular events and/or percutaneous intervention coronary arteries, because patients with type 2 diabetes mellitus is in high and very high cardiovascular risk.

5. Conclusions

Available data on atherogenesis indicate that there is a correlation between insulin resistance in diabetes mellitus, inflammatory conditions and adipokines. Adipose tissue can form adipokines capable of influencing atherogenesis, including vaspin and TNF-α.

Our study suggested that:

1. The study results demonstrated a higher serum vaspin level in patients with isolated DM-2 compared with the patients with CP, patients with the combined pathology and the control group patients. The level of serum vaspin was significantly lower in patients with DM-2 with longer duration and presence of an atherosclerotic plaque, compared with the patients with shorter duration of DM without an atherosclerotic plaque.

2. It has been noted that vaspin have a significant multidirectional correlations with next parameters: FPGL, IRI, HOMA-IR, $HbA1_c$ level, TG and LDL which depend on individual compensatory capabilities.

3. It was found that vaspin levels have positive correlation with CIMT in isolated pathology and negative correlation with the combination of the studied pathologies

4. The research carried out allowed according to obtained results set the value of vaspin/TNF-α ratio, which can be used as a marker of early atherosclerotic lesion of the vascular wall, and its reduction to a level below 0.5 pg/mL can be considered as an unfavorable factor indicating its thickening.

5. Vaspin have correlation with functional state of the pancreas – α-amylase in group with combined pathology.

6. The anti-inflammatory properties of vaspin were noted in the study, but we believe that hypervaspinemia occurs at the initial stages of inflammation.

Conflict of interests

The authors declare that they have no conflicts of interest.

References

[1] Kolesnikova, O. V. (2019). Chronic pancreatitis with a special type of diabetes mellitus: issues of diagnosis, course and correction. Modern Gastroenterology, 6, 59–67. doi: http://doi.org/10.30978/mg-2019-6-59

[2] Shaw, J. E., Sicree, R. A., Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Research and Clinical Practice, 87 (1), 4–14. doi: http://doi.org/10.1016/j.diabres.2009.10.007

[3] Urbanovich, A. M., Gopher, G. I. (2014). The role of leptin in the development of ischemic ailments of the heart in ailments of type 2 diabetes mellitus with revitalization. Experimental and clinical physiology and biochemistry, 2, 58–63.

[4] Urbanovich, A. M. (2015). The leptin and resistin plasma levels in patients with type 2 diabetes mellitus with different disease duration and arterial hypertension. Lviv medical journal, 21 (3), 14–18.

[5] Øygarden, H. (2017). Carotid Intima-Media Thickness and Prediction of Cardiovascular Disease. Journal of the American Heart Association, 6 (1). doi: http://doi.org/10.1161/jaha.116.005313

[6] Poznyak, A., Grechko, A. V., Poggio, P., Myasoedova, V. A., Alfieri, V., Orekhov, A. N. (2020). The Diabetes Mellitus-Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation. International Journal of Molecular Sciences, 21 (5), 1835. doi: http://doi.org/10.3390/ijms21051835

[7] Qi D, Wang, D., Zhang, C., Tang, X., He, J., Zhao, Y. et. al. (2017). Vaspin protects against LPS-induced ARDS by inhibiting inflammation, apoptosis and reactive oxygen species generation in pulmonary endothelial cells via the Akt/GSK-3β pathway. International Journal of Molecular Medicine, 40, 1803–1817. doi: http://doi.org/10.3892/ijmm.2017.3176

[8] Karbek, B., Bozkurt, N. C., Topaloglu, O., Aslan, M. S., Gungunes, A., Cakal, E. et. al. (2014) Relationship of vaspin and apelin levels with insulin resistance and atherosclerosis in metabolic syndrome. Minerva Endocrinologica, 39 (2), 99–105.

[9] Esaki, E., Adachi, H., Hirai, Y., Yamagishi, S., Kakuma, T., Enomoto, M. et. al. (2014). Serum vaspin levels are positively associated with carotid atherosclerosis in a general population. Atherosclerosis, 233 (1), 248–252. doi: http://doi.org/10.1016/j.atherosclerosis.2013.12.040

[10] Cardoso, C. R. L., Ferreira, M. T., Leite, N. C., Salles, G. F. (2013). Prognostic Impact of Aortic Stiffness in High-Risk Type 2 Diabetic Patients: The Rio de Janeiro Type 2 Diabetes Cohort Study. Diabetes Care, 36 (11), 3772–3778. doi: http://doi.org/10.2337/dc13-0506

[11] Liu, S., Dong, Y., Wang, T., Zhao, S., Yang, K., Chen, X., Zheng, C. (2014). Vaspin inhibited proinflammatory cytokine induced activation of nuclear factor-kappa B and its downstream molecules in human endothelial EA.hy926 cells. Diabetes Research and Clinical Practice, 103 (3), 482–488. doi: http://doi.org/10.1016/j.diabres.2013.12.002

[12] Petersen, M. C., Shulman, G. I. (2018). Mechanisms of Insulin Action and Insulin Resistance. Physiological Reviews, 98 (4), 2133–2223. doi: http://doi.org/10.1152/physrev.00063.2017

[13] Yang, L., Chen, S. J., Yuan, G. Y., Wang, D., Chen, J. J. (2015). Changes and clinical significance of serum vaspin levels in patients with type 2 diabetes. Genetics and Molecular Research, 14 (3), 11356–11361. doi: http://doi.org/10.4238/2015.september.25.2

[14] Feng, R., Li, Y., Wang, C., Luo, C., Liu, L., Chuo, F. et. al. (2014). Higher vaspin levels in subjects with obesity and type 2 diabetes mellitus: A meta-analysis. Diabetes Research and Clinical Practice, 106 (1), 88–94. doi: http://doi.org/10.1016/j.diabres.2014.07.026

[15] Domaa, A. M., El-Bagori, N. N., El-Sayd, M. M. (2012). The clinical significance of vaspin and chemerin in diabetic obese Libyan patients. Current Science International, 2, 1–5.

[16] Sato, K., Shirai, R., Yamaguchi, M., Yamashita, T., Shibata, K., Okano, T. et. al. (2018). Anti-Atherogenic Effects of Vaspin on Human Aortic Smooth Muscle Cell/Macrophage Responses and Hyperlipidemic Mouse Plaque Phenotype. International Journal of Molecular Sciences, 19 (6), 1732. doi: http://doi.org/10.3390/ijms19061732

[17] Feng, R.-N., Wang, C., Sun, C.-H., Guo, F.-C., Zhao, C., Li, Y. (2011). Vaspin in newly and previously diagnosed Chinese type 2 diabetic females: a case-control study. Asian Biomedicine, 5 (4), 525–529. doi: http://doi.org/10.5372/1905-7415.0504.069

[18] Dimova, R., Tankova, T. (2015). The Role of Vaspin in the Development of Metabolic and Glucose Tolerance Disorders and Atherosclerosis. BioMed Research International, 2015, 1–7. doi: http://doi.org/10.1155/2015/823481

[19] Kobat, M. A., Celik, A., Balin, M., Altas, Y., Baydas, A., Bulut, M. et. al. (2012). The investigation of serum vaspin level in atherosclerotic coronary artery disease. Journal of Clinical Medicine Research, 4, 110–113. doi: http://doi.org/10.4021/jocmr841w

[20] Leal, V. de O., Mafra, D. (2013). Adipokines in obesity. Clinica Chimica Acta, 419, 87–94. doi: http://doi.org/10.1016/j.cca.2013.02.003

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