

## Epicardial fat thickness and biomarkers of inflammation in patients with stable coronary artery disease: correlation with the severity of coronary atherosclerosis

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**Aim.** To study the relationship between the epicardial fat thickness (EFT), biomarkers of inflammation and metabolic dysfunction in patients with coronary artery disease (CAD) and various severity of coronary atherosclerosis.

**Material and methods.** The study consisted of 89 patients (47 men and 42 women) with stable CAD at the age of 62,2±6,5 years, who assessed the presence and severity of coronary atherosclerosis according to angiography with the calculation of the Gensini Score (GS). We conducted an ultrasonic evaluation of the EFT. We determined the content of glucose, lipid fractions, apoproteins, pro-inflammatory cytokines and adipokines, C-reactive protein by a highly sensitive method (hsCRP).

**Results.** In the total sample of patients, the median GS index was 13,5 (3,5; 43) points, the median EFT was 4,93 (3,95; 6,0) mm, the median hsCRP was 2,1 (1,02; 3,65) mg/l. There were no correlation relationships between the GS index and the body mass index, waist circumference, EFT, hsCRP, lipid and carbohydrate metabolism in the general group of patients. In the course of linear regression analysis, an independent contribution of hsCRP >2,1 mg/l to the formation of the first two tertiles of a sample of GS values was established (0 ≤ GS ≤ 28, paired linear regression hsCRP at GS β=0,55, p=0,0221), whereas in patients with GS values from the third tertile (GS >28 points), the growth of this parameter had an independent association with an increase in the EFT (estimation of the coefficient of paired linear regression of the EFT on GS β=0,56, p=0,0015). The range of hsCRP changes did not affect the value of the β coefficient in paired linear regression models in patients with GS >28 points (n=29) and in the subgroup of patients with GS >28 and hsCRP >2,1 mg/l (n=18).

**Conclusion.** The absence of an independent association between EFT and minor or moderate severity of atherosclerotic lesions of the coronary arteries (for GS ≤ 28 points) in patients with CAD, while an independent marker of GS index increase is higher than 2,1 mg/l. An independent contribution to the formation of a severe coronary atherosclerosis (with a GS value of >28 points) is equally made by thickening of EFT, and a moderately elevated level of hsCRP.

**Key words:** epicardial fat thickness, biomarkers of inflammation, coronary atherosclerosis, Gensini Score. Conflicts of interest: nothing to declare.

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Epicardial adipose tissue (EAT) is a metabolically active ectopic depot of visceral and perivascular fat cells not separated by fascia from the myocardium and coronary arteries (CA). Under disorders, it can activate local and paracrine secretion of various pro-atherogenic mediators [1]. Although many studies have shown that epicardial adiposity can be considered as a visual surrogate marker for CA and its severity [2-4], the pathophysiological mechanisms that mediate the relationship between epicardial adiposity and atherogenesis still need to be clarified. So far, the independent association between EAT thickness and CA have not been established; its diagnostic value as a tool for individual risk stratification in patients with coronary artery disease (CAD) also requires clarification. Based on the inflammatory hypothesis of atherosclerosis, assessing the biomarkers of chronic subclinical inflammation is widely used to clarify cardiovascular risk in CAD patients. Nevertheless, the data on the association of high-sensitivity C-reactive protein (hsCRP) increase with CAD are very contradictory. So, some authors suggest their close relationship [5], while others deny this [6, 7]. Since the EAT has a proven independent association with hsCRP increase [8], it is possible that the severity of EAT accumulation and its dysfunction can specify associations between the hsCRP content and CA. In the modern literature there is no comprehensive information about the nature of the relationship between EAT, the activity of chronic subclinical inflammation and the CA severity. Moreover, the characteristics of this relationship at different stages of atherogenesis are not clear. The aim of this paper was to study the relationships of EAT thickness, inflammatory biomarkers, and severity of metabolic dysfunction with CA of different extent using the Gensini Score (GS) in patients with CAD.

## Material and methods

The study was conducted in accordance with Good Clinical Practice guidelines and the principles of Declaration of Helsinki; the study protocol was approved by local independent ethics committee. The study included men and women aged 40 to 70 years with established stable CAD who underwent coronary angiography. All patients completed the informed consent.

Exclusion criteria were acute complication of atherosclerosis, less than 6 months ago and any inflammatory disease; diabetes with inadequate glycemic control and HbA1c > 10% or glycemia during the day > 11 mmol/L; chronic kidney disease above G3b, left

ventricular ejection fraction < 40%; oncological, hematological and immune diseases.

Table 1 presents the clinical characteristics of the included patients. The study consisted of 89 men and women with established stable CAD at the age of  $62,2 \pm 6,5$  years. About half of the patients had type 2 diabetes (T2D) and the same proportion was smokers. Metabolic disorders that met the criteria of metabolic syndrome [9] were determined in 72% of patients. Hemodynamically significant stenosis of at least one of the main coronary arteries was established in 68,6% of patients; coronary microvascular stenosis was observed in 23,6% of patients. In other cases, changes in coronary arteries were considered non-stenotic.

All patients underwent selective coronary angiography using the Cardio-scop-V apparatus and Digitron-3NAC software (Siemens (Germany)). The procedure was conducted by specialists of Endovascular Surgery Department headed by Ph.D. A. E. Baev. The severity of coronary artery injury was assessed by GS.

The EAT thickness was determined by parasternal long-axis echocardiographic left ventricle (LV) images obtained at end-systole [10]. The measurements were carried out over 3 cardiac cycles; the average of 3 serial measurement results was taken as the EAT value.

Body mass index (BMI) was used to assess the general obesity, waist circumference (WC) — abdominal obesity.

By the method of enzyme immunoassay, the content of hsCRP (Biomerica, Germany), insulin (Accu-Bind, USA), interleukin (IL) -6 (Vector-BEST, Russia), tumor necrosis factor (TNF)- $\alpha$  (Affymetrix, eBioscience, USA), resistin (Mediagnost, Germany), leptin (Mediagnost, Germany), adiponectin (Assay-pro, USA), apolipoprotein A1 (DiaSys, Germany) were determined in the blood serum. The blood glucose levels were determined by the glucose oxidase method; HbA1c proportion was determined by immunoturbidimetric assay (DiaSys, Germany). Blood lipids (total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) (sets by ZAO Diakon-DS, Russia) were studied.

**Statistical analysis.** Statistical analysis was carried out using the Statistica 10.0 software. The median and interquartile range between the 25th and 75th percentiles were used to describe distribution features. Differences in quantitative characters in independent groups of patients were identified using the Mann-Whitney and the Kruskal-Wallis tests. When studying the relationship of the GS with various bio-

**Table 1**  
**Clinical characteristics  
of the included patients (n=89)**

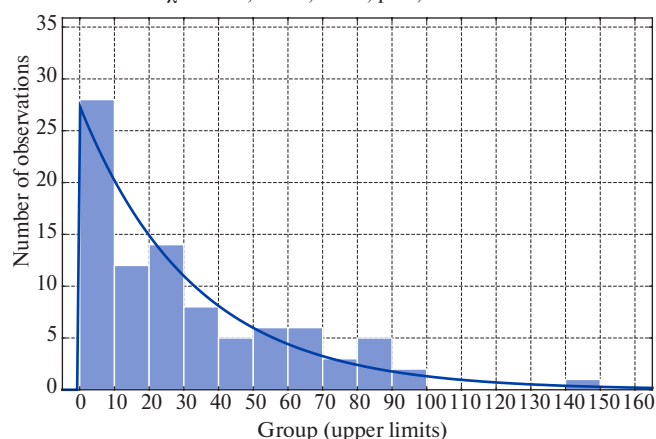
| Parameter                                                                 |             |
|---------------------------------------------------------------------------|-------------|
| Gender (men/women)                                                        | 47/42       |
| Age, years                                                                | 60,2±6,5    |
| The proportion of patients with a history of myocardial infarction, n (%) | 32 (36%)    |
| Duration of coronary artery disease, years*                               | 2 (1; 5)    |
| The proportion of patients with type 2 diabetes, n (%)                    | 37 (41,6%)  |
| Duration of diabetes, years*                                              | 5,5 (2; 12) |
| The proportion of patients with hypertension, n (%)                       | 18 (20,2)   |
| Duration of arterial hypertension, years*                                 | 10 (5; 15)  |
| Systolic blood pressure, mm Hg                                            | 127,2±14,1  |
| Diastolic blood pressure, mm Hg                                           | 77,7±8,4    |
| The proportion of smokers, n (%)                                          | 37 (41,6%)  |
| Body mass index, kg/m <sup>2</sup>                                        | 30,1±4,3    |
| The proportion of patients with overweight, n (%)                         | 42 (47,2%)  |
| The proportion of patients with obesity, n (%)                            | 42 (47,2%)  |
| Waist circumference, cm                                                   | 102,5±13,9  |
| Thigh circumference, cm                                                   | 104,7±8,1   |
| Waist circumference / thigh circumference                                 | 0,96±0,1    |
| LDL-C, mmol/L                                                             | 2,92±1,28   |
| Statin therapy, n (%)                                                     | 63 (70,8%)  |
| Hb <sub>A1c</sub> (patients with diabetes), %                             | 7,74±1,44   |
| Antihypertensive therapy, n (%)                                           |             |
| — RAAS inhibitors                                                         | 68 (76,4%)  |
| — β-blockers                                                              | 64 (71,9%)  |
| — calcium channel antagonists                                             | 26 (29,2%)  |
| — thiazide diuretics                                                      | 22 (24,7%)  |
| — β-blockers and diuretics                                                | 17 (19,1%)  |

**Note:** \* — data are presented as Me ((Q<sub>25%</sub>; Q<sub>75%</sub>)).

**Abbreviations:** CAD — coronary artery disease, RAAS — renin-angiotensin-aldosterone system, LDL-C — low density lipoprotein cholesterol.

markers, the Spearman's rank correlation coefficient (R<sub>s</sub>) was determined. In cases where significant correlation was identified, linear regression models were constructed. The relationship between the GS and qualitative characters was assessed using four-field contingency tables. The results of statistical analysis were considered statistically significant at p<0,05.

Variable: GS, Distribution: Exponential  
 $\chi^2$  test=4,40602, cc=6, p=0,62191



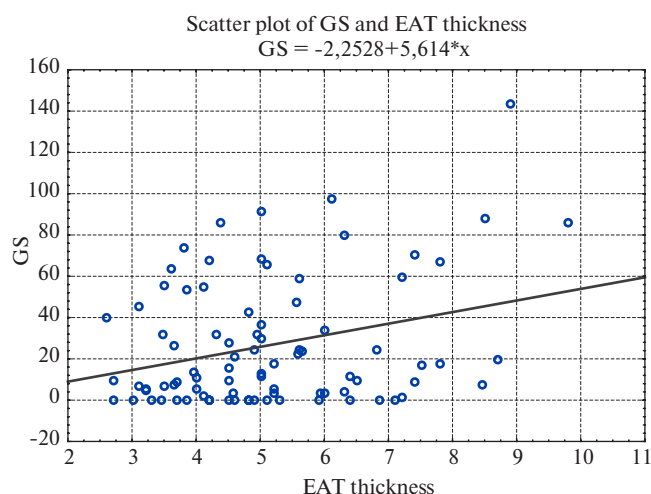
**Fig. 1.** The histogram of distribution of GS sample values.

## Results and discussion

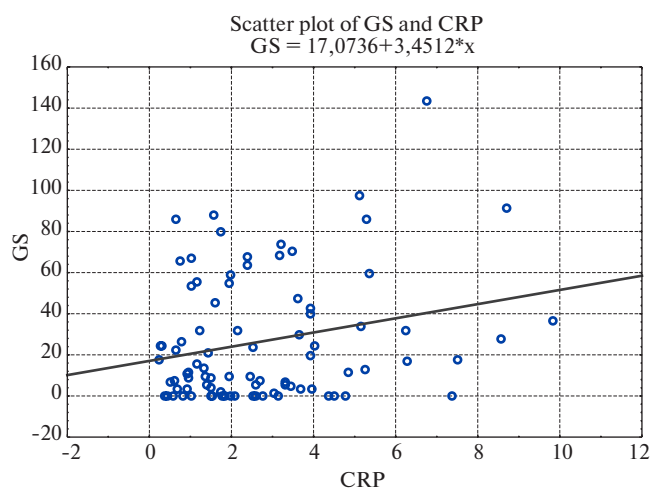
The histogram of distribution of GS sample values is shown in Fig. 1. As seen, the sampling of the GS values has a wide scatter: from 0 (in 21 patients) to 144. Fig. 2 and 3 show scatter plots characterizing the correlation between the GS and EAT thickness and hsCRP values.

In the general group of patients, the GS median was 13,5 (3,5; 43), the EAT thickness median — 4,93 (3,95; 6,0) mm, the hsCRP median — 2,1 (1,02; 3,65) mg/L. There were no correlation between the GS in its entire range and age, gender, BMI, WC, EAT thickness, hsCRP, TC, LDL-C, TG and carbohydrate metabolism in the general group of patients, but associations of the GS with IL-6 levels ( $R_s=0,33$ ) and HDL-C ( $R_s=-0,25$ ) were established (Table 2). Our data are consistent with the study by Caselli C, et al. (2015), which showed that the IL-6 and HDL-C determination allows to predict the presence and severity of CA determined by computed tomography [11]. At the same time, the values of EAT thickness in our sample did not correlate with GS, inflammatory biomarkers, parameters of lipid and carbohydrate metabolism, and showed linear associations with BMI ( $R_s=0,47$ ), abdominal obesity ( $R_s=0,42$ ), WC ( $R_s=0,36$ ) and leptin ( $R_s=0,36$ ). It should be noted that a EAT thickness  $\geq 5$  mm was determined in 21 patients (24%) with general and abdominal obesity (10 men and 11 women) without established CA or with insignificant coronary artery changes.

Since the sample values of the GS has a “zero-inflated” distribution, all patients were divided into three subgroups by GS tertiles: 0-5 (n=30), 6-28 (n=30) and more than 28 (n=29). The patients of the



**Fig. 2.** Scatter plot of GS and EAT thickness.



**Fig. 3.** Scatter plot of GS and CRP.

**Table 2**

**Correlations between the studied parameters in CAD patients**

| Parameters    | GS    | BMI  | WC    | EAT thickness | HDL-C | TG    | hsCRP | IL-6  | Leptin | Adiponectin |
|---------------|-------|------|-------|---------------|-------|-------|-------|-------|--------|-------------|
| GS            |       |      |       |               | -0,25 |       |       | 0,33  |        |             |
| BMI           |       |      |       | 0,47          |       | 0,25  | 0,29  |       | 0,60   |             |
| WC            |       |      |       | 0,36          |       |       | 0,25  |       |        | -0,26       |
| EAT thickness |       | 0,47 | 0,36  |               |       |       |       |       | 0,36   |             |
| HDL-C         | -0,25 |      |       |               |       | -0,28 |       | -0,23 |        | 0,39        |
| TG            |       | 0,25 |       |               | -0,28 |       | 0,23  |       |        | -0,23       |
| hsCRP         |       | 0,29 | 0,25  |               |       | 0,23  |       | 0,40  | 0,24   | 0,40        |
| IL-6          | 0,33  |      |       |               | -0,23 |       | 0,40  |       |        |             |
| Leptin        |       | 0,60 |       | 0,36          |       |       | 0,24  |       |        | 0,27        |
| Adiponectin   |       |      | -0,26 |               | 0,39  | -0,23 | 0,40  |       | 0,27   |             |

**Note:** all noted correlations are significant,  $p < 0,05$ .

**Abbreviations:** CAD — coronary artery disease, BMI — body mass index, WC — waist circumference, TG — triglycerides, EAT — epicardial adipose tissue thickness, HDL-C — high density lipoprotein cholesterol, GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein, IL-6 — interleukin-6.

first two tertiles were combined into group 1 ( $GS \leq 28$ ,  $n=60$ ), and the studied parameters were analyzed in comparison with the patients of group 2 from the GS third tertile ( $GS > 28$ ,  $n=29$ ) (Table 3).

As seen, there were no significant intergroup differences by gender, age, blood pressure (BM), BMI, EAT thickness, levels of LDL-C, TG,  $HbA_{1c}$  and adipokines, as well as the proportion of patients with T2D and taking lipid-lowering therap. Among patients of group 2, the proportion of smokers and the atherogenicity index were higher and the apoA1 level was lower, which reflects a characteristic decrease in the HDL-C anti-atherogenic potential in

patients with severe CA. In addition, patients of group 2 were characterized by a higher hsCRP levels in comparison with group 1, where  $hsCRP < 1$  mg/L were significantly more common (Table 4).

Dysfunctional EAT is an atherogenic trigger which can secrete both local and systemic mediators of atherogenesis, which contributes to the systemic formation of free radicals and the development of chronic subclinical inflammation [1]. Therefore, it was important to establish whether a quantitative assessment of EAT thickness can independently predict the presence and severity of CA in patients with established CAD.

Table 3

**Clinical characteristics, thickness of epicardial adipose tissue and laboratory parameters in patients with coronary artery disease depending on the presence and severity of coronary atherosclerosis, assessed by Gensini Score (Me (Q<sub>25%</sub>; Q<sub>75%</sub>))**

|                               | Group 1 (n=60)<br>GS 0-28 | Group 2 (n=29)<br>GS >28 баллов | p     |
|-------------------------------|---------------------------|---------------------------------|-------|
| GS                            | 5,25 (0; 12,5)            | 60 (43; 74)                     | 0,000 |
| Men/Women                     | 29 (48,3%)/31 (51,7%)     | 18 (62,1%)/11 (37,9%)           |       |
| Age, years                    | 61,5 (56; 66,5)           | 60 (55; 65)                     |       |
| Smoking, n (%)                | 20 (33,3%)                | 17 (58,6%)                      | 0,03  |
| Patients with T2D, n (%)      | 18 (30)                   | 10 (34,5)                       |       |
| Lipid-lowering therapy, n (%) | 41 (68,3%)                | 22 (75,9%)                      |       |
| BMI, kg/m <sup>2</sup>        | 29,6 (27,7; 31,1)         | 30 (26,3; 33,3)                 |       |
| WC, cm                        | 100 (94; 105)             | 102,5 (90; 108)                 |       |
| EAT thickness, mm             | 4,85 (3,90; 5,97)         | 5,0 (4,1; 6,1)                  |       |
| hsCRP, mg/L                   | 1,87 (0,94; 3,36)         | 3,14 (1,6; 5,12)                | 0,04  |
| IL-6, pg/ml                   | 1,36 (1,01; 1,85)         | 2,23 (1,48; 3,31)               | 0,003 |
| TNF-α, pg/ml                  | 0,50 (0,48; 0,91)         | 0,42 (0,30; 0,70)               |       |
| LDL-C, mmol/L                 | 2,50 (1,86; 3,63)         | 2,72 (2,29; 3,80)               |       |
| HDL-C, mmol/L                 | 1,08 (0,96; 1,32)         | 1,00 (0,83; 1,12)               | 0,04  |
| Triglycerides, mmol/L         | 1,43 (1,13; 2,06)         | 1,57 (1,13; 2,01)               |       |
| Atherogenic Index             | 2,96 (2,23; 4,49)         | 3,49 (2,80; 4,95)               |       |
| ApoA1, mg/dl                  | 151,6 (133,0; 170,2)      | 128,0 (106,8; 156,8)            | 0,005 |
| Hb <sub>A1c</sub> , %         | 6,34 (5,63; 7,20)         | 6,01 (5,40; 6,90)               |       |
| Leptin, ng/ml                 | 18,3 (7,7; 32,8)          | 15,2 (6,9; 26,4)                |       |
| Resistin, ng/ml               | 4,51 (3,48; 5,11)         | 4,75 (3,89; 5,62)               |       |
| Adiponectin, ng / ml          | 9,23 (6,20; 13,25)        | 7,59 (5,21; 10,26)              |       |

**Abbreviations:** CAD — coronary artery disease, BMI — body mass index, WC — waist circumference, T2D — type 2 diabetes, HDL-C — high density lipoprotein cholesterol, HDL-C — low density lipoprotein cholesterol, GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein, IL-6 — interleukin-6, TNF-α — tumor necrosis factor α.

Table 4

**Distribution of patients by hsCRP levels depending on the range of GS values**

| GS            | hsCRP <1 mg/L, n (%) | hsCRP 1-3 mg/L, n (%) | hsCRP ≥3 mg/L, n (%) |
|---------------|----------------------|-----------------------|----------------------|
| Group 1: 0-28 | 16 (83,1%)           | 24 (58,6%)            | 20 (48,3%)           |
| Group 2: >28  | 2 (16,9%)*           | 12 (41,4%)            | 15 (51,7%)           |

**Note:** \* — differences between gr. 1 and column 2 are statistically significant (p<0,0001).

**Abbreviations:** GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein.

There were no significant correlations between the GS and parameters of general and abdominal obesity, EAT thickness, inflammatory biomarkers and metabolic parameters in patients without CA or mild and moderate CA (group 1, GS ≤28,

n=60). At the same time, after applying the group limiting on the hsCRP level more than the median (>2,1 mg/L), according to the data of linear regression analysis, an independent contribution of hsCRP >2,1 mg/L to the formation of low GS was

Table 5

**Model of dual linear regression of hsCRP on GS  
in patients with GS  $\leq 28$  and hsCRP  $> 2,1$  mg/L (n=17)**

|    | Beta coefficient* | Standard error of beta* | p      |
|----|-------------------|-------------------------|--------|
| GS | 0,55              | 0,22                    | 0,0221 |

**Note:** \* — differences between groups 1 and 2 are statistically significant ( $p < 0,0001$ ).

**Abbreviations:** GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein.

Table 6

**Model of dual linear regression of the EAT thickness  
on GS in patients with GS  $> 28$  (n=29)**

|               | Beta coefficient* | Standard error of beta* | p      |
|---------------|-------------------|-------------------------|--------|
| EAT thickness | 0,56              | 0,16                    | 0,0015 |

**Note:** \* — differences between groups 1 and 2 are statistically significant ( $p < 0,0001$ ). Concordance rate  $R^2 = 0,52$ .

**Abbreviations:** GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein.

determined. This reflects initial stages of atherogenesis (Table 5).

Linear regression analysis in patients with severe CA (group 2, GS  $> 28$ ) showed an increase of GS and EAT thickness (Table 6). These findings did not depend on the range of hsCRP changes, since the beta coefficient in the dual linear regression model in group 2 practically did not differ from the subgroup of patients having hsCRP  $> 2,1$  mg/L ( $\beta^* = 0,555$ ,  $p = 0,0178$ ).

The results show that there is no direct linear relationship between EAT thickness and the GS, reflecting mild and moderate CA, and its independent determinant is the hsCRP levels more than 2,1 mg/L. At the same time, an independent association between the EAT thickness and the GS is determined only in patients with severe CA (GS  $> 28$ ), and this is not clearly dependent on the range of hsCRP changes. Although a number of cross-sectional and case-control studies have shown the association between increased hsCRP levels and CA severity [5]; some other studies have denied this association [6-7]. Our results suggest that hsCRP levels more than 2,1 mg/L at the initial stages can have an important pathogenetic value, regardless on epicardial adiposity. At the same time, in advanced stages of CA, its severity is equally specified by excessive EAT accumulation and hsCRP increase. It cannot be ruled out that it is the phase nature of the interaction of EAT with inflammatory biomarkers at different stages of atherogenesis that may be the reason for the previously obtained contradictory results [3, 5-7, 12].

It should be noted that in our study, groups of patients with CA of various severity showed no differences in EAT thickness. This does not preclude the possibility that patients with GS  $\leq 28$  may have factors that can “smooth” the atherogenic potential of the EAT depot. In particular, in the group of patients with the GS  $\leq 28$ , there was a higher levels of HDL-C and ApoA1, lower hsCRP level, while in the general sample, negative association between HDL-C and GS was determined. The results of a study by Chechi K, et al. (2013) allow interpreting these results in relation to their association with the EAT depot activity [13]. Thus, the authors revealed a higher expression of the marker of brown adipose tissue thermogenin (UCP-1) in the epicardial fat depot than in the mediastinal and subcutaneous fat depots. UCP-1 is involved in the thermogenesis, and authors established a direct association between the UCP-1 gene expression and HDL-C levels, which indicates the protective effects of EAT [13]. Our data on the absence in the general group of an independent association of EAT thickness with the CA severity of may be associated with a high proportion of women in the study. In women, the role of epicardial fat depot as an atherogenic factor may be less significant than in men [14]. This is due to the cardioprotective effects of higher aromatase activity of subcutaneous fat [15].

The limitations of our study are: cross-sectional design; the small sample, which does not allow us to establish potential gender differences in the relationship between the CA severity and the EAT accumula-

tion and features of subclinical inflammation; some conventionality for dividing the GS range; no statin therapy at the time of the study in 29,2% patients.

Thus, the results of our study indicate the absence of independent association between EAT thickness and mild or moderate CA ( $GS \leq 28$ ) in patients with established CAD, while an independent marker of an GS increase in such patients is the hsCRP  $> 2,1$  mg/L. The thickening of EAT and the hsCRP

increase is independently associated with severe CA ( $GS > 28$ ), equally. The obtained results suggest that the phenotypic and functional properties of EAT can significantly change during atherogenesis. In further papers, correlations of the cellular and molecular properties of EAT with its quantitative assessment should be studied.

**Conflicts of Interest:** nothing to declare.

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