

CARDIOLOGY

ASSOCIATION OF SEX AND AGE WITH THE CERAMIDE PROFILE OF ADIPOSE TISSUE IN PATIENTS WITH CORONARY ARTERY DISEASE

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ABSTRACT

Background. Coronary artery disease (CAD) is associated with complex molecular changes in adipose tissue (AT) that go beyond simple energy storage. Current studies indicate the active participation of AT in metabolic regulation and secretion of bioactive lipid mediators, including ceramides, the role of which in CAD pathogenesis remains poorly understood, particularly with regard to age and sex differences.

Aim. To characterize the ceramide profile in subcutaneous, epicardial and perivascular AT (SAT, EAT, PVAT) in patients with CAD, with regard to age and sex differences.

Materials and Methods. A lipidomic study of the ceramide profile was conducted in SAT, EAT, PVAT samples obtained from 58 patients with CAD who underwent coronary artery bypass grafting (single-center prospective clinical study). The ceramide composition was analyzed by high-performance liquid chromatography with tandem mass spectrometric detection.

Results. Age- and sex-related differences in the AT ceramide profile were identified. In men, the concentrations of cardioneutral ceramides (Cer d18:1/14:0, Cer d18:1/18:0, Cer d18:1/20:0, Cer d18:1/22:0) and Cer d18:1/24:1 were higher ($p < 0.05$). In PVAT of men, the levels of Cer 14:0, 16:0 and 22:4 were increased ($p < 0.001$). In EAT and PVAT of women, increased levels of Cer 18:0 and 23:0 were noted ($p < 0.05$). In EAT and PVAT of women, the concentrations of Cer 20:0, 22:0 and 24:1 were higher ($p < 0.05$). The highest levels of cardioneutral ceramides were observed in PVAT of patients aged over 75 years. The ratio of cardioneutral to cardioprotective ceramides was higher in EAT in individuals aged 60–74 years and in PVAT in those aged over 75 years.

Conclusion. Significant sex- and age-related differences in the AT ceramide profile of patients with CAD were identified, emphasizing the need to consider these factors when assessing cardiovascular risk. The data obtained may contribute to the development of new therapeutic strategies aimed at modulating the ceramide profile of AT to reduce cardiovascular risk.

Keywords: ceramides, age, sex, epicardial adipose tissue, perivascular adipose tissue, risk factors, coronary artery disease

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АССОЦИАЦИЯ ПОЛА И ВОЗРАСТА С ЦЕРАМИДНЫМ ПРОФИЛЕМ ЖИРОВОЙ ТКАНИ ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

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РЕЗЮМЕ

Актуальность. Ишемическая болезнь сердца (ИБС) связана с комплексными молекулярными изменениями в жировой ткани (ЖТ), выходящими за рамки простого хранения энергии. Современные исследования указывают на активное участие ЖТ в метаболической регуляции и секреции биоактивных липидных медиаторов, включая церамиды, роль которых в патогенезе ИБС остается недостаточно изученной, особенно с учетом половозрастных характеристик.

Цель. Охарактеризовать церамидный профиль в подкожной, эпикардимальной и периваскулярной ЖТ (ПЖТ, ЭЖТ, ПВЖТ) у пациентов с ИБС с учетом половозрастных особенностей.

Материалы и методы. Проведено липидомическое исследование церамидного профиля в образцах ПЖТ, ЭЖТ, ПВЖТ, полученных от 58 пациентов с ИБС, которым выполнялось коронарное шунтирование (одноцентровое проспективное клиническое исследование). Анализ церамидного состава осуществлялся методом высокоэффективной жидкостной хроматографии с тандемным масс-спектрометрическим детектированием.

Результаты. Выявлены половозрастные различия в церамидном профиле ЖТ. У мужчин концентрации кардионегативных церамидов (Cer d18:1/14:0, Cer d18:1/18:0, Cer d18:1/20:0, Cer d18:1/22:0) и Cer d18:1/24:1 были выше ($p < 0,05$). В ПВЖТ мужчин уровни Cer 14:0, 16:0 и 22:4 были повышены ($p < 0,001$). В ЭЖТ и ПВЖТ женщин отмечалось повышение уровней Cer 18:0 и 23:0 ($p < 0,05$). В ЭЖТ и ПЖТ женщин концентрации Cer 20:0, 22:0 и 24:1 были выше ($p < 0,05$). Наибольшие уровни кардионегативных церамидов наблюдались в ПВЖТ пациентов старше 75 лет. Соотношение кардионегативных и кардиопротективных церамидов было выше в ЭЖТ у лиц 60–74 лет, а в ПВЖТ – старше 75 лет.

Заключение. Выявлены значимые половые и возрастные различия в церамидном профиле ЖТ у пациентов с ИБС, что подчеркивает необходимость учета этих факторов при оценке риска сердечно-сосудистых осложнений. Полученные данные могут способствовать разработке новых терапевтических стратегий, направленных на модуляцию церамидного профиля ЖТ для снижения сердечно-сосудистого риска.

Ключевые слова: церамиды, возраст, пол, эпикардимальная жировая ткань, периваскулярная жировая ткань, факторы риска, ишемическая болезнь сердца

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INTRODUCTION

Complex molecular changes in adipose tissue (AT) play a crucial role in the pathogenesis of coronary artery disease (CAD). Adipose tissue is no longer seen as merely a passive energy store, but rather as an active participant in metabolic regulation. It has been shown to secrete bioactive lipid mediators, such as ceramides [1].

Ceramides (Cer) are a class of sphingolipids with both structural and signaling functions. They act as secondary messengers, influencing various cellular processes, including growth, proliferation, differentiation, and apoptosis [2]. Given their importance in regulating cellular functions under both normal and pathological conditions, the impact of ceramides on the cardiovascular system (CVS) and the development of cardiovascular diseases (CVD) have been actively investigated in recent decades.

Under conditions of metabolic stress, the accumulation of lipid metabolites in tissues poses a significant threat. Lipidomics studies have demonstrated that ceramides exhibit pronounced toxic effects, leading to lipotoxicity, which, in turn, results in mitochondrial dysfunction and cellular hypoxia. This process serves as a crucial mechanism in the development of various cardiometabolic disorders [3].

Although there is interest in investigating plasma ceramide levels as biomarkers of cardiovascular risk, information on the characteristics of ceramide profiles in different AT depots in patients with CAD remains limited, particularly regarding age- and sex-related differences [4].

A comprehensive analysis of the composition of ceramides in AT can help identify specific lipid biomarkers associated with different stages of disease progression and develop novel diagnostic and therapeutic approaches aimed at regulating ceramide metabolism and reducing cardiovascular risks.

AIM

To characterize the ceramide profile in subcutaneous, epicardial and perivascular AT (SAT, EAT, PVAT) in patients with CAD, with regard to age and sex differences.

MATERIALS AND METHODS

A lipidomic study of the ceramide profile was performed in subcutaneous, epicardial, and perivascular adipose tissues (SAT, EAT, and PVAT) from patients with coronary artery disease (CAD) who required surgical myocardial revascularization through coronary artery bypass grafting (CABG). The study was approved by the local ethics committee of the Research Institute for Complex Issues of Cardiovascular Diseases (Protocol No. 12, dated March 20, 2023) and it adhered to the principles outlined in the Declaration of Helsinki

of the World Medical Association (as amended in 2013) and the "Clinical Practice Guidelines of the Russian Federation".

The study included 58 participants, with a majority of male patients (58 %). The mean age of participants was 64.9 (47.8; 78.5) years, and the median body mass index was 26.4 (22.5; 30.2) kg/m². A significant number of participants had comorbid conditions, including arterial hypertension (56.9 %), dyslipidemia (43.1 %), diabetes mellitus (24.1 %), and chronic kidney disease (10.3 %). A history of myocardial infarction was present in 70.7 % of patients. Among women (41.4 % of total), postmenopausal status was confirmed in 87.5 %, indicating a high proportion of postmenopausal women in this group. Patients predominantly had angina pectoris classes II (46.6 %) and III (50.0 %), as well as chronic heart failure classes I (39.7 %) and II (13.8 %). Extensive coronary artery (CA) atherosclerosis was also observed, with 81 % of patients having three or more affected coronary arteries. The median left ventricular ejection fraction was 53.6 (46.3; 58.9) %. Patients had elevated levels of total cholesterol (5.89 (4.12; 8.25) mmol/L), LDL cholesterol (3.31 (2.95; 5.65) mmol/L), and triglycerides (1.75 (1.52; 2.83) mmol/L), as well as an atherogenic index above the normal range (3.38 (2.75; 4.33)). Most patients received standard pharmacological treatment, including aspirin (93.1 %), beta-blockers (89.7 %), ACE inhibitors (77.6 %), and statins (100 %).

Collection and Storage of Adipose Tissue Samples

During elective CABG surgery, AT samples were collected: SAT from the subcutaneous fat of the lower angle of the median sternotomy incision; EAT from the right heart chambers (atrium and ventricle); and PVAT from the region around the left main coronary artery. To preserve the lipid content, the samples were immediately placed in liquid nitrogen for freezing and then stored at -150°C.

Lipid Extraction

A modified Folch method (1957) was employed to extract lipid components from homogenized AT samples. Approximately 100 mg of tissue was homogenized in a 2:1 (v/v) chloroform/methanol mixture. The samples were then subjected to sonication for 10 minutes to enhance extraction efficiency. Purified water was added, and the mixture was vigorously vortexed and centrifuged to separate the organic and aqueous layers. The organic layer was collected, re-extracted with a fresh aliquot of chloroform/methanol solution, and both organic phases were combined and allowed to evaporate to dryness under a nitrogen stream at room temperature. The resulting dried residue was reconstituted with a solution of isopropanol and acetonitrile (50:50, v/v) and further centrifuged to remove any insoluble impurities.

Ceramide Profile Analysis

High-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) was used to determine ceramide composition. The methodology for ceramide profile analysis by mass spectrometry

has been thoroughly described previously [5], ensuring the reproducibility and comparability of the results obtained.

The quantification of ceramides (ng/mL) in AT samples was performed using the Cer d18:1/17:0 standard (17:0 Ceramide N-heptadecanoyl-D-erythro-sphingosine, >99%, Avanti). For the preparation of the Cer d18:1/17:0 stock solutions, 5 mg of the Cer d18:1/17:0 standard was placed into a 15 mL screw-cap vial, dissolved in 2.5 mL of solvent, and an additional 2.5 mL of the same solvent was added, and the mixture was vortexed. The concentration of the resulting solution was 1 mg/mL, calculated as Cer d18:1/17:0. The solution was stored at -70°C. The work was conducted using the equipment provided by the Shared Research Facility "Clinical Mass Spectrometry" of the National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov, Ministry of Health of the Russian Federation.

Statistical Analysis

Statistical analysis was conducted using GraphPad Prism 8 software (GraphPad Software). Quantitative data are presented as the median with an interquartile range (25th and 75th percentiles). A non-parametric Kruskal – Wallis test was used to compare the three independent groups, followed by a pairwise comparison using the Mann – Whitney U test. Categorical variables were analyzed using either the χ^2 test or Fisher's exact test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Ceramides (N-acylsphingosines) are a subgroup of sphingolipids that have the structural backbone of the alcohol sphingosine. Sphingosine has 18 carbon atoms and contains one trans-double bond between C4 and C5. This fragment, designated as d18:1, is bonded to a fatty acid (FA) residue through an amide bond, forming the ceramide molecule. Ceramides may contain various FAs, including saturated fatty acids such as C14:0 (myristic), C15:0 (pentadecanoic), C16:0 (palmitic), C17:0 (margaric), C18:0 (stearic), C19:0 (nonadecanoic), C20:0 (arachidic), C21:0 (heneicosanoic), C22:0 (behenic), C23:0 (tricosanoic), C24:0 (lignoceric), C25:0 (pentacosanoic), C26:0 (cerotic) and unsaturated FAs (C18:1 (oleic), C22:1 (erucic), C24:1 (nervonic), C22:2 (docosadienoic), C22:4 (docosatetraenoic), and C22:5 (docosapentaenoic).

A wide range of ceramides was identified in the PVAT, EAT, and SAT from CAD patients. All ceramides detected contained the C18 sphingoid base, also known as sphingosine (d18:1). In the AT samples analyzed, ceramides containing both saturated FAs (Cer d18:1/14:0, Cer d18:1/15:0, Cer d18:1/16:0, Cer d18:1/17:0, Cer d18:1/18:0, Cer d18:1/19:0, Cer d18:1/20:0, Cer d18:1/21:0, Cer d18:1/22:0, Cer d18:1/23:0, Cer d18:1/24:0, Cer d18:1/25:0, Cer d18:1/26:0) and unsaturated FAs (Cer d18:1/18:1, Cer

d18:1/22:1, Cer d18:1/24:1, Cer d18:1/22:2, Cer d18:1/22:4, Cer d18:1/22:5) were identified.

Given the known cardiovascular effects of various ceramides, the identified compounds were divided into groups associated with cardioneegative (Cer d18:1/14:0, Cer d18:1/16:0, Cer d18:1/18:0, Cer d18:1/20:0, Cer d18:1/24:1) and cardioprotective (Cer d18:1/23:0, Cer d18:1/24:0, Cer d18:1/25:0, Cer d18:1/26:0) properties [2].

Analysis of ceramide concentrations in AT samples, considering patient sex, revealed statistically significant differences in the levels of individual ceramide species within AT in men, regardless of location. In particular, the concentrations of Cer d18:1/14:0, Cer d18:1/18:0, Cer d18:1/20:0, and Cer d18:1/22:0, containing saturated FAs and associated with cardioneegative effects that were significantly higher in male AT. Furthermore, increased levels of Cer d18:1/24:1, containing a mono-unsaturated FA and exhibiting potential pathological effects on the cardiovascular system, including proathrogenic action, were observed [2]. Notably, a concurrent increase in the concentration of Cer d18:1/23:0, which has cardioprotective properties, was also noted (Fig. 1).

Considering the sex and anatomical location of the patients, it was found that PVAT of males had elevated levels of certain ceramides compared to that of females: Cer 14:0 (1.7-fold, $p = 0.000017$), Cer 16:0 (1.4-fold, $p = 0.0005$), and Cer 22:4 (1.4-fold, $p = 0.00002$). At the same time, in EAT of females, an increase in Cer d18:1/17:2 concentration was observed (1.5-fold, $p = 0.006$). In EAT and PVAT of females, levels of Cer 18:0 (1.6-fold, $p = 0.0005$ and 1.4-fold, $p = 0.045$, respectively) and Cer 23:0 (1.2-fold, $p = 0.045$ and 1.7-fold, $p = 0.0005$, respectively) were higher compared to that of males. In EAT and SAT of females, concentrations of certain ceramides were higher than in the male group: Cer 20:0 (1.2-fold, $p = 0.004$ and 1.7-fold, $p = 0.045$, respectively), Cer 22:0 (1.8-fold, $p = 0.007$ and 1.5-fold, $p = 0.00001$, respectively), and Cer 24:1 (1.7-fold, $p = 0.006$ and 1.5-fold, $p = 0.00001$, respectively). In SAT of females, elevated levels of Cer d18:1/22:2 (1.6-fold, $p = 0.0005$), Cer 22:4 (1.2-fold, $p = 0.046$), and Cer 22:5 (1.4-fold, $p = 0.000017$) were found compared to that of males.

Patients with CAD were then divided into three age groups: ≤ 60 years, 60–74 years, and ≥ 75 years. Based on this stratification, it was found that the highest levels of ceramides with adverse cardiovascular effects were seen in PVAT of patients aged 75 and over: Cer d18:1/14:0, Cer 16:0, and Cer 22:0 compared to patients under the age of 60 and those aged 60–74 years ($p < 0.005$).

The level of Cer d18:1/14:0 in EAT of individuals aged 60–74 years was statistically significantly higher compared to the group under the age of 60 and showed a trend towards an increase compared to the group over the age of 75. The highest levels of Cer d18:1/18:0 in EAT and PVAT were found in the group aged over the age of 75. Cer d18:1/20:0 was higher in EAT of patients aged 60–74 years and in PVAT of the group aged over 75 years.

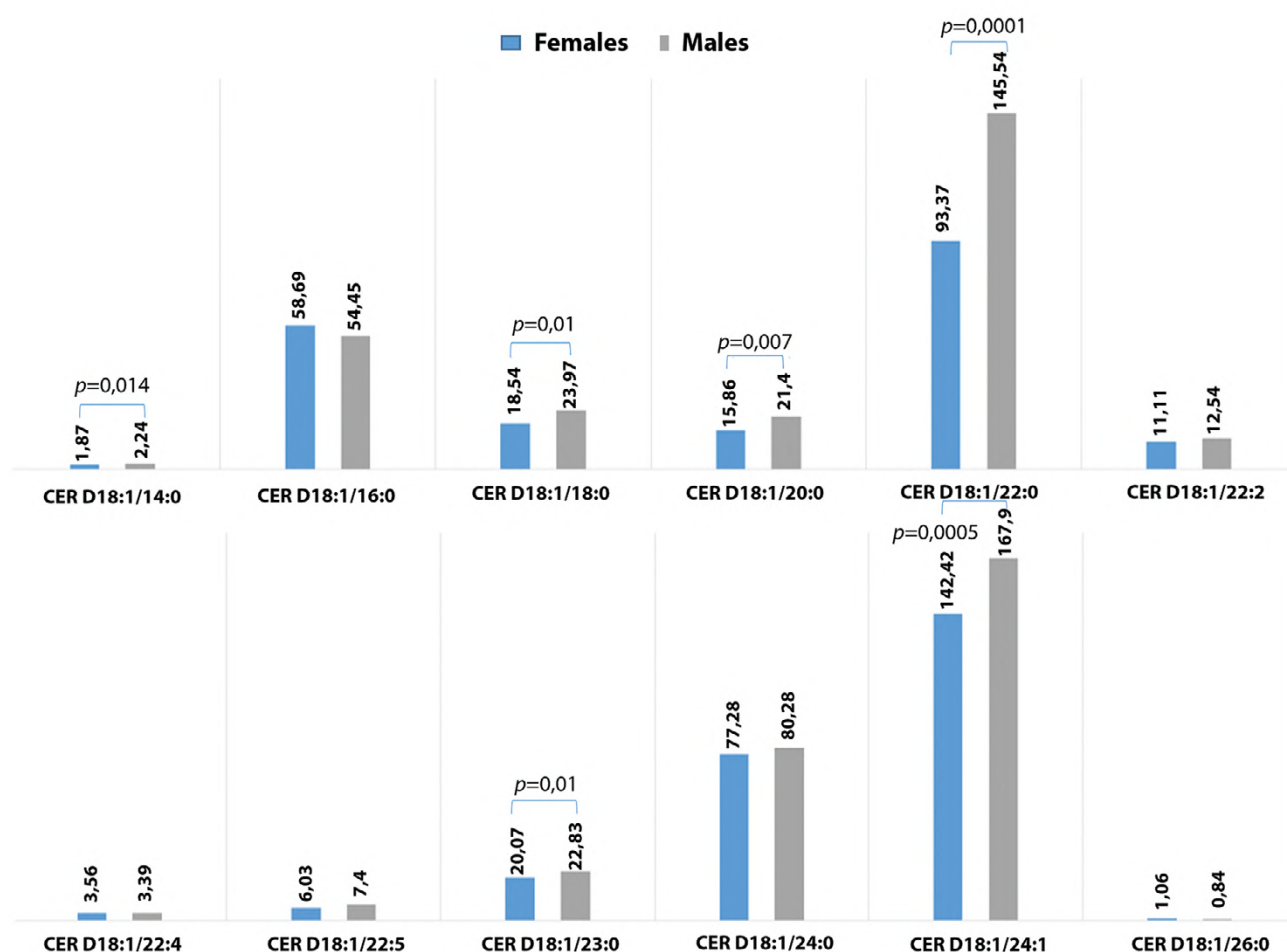


FIG. 1.
Concentration of ceramides in adipose tissue of patients with CAD, ng/ml

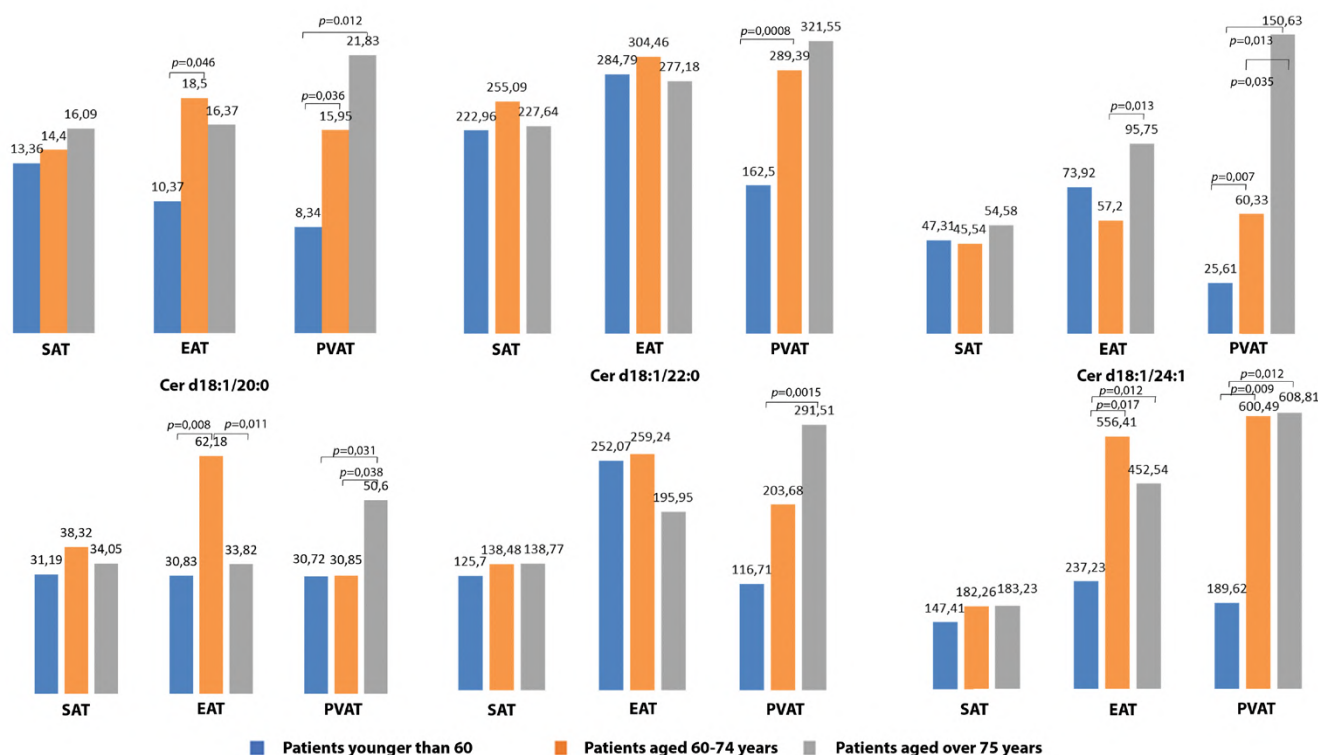
Levels of Cer d18:1/24:1 in cardiac AT of patients aged 60–74 and over the age of 75 exceeded those in patients under the age of 60 (Fig. 2).

The concentration of the cardioprotective ceramide Cer d18:1/23:0 in PVAT of patients aged 60–74 years and those older than 75 years was higher compared to the group younger under the age of 60. Levels of Cer d18:1/24:0 in EAT and PVAT in the 60–74 and ≥ 75 age groups exceeded those in patients younger than 60. The lowest concentrations of Cer d18:1/26:0 in both EAT and PVAT were observed in the 60–74 age group compared to those older than 75 and younger than 60 (Fig. 3).

The highest levels of ceramides with uncertain effects on the cardiovascular system (CVS) were observed in the following: Cer d18:1/15:0 was elevated in SAT ($p = 0.018$) and PVAT ($p = 0.024$) of patients over the age of 75; Cer d18:1/18:1 was elevated in SAT of patients aged 60–74 compared to those over 75

($p = 0.031$); Cer d18:1/19:0 was elevated in SAT of patients over 75 ($p = 0.015$) and in PVAT of patients aged 60–74 ($p = 0.028$). In contrast, the concentration of Cer d18:1/17:0 in AT did not significantly differ according to age among CAD patients ($p > 0.05$).

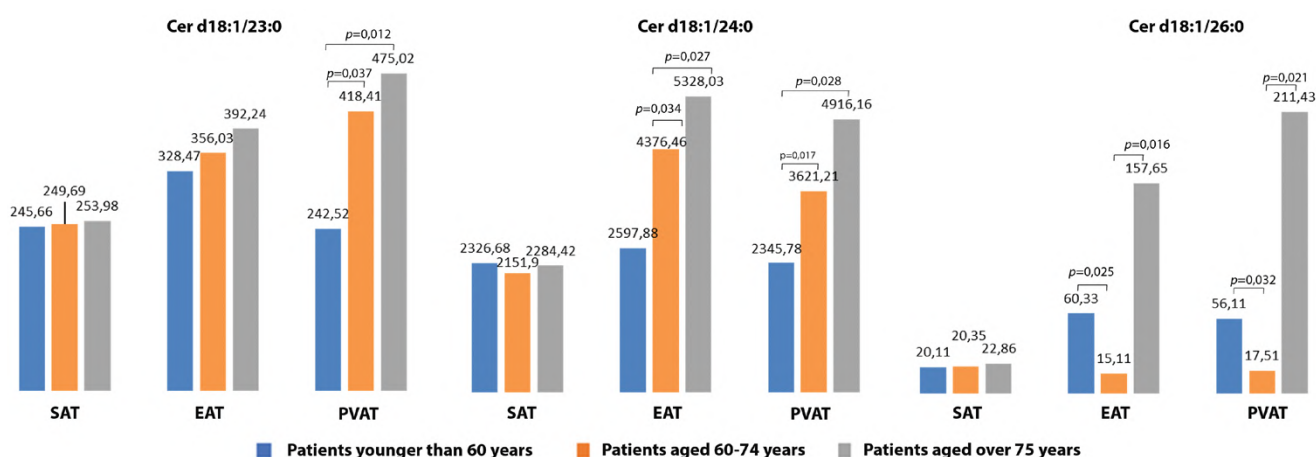
When calculating the ratios of Cer 16:0/24:0, Cer 18:0/24:0, Cer 18:1/24:0, and Cer 24:1/24:0, the Cer 16:0/24:0 ratio was significantly higher in EAT of patients under the age of 60 ($p = 0.023$) and those aged 60–74 ($p = 0.011$) than in patients older than 75 years, with no differences observed between the first two groups. The highest Cer 18:0/24:0 ratio was found in SAT ($p = 0.012$) and PVAT ($p = 0.017$) of patients aged over 75 years and in EAT of patients under the age of 60 ($p = 0.039$). The Cer 18:1/24:0 ratio was highest in EAT of patients aged 60–74 years ($p = 0.0004$) compared to those older than 75 years. The Cer 24:1/24:0 ratio was highest in EAT ($p = 0.027$) and PVAT ($p = 0.013$) among the 60–74 age group.



Note. PVAT – perivascular adipose tissue; SAT – subcutaneous adipose tissue; EAT – epicardial adipose tissue; Cer – ceramides.

FIG. 2.

Concentration of ceramides with adverse cardiovascular effects in tissue lipid extracts of local fat depots of patients with CAD depending on age, ng/ml



Note. PVAT – perivascular adipose tissue; SAT – subcutaneous adipose tissue; EAT – epicardial adipose tissue; Cer – ceramides.

FIG. 3.

Concentration of ceramides with cardioprotective properties in lipid extracts of tissues of local fat depots of patients with CAD depending on age, ng/ml

DISCUSSION

Regardless of AT location, a consistent increase in Cer d18:1 with saturated fatty acid residues (C14:0, C18:0, C20:0, C22:0, and C23:0) and monounsaturated fatty acid (C24:1) was observed in men with CAD. These findings are consistent with the data from Blachnio–Zabielska A.U. et al., who demonstrated that men exhibit preferential accumulation of Cer (d18:1/18:0), Cer (d18:1/20:0), and Cer (d18:1/22:0) in AT. Moreover, the total ceramide content (pg/adipocyte) was also higher in men compared to women (34 % vs. 31 %) [6]. However, in our study, Cer C24:1 levels were higher in male AT, which contradicts the results of these authors, who found that the concentration of this ceramide was higher in female AT. This discrepancy may be explained by differences in the AT location used for analysis. Specifically, Blachnio–Zabielska A.U. et al. exclusively focused on SAT collected laterally to the umbilicus through needle liposuction. Our study involves the analysis of visceral depots, EAT and PVAT, allowing us to assess their contribution to the pathogenesis of cardiometabolic diseases [7]. Considering that women exhibit an increase in superficial SAT precisely in the lateral area around the umbilicus [8], Cer C24:1 concentration in their SAT might be underestimated when analyzing other depots. The concentration of Cer (d18:1/16:0) in female AT was found to be significantly higher than that in males, which confirms the results of Brusatori M. et al. [7], who identified a specific accumulation of this ceramide in the visceral AT of women.

In our study, PVAT of men was characterized by elevated levels of Cer 14:0, 16:0, and 22:4 compared to women. At the same time, EAT of women showed an increase in Cer d18:1/17:2 concentrations. Additionally, both EAT and PVAT showed an increase in Cer 18:0 and 23:0 compared to men. In EAT and SAT of women, the concentrations of the following ceramides were higher than in the male group: Cer 20:0, 22:0, and 24:1. In SAT of women, elevated levels of Cer d18:1/22:2, 22:4, and 22:5 were found compared to men.

The identified differences in AT ceramide profiles may be due to differences in dietary habits between men and women. It is known that men on average consume more saturated fats than women, which stimulates the activity of ceramide synthase (CERS), enzymes that catalyze ceramide synthesis [9]. This leads to increased concentrations of ceramides containing saturated FAs, such as C16:0 and C18:0, in the AT. Therefore, increased saturated fat intake may contribute to the accumulation of cardioneegative saturated FA ceramides in male AT and, consequently, to the development of metabolic dysfunction [10].

The influence of sex hormones on ceramide synthesis and degradation should also be considered. Androgens, such as testosterone, can inhibit ceramide synthesis enzymes, e.g., CERS6. Six different CERS (CERS1-6) have been identified in mammals, with each having a specific fatty acid specificity. CERS6 plays

a primary role in the synthesis of ceramides containing palmitic and stearic FAs, which have been associated with adverse effects on the CVS [11]. The inhibition of CERS6 by testosterone observed in mouse experiments explains the lower levels of Cer C16:0 and C18:0 in the liver of males compared to females [12]. However, data suggest that sphingolipids and their metabolites can modulate steroid hormone secretion by regulating both their release and homeostasis [13]. This creates a feedback loop in which changes in the ceramide profile may affect hormonal status and in turn influence ceramide synthesis. Therefore, the ability of sex hormones to affect ceramide synthesis enzymes in human AT requires further study. The identified sex differences in AT ceramide profiles among CAD patients may be of prognostic significance, as elevated concentrations of certain ceramides, particularly those containing saturated FAs, are associated with increased cardiovascular risk [14].

Previous studies have convincingly demonstrated the relationship between circulating long-chain ceramides and age [15]. Age has also been shown to be closely associated with the prevalence of CAD [16]. Although there is a well-established association between blood long-chain ceramide levels and age [17], data on ceramide content in AT, especially in cardiac and vascular depots, and its age-related changes are extremely limited.

In this study, we identified a wide range of ceramides in AT, including those with both saturated and unsaturated acyl chains. Our data indicate that AT, especially EAT and PVAT, which are localized close to atherosclerotic lesion sites, may serve as a source of ceramides that can have both favorable and adverse effects [18].

We determined the characteristics of ceramide content in AT of different locations, depending on age, in CAD patients. The highest levels of cardioneegative ceramides Cer d18:1/14:0, 16:0, 18:0, and 22:0 were observed in EAT of individuals aged 60–74 years, and in PVAT of patients older than 75 years. The lowest concentrations of the cardioprotective ceramide Cer d18:1/26:0 in cardiac AT were found in the 60–74 age's group, which may be an unfavorable indicator for individuals of this age group. It is possible that cardiac AT undergoes more significant remodeling with age.

Bonzón–Kulichenko E. et al. [19] showed increased levels of Cer 18:0, 20:0, 22:0, and 24:1 in brown adipose tissue (BAT) and increased levels of Cer 18:1 and 20:0 in white adipose tissue (WAT) of 15-month-old male rats when compared to 2-month-old males. Moreover, in 24-month-old male rats, there were increased levels of Cer 16:0 and 20:0, and decreased levels of Cer 24:1 in WAT when compared to 3-month-old animals [20]. These findings suggest that the age-associated changes in the AT ceramide profile may vary depending on AT type and ceramide acyl chain length.

In addition to the acyl chain length, the presence of double bonds in the FA residues of ceramides must

be considered. Unsaturated FAs in ceramides are more prone to oxidation, which may lead to the formation of reactive oxygen species (ROS) and increased oxidative stress. Notably, in older patients with CAD, increased levels of ceramides containing double bonds have been observed [20]. This finding is consistent with the data on the differential effects of saturated and unsaturated ceramides on the CVS: for example, Cer 24:0 has a protective effect, while Cer 24:1 does not [21]. These differences may be due to the dysregulation of ceramide metabolism in CVD.

We then calculated the ratio of cardioneutral to cardioprotective ceramides in AT for each age group of CAD patients. The highest EAT ceramide ratios were observed in CAD patients aged 60–74 years, which may indicate an increased risk of adverse cardiovascular events and mortality from these diseases in this age group. This is consistent with the findings of Akawi N. et al. [22], who showed that elevated Cer d18:1/16:0 levels in EAT were associated with an increased risk of heart failure among elderly patients. Age-associated changes in the EAT phenotype, such as increased secretion of pro-inflammatory adipokines, are likely to contribute to the development of cardiomyopathy and myocardial fibrosis [23].

CONCLUSION

Significant sex- and age-related differences in the AT ceramide profile have been identified in patients with CAD. Our data suggest that there is an age-related modulation of ceramide synthesis, while sex-specific differences in the ceramide profile indicate a possible influence of hormonal factors on this process. When analyzing the AT ceramide profile and its impact on cardiovascular risk, it is important to consider sex. With age, the cardiac and vascular AT undergo significant remodeling. The observed age-related shift in lipid balance, manifested by an increased ratio of cardioneutral to cardioprotective ceramides in EAT in patients aged 60–74 years and in PVAT in patients older than 75 years, suggests a potential increase in cardiovascular risk in these age subgroups. Modifying the ceramide profile of EAT and PVAT in these age groups represents a promising therapeutic approach to reducing cardiovascular risk and requires further prospective study.

Conflicts of interest

The authors declare no conflicts of interest.

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