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Obesity, visceral adiposity and carotid atherosclerosis

Maciej Haberka [a,*], Michael Skilton [b], Małgorzata Biedroń [a], Karolina Szóstak-Janiak [a], Małgorzata Partyka [c], Monika Matla [a], Zbigniew Gąsior [a]

[a] *Department of Cardiology, School of Health Sciences, Medical University of Silesia, Katowice, Poland*
[b] *Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, Sydney Medical School, University of Sydney, Australia*
[c] *Department of Diagnostic Imaging, City Hospital, Chorzów, Poland*

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ABSTRACT

Carotid artery atherosclerosis is a complex and multifactorial chronic disease. Our aim was to assess the associations between obesity, fat depots and carotid artery stenosis (CAS) in patients with high cardiovascular (CV) risk.
Methods: The study group included 391 patients (F/M: 136/255 pts.; age: 61.8 ± 8 years) scheduled for elective coronary angiography. A comprehensive clinical assessment included a carotid artery and abdominal ultrasound involving the following fat depots: (1) carotid extra-media thickness (EMT) indexed to the body mass index (perivascular adipose tissue [PVAT]), and (2) abdominal visceral and subcutaneous fat.
Results: Patients with a ≥50% stenosis of internal carotid artery (ICA) were older (65.9 ± 7 vs 60.3 ± 7 years, $p < 0.0001$) and had increased PVAT (836 ± 120 vs 779 ± 127 μm, $p < 0.01$) compared to individuals with <50% internal carotid artery stenosis. None of the CAS parameters were associated with any measures of obesity. Multivariable regression model showed that age ($p < 0.0001$), PVAT ($p < 0.0001$) and smoking ($p = 0.04$) were independently associated with the severity of ICA stenosis.
Conclusions: Our study showed that carotid extra-media thickness, an index measure of PVAT, is associated with CAS severity. It is a strong and independent predictor of significant ICA stenosis. None of the obesity measurements revealed associations with carotid atherosclerosis.

1. Introduction

Atherosclerosis is a multifactorial and complex chronic disease affecting various vascular beds. Although atherosclerosis is a systemic disease sharing common major risk factors, the strength and impact differs per arterial site.[1] Age, smoking, hypertension, dyslipidemia or diabetes are the main predictors of peripheral artery disease, including carotid artery disease. The prevalence of carotid artery stenosis (CAS) ranges from 4% to 12% with higher rates among men and older (>70-year-old individuals).[2]

Obesity is a highly prevalent disease leading to metabolic complications, which may increase cardiovascular (CV) risk over a long-time exposure.[3–6] However, adiposity is a very heterogeneous condition, in which fat quantity, distribution, metabolic function and specific visceral fat depots are closely associated with CV risk.[7,8]

Carotid extra media thickness (EMT) is a unique ultrasound index for the common carotid artery. Although it corresponds to various tissues, including perivascular adipose tissue (PVAT), arterial adventitia, interstitial tissue and venous wall,[9,10] the main components are PVAT and adventitia. Carotid EMT is associated with metabolic syndrome, cardiovascular risk and carotid intima-media thickness,[11,12] it is significantly increased in patients with coronary artery disease (CAD), and it is associated with the severity and the complexity (Syntax Score) of CAD.[11,12] The great majority of studies on PVAT were focused on direct or indirect measures of epicardial fat in patients with CAD.[13,14] However, there is an evidence gap in the field of PVAT, adiposity and CAS. Therefore, our aim was to assess the associations between obesity, fat depots and carotid atherosclerosis in high-risk patients.

2. Materials and methods

The study group included 400 consecutive patients admitted to our Department of Cardiology for an elective diagnostics of CAD. All the patients had a comprehensive clinical assessment focused on CV risk factors and a carotid artery ultrasound. Nine patients were excluded from the study for suboptimal quality of carotid ultrasound images and finally 391 individuals were included in the further analysis. The main exclusion criteria were as follows: heart failure, severe primary heart valve disease

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All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All the authors declare no conflicts of interests.

* Corresponding author at: Ziołowa 45/47, 40-635 Katowice, Poland.
E-mail address: mhaberka@sum.edu.pl (M. Haberka).

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or any other extracardiac chronic disease causing at least 10% unintentional weight loss (prior 3 months), secondary causes of obesity or medical interventions aimed at weight loss (prior 12 months), neck or abdomen surgery, neck radiotherapy, a very poor carotid artery image quality, and confirmed diagnosis of genetic predisposition for CV diseases. All the patients were recruited in the Department of Cardiology at the Medical University of Silesia. The study had a cross-sectional design with the study protocol approved by the local Medical University of Silesia Ethic Committee.

Dyslipidemia, diabetes, obesity and arterial hypertension were defined as previously described.[15–17] The diagnosis of CAD was confirmed in coronary angiography performed during the index hospitalization. The data on peripheral artery disease (other than carotid atherosclerosis) was obtained from the available medical records. The bioelectric impedance analysis (BIA, Bodystat 1500) was used to measure the patients' body composition with body fat percentage (BF%) according to the manufacturer's manual.

2.1. Carotid artery ultrasound and fat indexes

All the carotid images were obtained by one experienced researcher using constant settings. Afterwards, single images of the region of interest were randomly analyzed offline by one observer blinded to patient's data and characteristics. All the measurements were identical in all patients and were obtained with a high-resolution ultrasound (GE Vivid 9, Milwaukee, US) with a linear or convex transducer.

Carotid artery ultrasound was performed according to the recommendations[18] and the estimation of carotid artery stenosis was based on the NASCET method and the Doppler peak velocity parameters. The following measures of carotid atherosclerosis were provided: maximum unilateral internal carotid artery (ICA) stenosis, mean bilateral ICA stenosis, the sum of bilateral ICA stenoses, total carotid artery plaque area and the presence of plaques in the common carotid artery, bulb and ICA.

Carotid intima-media thickness (IMT) was used as a well-evidenced vascular index and it was obtained according to the Mannheim Consensus guidelines.[19] Carotid EMT was used as a measure of PVAT and it was measured as a distance between the carotid media-adventitia border and the jugular wall-lumen interface averaged from both common carotid arteries (CCA) with visualization of the zoomed interface between the near wall of the distal segment of the CCA and the neighbouring jugular vein. The precise method for carotid EMT was described in our previous manuscript.[20]

Finally, the distance between the skin and external surface of the rectus abdominis muscle representing subcutaneous fat and the distance between the internal surface of the rectus abdominis muscle and anterior wall of the aorta (abdominal visceral fat) were measured in transversal view 1 cm above umbilicus. The transducer (7.5 MHz for subcutaneous and 3.5 MHz for visceral fat) with a thick ultrasound gel layer was placed vertically on a skin as lightly as possible to prevent compression of the layers and to perform breath-hold measurements.

2.2. Statistical analysis

All results presented in the text, tables and figures are expressed as means ± standard deviation or number and percentage. The data normal distribution was analyzed with the Kolmogorov-Smirnov test. Baseline clinical parameters or the ultrasound measures were compared between the subgroups using the *t*-tests for normally distributed continuous variable (Student's *t*-test); in case of abnormal distribution, the Mann-Whitney *U* test was used. Multiple comparisons analysis was performed using the ANOVA with Bonferroni correction. Prior to the ANOVA test, Levene's test for equality of variances was performer. The differences between the subgroups were analyzed using one-way analysis of variance (ANOVA). Associations between parameters were assessed using Pearson or Spearmen correlation analysis respectively for the parametric or nonparametric variables. A value $p < 0.05$ was considered statistically significant. Statistical analysis was undertaken using Statistica software (version 10.0, Stat Soft, PL).

3. Results

3.1. Study group clinical characteristics

The study group (F/M: 136/255 pts.; age: 61.8 ± 8 years) included patients with high or a very high CV risk. Most of the patients revealed classical risk factors: dyslipidemia (100%), hypertension (78%), obesity (47%), diabetes (39%) and nicotinism (current or past in 66%).

CAD was found in 82% of patients (≥50% stenosis in coronary angiography) and peripheral artery disease of lower limbs was shown in 12%. Carotid atherosclerosis parameters and the detailed clinical characteristics of the study patients are presented in the Online Supplementary Appendix 1. There were 151 patients with diabetes, mostly treated with oral antidiabetic drugs (72%) or insulin (28%). Although some of the patients had a long history of disease (>10 years in 42 cases), there were no association between time from diagnosis and the severity of ICA stenosis ($p =$ ns).

3.2. Carotid atherosclerosis and obesity

Patients were divided into two subgroups based on the CAS severity (≥50% and <50%) and uni- or bilateral ≥50% stenosis (Table 1). Patients with more significant CAS were older with increased measures of PVAT, decreased abdominal visceral fat and similar body mass index (BMI) and general BF%. There was no difference in age of individuals with uni- and bilateral CAS. Moreover, none of the parameters of CAS were different between patients with obesity (BMI ≥ 30 kg/m^2) and individuals with BMI <30 kg/m^2 (Online Supplementary Appendix 2). Perivascular fat indexed to general obesity (EMT/BMI) was associated with both ipsilateral and contralateral ICA stenosis (Online Supplementary Appendix 3). Age and perivascular fat (EMT/BMI) showed significant associations with all CAS measures: maximum, mean and both (the sum of both sides ICA maximum stenosis) ICA stenosis values (Table 2). Multivariable regression model showed that age, EMT/BMI, smoking ($p = 0.04$) and body fat% ($p = 0.04$) were independently associated with the severity of ICA stenosis (Table 3).

There were no differences in the maximum CAS (35.3 ± 18 vs 33.8 ± 21%; $p = 0.6$) between patients with and without diabetes. Moreover, perivascular fat (EMT/BMI) was significantly increased in patients with ≥50% CAS compared to individuals with <50% CAS in both subgroups: diabetic (28.5 ± 5 vs 24.7 ± 4, $p < 0.0001$) and non-diabetic patients (28.8 ± 6 vs 26.1 ± 3.8, $p < 0.001$). The associations between EMT/BMI and CAS were also significant in both subgroups with a slightly better correlation coefficients in diabetes ($r = 0.45$ vs $r = 0.2$, $p < 0.05$).

3.3. The ROC analysis and the prediction of significant carotid artery stenosis

Given the above results, five variables (age, BMI, waist circumference, abdominal visceral fat and perivascular fat) were assessed as predictors of either ≥50% ICA stenosis or ≥70% ICA stenosis (Table 4). All the parameters revealed a significant predictive value in both models. Given the area under the curve (AUC) for each of the variable, age showed the best prediction of significant CAS (≥50%). However, perivascular fat indexed to BMI (EMT/BMI) revealed a significantly greater AUC compared to age and other variables ($p < 0.05$) in the prediction of ≥70% ICA stenosis (Table 4, Fig. 1). Perivascular fat revealed significant prediction of ICA stenosis in both diabetic and non-diabetic individuals (data not shown).

Table 1
Obesity-related indexes and ICA stenosis.

Obesity-related indexes	ICA stenosis		p	ICA stenosis ≥50%		p
	<50%	≥50%		Unilateral	Bilateral	
Age	60.3 ± 7	65.9 ± 7.7	**<0.0001**	66.3 ± 7.9	65.1 ± 7.5	0.5
Body mass index	30.9 ± 5.9	30 ± 5.6	0.2	30.7 ± 5.7	28.6 ± 5.3	0.1
Body fat %	31.6 ± 9.6	33.5 ± 10	0.09	33.7 ± 10.2	33 ± 9.6	0.7
Abdominal visceral fat	76.6 ± 26.1	70.2 ± 26.3	**0.04**	74.1 ± 26.1	61.1 ± 25	**0.02**
Abdominal subcutaneous fat	16.2 ± 7.9	15.2 ± 9.1	0.3	15.6 ± 9.7	14.3 ± 7.8	0.5
mean EMT	779.6 ± 127	836.6 ± 120	**<0.0001**	821.2 ± 105	872.6 ± 142	**0.04**
mean EMT/BMI	25.7 ± 4.1	28.6 ± 5.8	**<0.0001**	27.5 ± 5.2	31.2 ± 6.3	**0.002**

BMI – body mass index; EMT – extra media thickness.
Bold values indicates significance at $p < 0.05$.

4. Discussion

The major finding of the study was that carotid EMT is a strong and independent predictor of the severity of ICA stenosis with even a greater prediction of at least 70% CAS compared to other strong associates (age, smoking). As expected, obesity and the measures of obesity (body mass index [BMI], body fat [BF]%) were not associated with the severity of CAS. Central obesity measurements provide confusing results with paradoxically lower ultrasound abdominal visceral fat index in patients with greater ICA stenosis and no significant associations in correlation analysis or multivariable regression analysis.

To the best of our knowledge, this is the first study providing results on carotid EMT and the severity of CAS. The study group was representative for a real-life population of high-risk patients with CV diseases. The prevalence of carotid atherosclerosis and significant CAS found in our study group was typical for patients with a primary suspicion of CAD.[1]

4.1. Carotid artery atherosclerosis and obesity

Carotid atherosclerosis was associated with age and smoking as previously reported.[21] Patients with obesity (BMI ≥ 30 kg/m^2) revealed similar ultrasound CAS parameters compared to patients with BMI <30 kg/m^2. Moreover, neither BMI nor BF% was associated with any CAS measures, including: the maximum or mean severity of carotid stenosis or atherosclerotic plaque burden. Although obesity is a CV risk factor, our results suggesting no relationship with CAS are in line with previous reports.[22–24]

4.2. Perivascular fat and carotid stenosis

Carotid EMT is a measure corresponding to PVAT and arterial adventitia.[9] Tissue specimens of this region of interest and our previous studies showing several associations with clinical and ultrasound indexes of adiposity suggested that EMT may be a surrogate index of PVAT.[10,11] However, our study design precludes us from differentiating the effects of EMT tissue components on CAS severity. The study showed that PVAT is associated with the severity of CAS, but not with indexes of atherosclerotic plaques number or expanse. Given that carotid EMT is measured in the distal segment of CCA and carotid atherosclerosis mostly occurs in the carotid bulb and proximal segment of ICA, it is not possible to draw direct conclusions about local PVAT effects. Still, we found that the relationship between the given carotid EMT and CAS is not local and ipsilateral, but rather systemic. Further analysis showed that PVAT is a predictor of ≥70% CAS, even stronger than other CV risk factors, including age, which is the primary determinant of carotid atherosclerosis.[25] Obesity, clinical measures of adiposity and carotid EMT showed discrepant associations with carotid atherosclerosis, which confirms that PVAT is not just a simple derivative of obesity. Moreover, we used EMT indexed to BMI as a major measure of PVAT in order to weaken its dependence on general obesity.

All large body arteries are at least partly surrounded by fat tissue, which shows only moderate associations with general obesity.[26] Several studies published in recent years have dispelled the historical paradigm that PVAT holds only a structural role.[27] PVAT was found to produce various adipokines and cytokines, which affect endothelial function, vasoreactivity and interferes with arterial wall structure.[28] Moreover, PVAT depots may increase their volume and expand through differentiation or infiltration of cells, including fibroblasts, mast cells, stem cells, macrophages, or lymphocytes.[26–28] Finally, such dysfunctional PVAT is involved in various pathways of atherogenesis, including local hypoxia, proinflammatory state, oxidative stress, activation of coagulation cascade, impaired systemic renin angiotensin aldosterone system, increased vascular resistance and vascular wall remodeling.[27,28–33] However, in physiology, PVAT depots also exert anti-atherogenic effects. Li C et al.[34] showed that pericarotid fat secreted adiponectin, which suppressed atherosclerotic plaque formation by inducing macrophage autophagy. Fat depot infiltration found in tissue specimens and increased inflammatory activity observed in positron emission tomography-computer tomography (PET-CT) are strong indicators of dysfunctional adipose tissue.[35]

A great majority of clinical or experimental data on PVAT is focused on pericoronary fat.[31] However, CAD and peripheral artery disease share only partial similarities with differences in risk factors or

Table 2
Correlation analysis between obesity-related indexes and ICA stenosis.

Obesity-related indexes	Max ICA stenosis	Both ICA stenosis	Mean ICA stenosis
Age	$\mathbf{r = 0.35; p < 0.0001}$	$\mathbf{r = 0.37; p < 0.0001}$	$\mathbf{r = 0.36; p < 0.0001}$
Body mass index	$r = -0.1; p = 0.05$	$r = -0.1; p = 0.06$	$r = -0.1; p = 0.04$
Fat %	$r = 0.05; p = 0.3$	$r = 0.07; p = 0.3$	$r = 0.06; p = 0.3$
Waist circumference	$r = -0.04; p = 0.4$	$r = -0.04; p = 0.4$	$r = -0.04; p = 0.4$
Abdominal visceral fat	$r = -0.07; p = 0.2$	$r = -0.08; p = 0.2$	$r = -0.09; p = 0.2$
Abdominal subcutaneous fat	$r = -0.09; p = 0.08$	$r = -0.08; p = 0.07$	$r = -0.09; p = 0.06$
mean EMT	$\mathbf{r = 0.27; p < 0.0001}$	$\mathbf{r = 0.28; p < 0.0001}$	$\mathbf{r = 0.29; p < 0.0001}$
mean EMT/BMI	$\mathbf{r = 0.4; p < 0.0001}$	$\mathbf{r = 0.4; p < 0.0001}$	$\mathbf{r = 0.4; p < 0.0001}$

ICA – internal carotid artery; EMT – extra media thickness.
Bold values indicates significance at $p < 0.05$.

Table 3
Multivariable regression model: ICA stenosis and risk factors.

	ICA stenosis			
	β	SE	*t*	*p*
Age (years)	0,81	0,12	6,28	<**0,0001**
Fat (%)	0,22	0,10	1,32	0,04
Waist circumference (cm)	0,13	0,10	1,31	0,19
Abdominal visceral fat (mm)	0,01	0,04	0,27	0,78
Perivascular fat (EMT/BMI)	1,73	0,23	7,30	<**0,0001**
Smoking	2,21	1,09	2,00	**0,04**

ICA – internal carotid artery; EMT – extra media thickness.
Bold values indicates significance at $p < 0.05$.

pathophysiology.[36] Therefore, both diseases do not always coexists in the same patients – most patients with CAD do not have CAS, and conversely most patients with CAS show coronary atherosclerosis.[1]

4.3. Abdominal visceral fat and obesity

The baseline comparison between subgroups with and without at least 50% CAS or with unilateral or bilateral CAS showed lower indices of abdominal visceral fat in patients with more advanced carotid atherosclerosis. This finding was unexpected and could be explained by a relatively high rate of current or past smokers, a habit known to decrease body fat.[37] However, further analysis revealed no association between waist circumference or ultrasound indices of visceral or subcutaneous fat with CAS severity. Our previous study[11] showed only a weak association between visceral fat and CAD severity and no predictive value for CAD complexity. It seems, that central obesity and the amount of abdominal visceral fat do not predict carotid atherosclerosis in patients with CAD. There are unequivocal results on the association between visceral fat and carotid atherosclerosis in obesity,[38–41] which might be explained by important differences among study population's characteristics (metabolic abnormalities). Moreover, none of those studies assessed the severity of CAS as they used mostly carotid IMT or just a plaque burden (plaque area), which may also explain the different conclusions. The CardioPrev study showed that among coronary patients, metabolic phenotype (in contradiction to body weight only) is a major determinant of carotid IMT. Patients with obesity revealed increased IMT when compared to a composite group of non-obese individuals (normal weight and overweight).[40] It is in line with a body of evidence showing that patients with CAD and overweight or even mild obesity, but normal metabolic status and high physical activity may have a non-inferior CV risk compared to individuals with normal weight.[7]

Abdominal visceral fat is an independent predictor of cardiometabolic complications,[42] it is not associated with the presence of CAD or its severity.[12,11] It suggests that the abdominal visceral compartment is involved in metabolic complications rather than atherosclerosis or its ultrasound measure is not a precise enough index of abdominal visceral adipose tissue. Finally, we cannot confirm a beneficial association between an increased subcutaneous fat in patients with decreased severity of CAS.[39]

Table 4
Comparison of ROC curves in prediction of carotid artery stenosis.

Obesity-related measures	AUC	SE	95% CI
Prediction of ≥70% ICA stenosis			
Age (years)	0,671	0,049	0,622 to 0,718
Body mass index (kg/m^2)	0,645	0,054	0,595 to 0,693
Abdominal visceral fat (mm)	0,644	0,051	0,593 to 0,691
Waist circumference (cm)	0,585	0,059	0,534 to 0,635
Perivascular fat (EMT/BMI)	0,806	0,044	0,763 to 0,843
Prediction of ≥50% ICA stenosis			
Age (years)	0,701	0,03	0,653 to 0,747
Body mass index (kg/m^2)	0,536	0,034	0,485 to 0,587
Abdominal visceral fat (mm)	0,56	0,034	0,509 to 0,610
Waist circumference (cm)	0,503	0,035	0,452 to 0,554
Perivascular fat (EMT/BMI)	0,653	0,037	0,604 to 0,701

AUC – area under curve; CI – confidence interval; EMT – extra media thickness; ROC – receiver operating characteristic; SE – standard error.

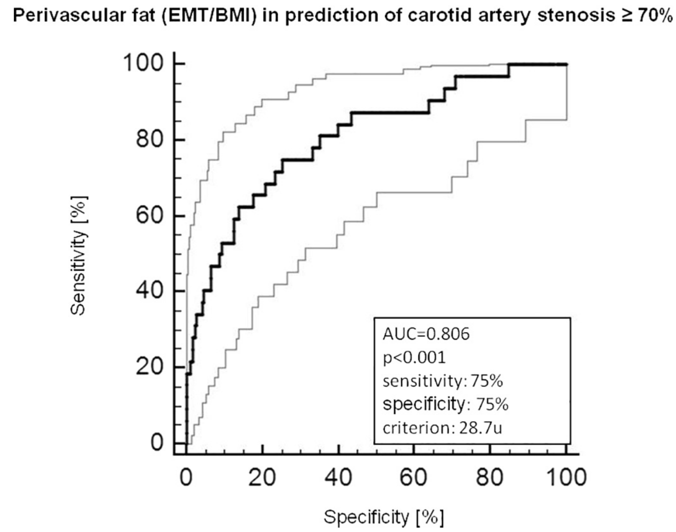

Fig. 1. Perivascular fat (EMT/BMI) in prediction of ≥70% ICA stenosis. BMI – body mass index; EMT – extra-media thickness; receiver operating characteristic curve presenting sensitivity in function of specificity for different cut-off points (black bold curve) with a 95% confidence bounds (grey curve).

4.4. Limitations and conclusions

To the best of our knowledge, we present the first results concerning the pericarotid fat index and the severity of carotid atherosclerosis. Our findings are based on a cross-sectional study and we cannot draw conclusions on causality between EMT and CAS. Moreover, we did not evaluate any aspects of adipose tissue dysfunction. Finally, the tissue region of interest, which corresponds to carotid EMT includes not only PVAT and we cannot separate the effects of different tissues (PVAT or adventitia) on CAS. Although the local amount of adipose tissue is larger than adventitia,[10] a previous study using ultrasound and magnetic resonance[11] confirmed that the adventitia layer is also a determinant of carotid EMT.

Our study showed that pericarotid adipose tissue is associated with CAS severity. It is a strong and independent predictor of significant ICA stenosis. None of the obesity measures revealed associations with carotid atherosclerosis.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.01.002.

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