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Parapharyngeal Fat Tissue Accumulation and Its Association with Carotid Intima-Media Thickness in Discordant Twin Pairs

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Abstract: Background: Recurrent upper airway obstruction during sleep is a common feature of obstructive sleep apnea (OSA). Risk factors for the development of OSA include obesity, male gender and smoking. In addition, anatomical factors contribute to the development of the disease; however, the heritability of the anatomical structures that determine upper airway narrowing is poorly understood. In this study, we aimed to investigate the background of anatomical structures associated with upper airway narrowing in discordant monozygotic (MZ) twin pairs. Methods: 33 adult MZ twin pairs (median age and Q1-Q3: 50 (42–56) years) from the Hungarian Twin Registry underwent head and neck MR (Philips Ingenia 1.5 T). T1- and T2-weighted images in sagittal, coronal and axial planes were used to measure cephalometric, soft tissue and adipose tissue structures. In addition, the twin pairs underwent carotid and femoral ultrasound scans (Samsung RS85) and full-body composition measurements (OMRON BF500). The analysis of discordant MZ twins for anatomical markers in relation to clinical background, blood test, vascular ultrasound and body composition results was performed using a paired permutation test. Results: We found a significant association between parapharyngeal adipose tissue area and body weight, waist circumference and metabolism ($p < 0.05$). Submental adipose tissue thickness showed an association with lower body muscle percentage (<0.05). Carotid intima-media thickness showed a negative association with parapharyngeal adipose tissue, tongue volume and submental adipose tissue thickness (<0.05). Conclusions: Our study found a significant association between anatomical structures potentially involved in upper airway narrowing and obesity-related markers such as weight, BMI, hip and waist circumference, and whole body composition analysis results (body fat percentage, visceral fat percentage, muscle percentage). This study may help to better understand the background of anatomical structures potentially involved in upper airway narrowing and the possible development of obstructive sleep apnea.

Keywords: obstructive sleep apnea; twin study; atherosclerosis; obesity; heritability; anatomy; body mass index; body fat percentage

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1. Introduction

The parapharyngeal fat pad is an accumulated fatty tissue located in the parapharyngeal space between the upper lateral region of the pharyngeal wall, the masticator space and the parotid space [1,2]. The distribution patterns of parapharyngeal fat tissue are associated with cervical mass lesions [3]. The increased amount of adipose tissue in this area is associated with obesity [4]. Parapharyngeal fat accumulation plays a role in the development of obstructive sleep apnea (OSA) as well by leading to upper airway narrowing [5]. OSA is defined by intermittent episodes of partial or total obstruction of the upper airways during sleep leading to hypoxia and sleep fragmentation [6]. OSA could contribute to a decrease in a patient's life quality and could increase the risk of developing heart and vascular, metabolic, or neurological diseases [7]. Several risk factors have been associated with OSA such as older age, male sex, smoking and craniofacial anatomical abnormalities [8,9]. However, the leading factor contributing to the development of OSA currently is obesity by reducing lung capacity and by parapharyngeal fat tissue accumulation which could lead to the narrowing of the upper airways resulting in reduced air flow [10]. Obesity is considered a pandemic disease globally, and as the number of affected patients is growing every day, the prevalence of OSA patients is expected to increase drastically [11,12].

Carotid intima-media thickness (CIMT) is the thickness of the inner layers (tunica intima and media) of the carotid artery. The widening of the CIMT is a subclinical marker of atherosclerosis and has been associated with an increased risk of cardiovascular disease and stroke [13]. Inflammation could lead to increased CIMT as the repeated cycles of oxygen deprivation and arousal from sleep during OSA can contribute to the activation of inflammatory pathways and oxidative stress, which could lead to an increase in reactive oxygen species (ROS) and endothelial dysfunction [14]. This could result in the thickening of the CIMT and plaque development. Perivascular adipose tissue (PVAT) induces pro-inflammatory adipocytokines which may lead to atherosclerosis as well [15].

In a recent study, we examined the heritability of OSA-associated anatomical features in twins by measuring parameters on head and neck MRI scans [16]. In our study group, there was a strong heritability of the anteroposterior diameter of the tongue and the thickness of the submental fatty tissue of the neck, meanwhile, we found a strong environmental effect in the thickness of the parapharyngeal fatty tissue, the thickness of the pharyngeal wall, as well as the smallest diameter of the posterior upper airways [16]. Other parameters of the tongue, soft palate, uvula and parapharyngeal fat have proven to be similarly influenced by genetic and environmental factors [16].

Our aim during this study was to further investigate the background of the measured traits by analyzing monozygotic twin pairs discordant for anatomic features associated with possible upper airway narrowing. We hypothesized that between these pairs the subjects with more accumulated fat tissue, a larger tongue, or thicker parapharyngeal wall would present higher values in markers for obesity (such as elevated cholesterol levels, higher body mass index (BMI), wider hip and waist circumference and higher body fat percentage) and would demonstrate thicker CIMT during carotid ultrasound (US) compared to their healthy twin control.

2. Materials and Methods

In the current cross-sectional twin study we examined 66 monozygotic (MZ) healthy voluntary adult twins (33 pairs) from the Hungarian Twin Registry from November 2018 to March 2020 [17]. We collected demographic data, medical history and health and lifestyle information of the subjects on self-report questionnaires. We excluded participants with previous carotid artery or other neck surgery, current acute respiratory, cardiac or renal failure, or any contraindications for MRI imaging, such as patients with cardiac implantable electronic devices, a metallic foreign body, severe claustrophobia, or current pregnancy. The patients underwent head and neck MRI imaging, carotid and femoral artery US imaging, blood test and full body composition analysis on the same day. In case it was arrangeable, we examined both twin pairs on the same day as well. We instructed the patients not to consume alcohol, caffeine or to smoke for 10 h before arrival. We also required a one-hour fasting period before the examinations. For the methodology and measurements of the anatomic features on MRI scans, we refer to our recent publication [16]. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (TUKEB 30/2014 and 189/2014).

2.1. Body Composition

We measured the height of the patients in a standing position without shoes and registered hip and waist circumference. After that, we measured the weight, BMI, body fat, visceral fat and muscle percentage, and basic metabolic rate (kcal) of the subjects on a medical body analyzer scale (OMRON BF500, Omron Healthcare Ltd., Kyoto, Japan). This device provides information on whole body composition based on biometric impedance analysis after entering the age, sex and height of the patient.

2.2. Lipid Profile

We analyzed blood lipid profiles such as triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), apoA1, apoB and lipoprotein-A from venous blood samples collected from cubital veins by a professional nurse.

2.3. Carotid and Femoral Ultrasound

The carotid US scans were performed at the Medical Imaging Centre of Semmelweis University on a Samsung RS85 US device (Samsung Electronics Co., Ltd., Seoul, Republic of Korea) using a high-resolution linear LM4-15B (15 MHz) transducer. Measurements were maintained by an experienced radiologist blinded to any previous examinations of the patients. During the examination, patients were lying in a supine position. On the left and right common carotid artery (CCA) and the proximal segment of the internal carotid artery (ICA), and left and right common femoral artery (CFA) plaque presence was registered and the mean and maximal IMT of the carotid and femoral arteries were measured using a semi-automated Arterial Analysis software which evaluates a segment of the artery wall distal from the transducer that can be adjusted by the examiner (Figure 1). Extra-medial thickness (EMT) was assessed by measuring the thickness from the common carotid artery media-adventitia interface to the jugular vein lumen on a longitudinal plane based on the methodology of previous studies (Figure 2). [18–20]

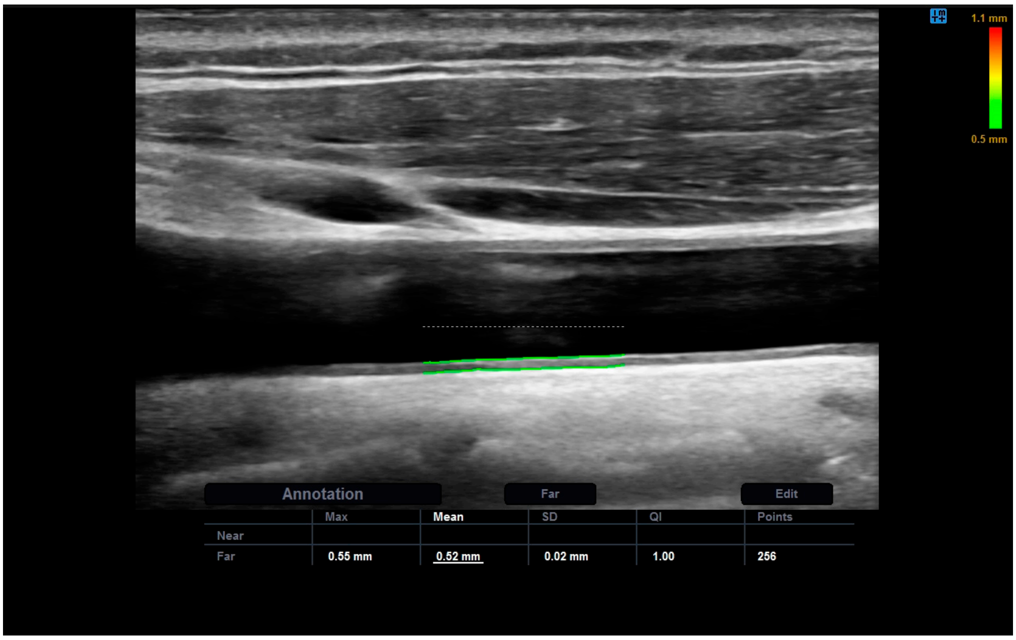

Figure 1. Demonstrative image of semi-automatic IMT measurements on carotid artery US.

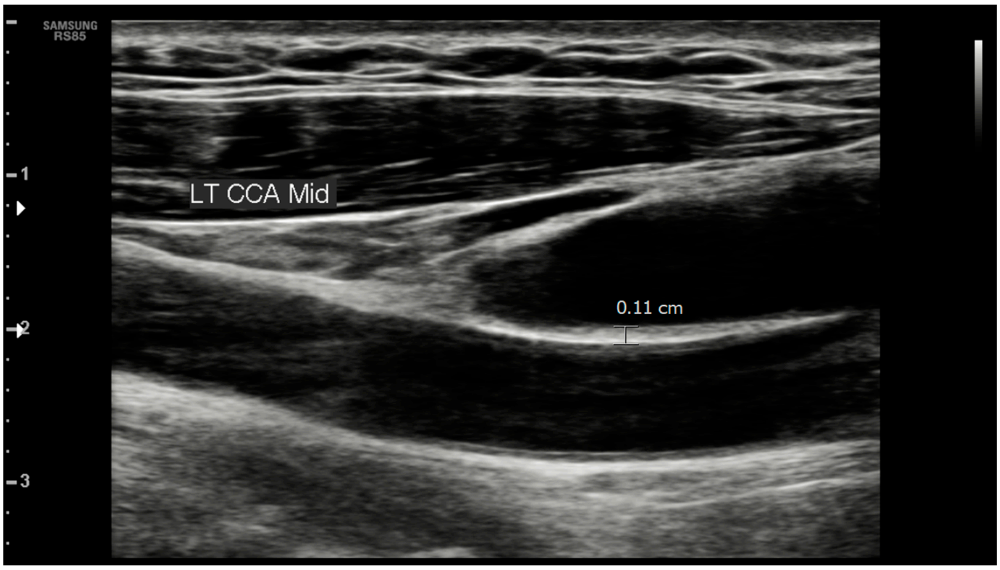

Figure 2. Demonstrative image of EMT measurements on carotid artery US.

2.4. Statistical Analysis

Twin research requires the use of special statistical techniques that assess the similarities and differences among twins within a single dataset. Discordant twins are identical twins who differ in their phenotype or traits. The discordant twin statistical analysis involves comparing the environmental factors and other individual features of the two twins to understand the cause of the difference in phenotypes. This method can be used in studying complex diseases where multiple factors play a role in the development of the disorder. We identify twin pairs who are discordant for a particular trait or disease, then compare environmental factors such as diet, exercise or lifestyle to identify any differences that may have contributed to the disease. It can also help identify potential targets for intervention or prevention strategies.

In the current study, we defined discordancy based on the previously measured MRI parameters. As there is currently no literature available on suggested discordancy values regarding our measurement, we determined them after careful consideration based on the average and standard deviation of our data sets from our previous study (Table 1). We examined the possible association of the anatomic features with a wide range of selected phenotypic variations (Table 2). For group comparisons, we applied a paired permutation test.

Table 1. Measured parameters on MRI and determined discordancy values.

Measured Parameter	Average (±SD)	Discordancy Value
Tongue thickness (mm)	49.01 (±3.50)	3 mm
Tongue volume (mm^3)	118.22 (±38.71)	15 mm^3
Parapharyngeal wall thickness from pharynx (mm)	6.18 (±2.03)	1 mm
Parapharyngeal wall thickness from carotid artery (mm)	14.46 (±2.55)	2 mm
Parapharyngeal fat area (in axial plane) (mm^2)	346.46 (±152.82)	50 mm^2
Submental fat tissue thickness (mm)	8.08 (±2.91)	1 mm
Posterior airway space occlusal width (mm)	4.74 (±2.36)	1 mm

Table 2. Examined parameters.

Clinical Background	Blood Test	Ultrasound Parameters	Body Composition
• Smoking activity • Hypertension • Diabetes Mellitus • Dyslipidemia	• Cholesterol • HDL • LDL • Triglyceride • ApoA1 and apoB • Lipoprotein-A	• Carotid and femoral IMT mean and max (Left and right CCA and ICA) • IMT mean and max (left and right CFA) • EMT thickness (left and right CCA) • Number of plaques	• Height • Weight • BMI • Hip and waist circumference • Body fat percentage • Visceral fat percentage • Muscle percentage • Metabolism (kcal)

HDL: high-density lipoprotein, LDL: low-density lipoprotein, IMT: intima-media thickness, CCA: common carotid artery, ICA: internal carotid artery, CFA: common femoral artery, EMT: extra-medial thickness, BMI: body-mass index.

In all our calculations, a *p*-value of <0.05 was considered significant. Statistical analysis was conducted using R studio, version 1.1.463, and SPSS, version 24 (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Study Population

The descriptive characteristics of the study population (66 twins, age median, and Q1–Q3: 50 (42–56) years) are summarized in Table 3.

Table 3. Demographics and descriptive clinical characteristics of the study subjects. The continuous variables are expressed as the median (Q1–Q3) deviation.

Number of participants, N	66
Age, (years) median (Q1-Q3)	50 (42–56)
Sex, N (%)	Males: 24 (36.4) Females: 42 (63.6)
BMI, median (Q1-Q3)	24.3 (22.2–27.2)
Smoking, N (%)	13 (19.7)
Hypertension, N (%)	12 (18.2)
Diabetes Mellitus, N (%)	3 (4.5)
Dyslipidemia, N (%)	9 (13.6)

3.2. Discordancy Analysis

Twelve pairs were discordant regarding the parapharyngeal fat tissue area. Higher values of parapharyngeal fat tissue were associated significantly with higher values of weight, waist circumference, and basic metabolism meanwhile it was also associated with lower mean and max CIMT of both CCA and mean IMT of right CFA ($p < 0.05$). Seven pairs showed discordancy regarding submental neck fat and higher submental fat thickness presented a significant association with lower body muscle percentage and lower right CCA mean CIMT ($p < 0.05$). Nine pairs were discordant for tongue volume (and therefore, tongue fat tissue accumulation as well) and a higher value was significantly associated with lower mean IMT in left ICA and left CFA. Sixteen pairs were discordant for posterior airway space occlusal width which is the narrowest point of the upper airways. We found a significant association between narrower upper airways and higher left ICA and CFA mean IMT, left CCA EMT and elevated values of BMI (Table 4). We found no significant correlation regarding the rest of the parameters. The number of discordant pairs and results are collected in Table 5.

Table 4. Significant associations between discordant anatomic parameters and individual parameters determined by paired permutation tests.

Discordant Parameter	Investigated Parameter	Mean Difference	*p* Value
Submental neck fat thickness	Muscle percentage (%)	−1.067	<0.05
	Right CCA mean CIMT (mm)	−0.066	<0.05
Parapharyngeal fat area	Weight (kg)	5.986	<0.05
	Waist circumference (cm)	6.589	<0.05
	Metabolism (kcal)	91.244	<0.05
	Left CCA mean CIMT (mm)	−0.008	<0.05
	Right CCA mean CIMT (mm)	−0.067	<0.05
	Right CFA mean IMT (mm)	−0.026	<0.05
Tongue volume	Left ICA mean CIMT (mm)	−0.012	<0.01
	Left CFA mean IMT (mm)	−0.044	<0.05
Posterior airway space occlusal width	Left ICA mean CIMT (mm)	−0.059	<0.05
	Left CFA mean IMT (mm)	−0.035	<0.05
	Left CCA EMT (mm)	−0.12	<0.05
	BMI (kg/m^2)	−0.764	<0.05

IMT: intima-media thickness, CIMT: carotid intima-media thickness, CCA: common carotid artery, ICA: internal carotid artery, CFA: common femoral artery, EMT: extra-medial thickness, BMI: body-mass index.

Table 5. Discordant parameters. '+' indicates positive association and '-' indicates negative association between parameters.

Measured Parameter	Number of Discordant Pairs	Significant Association ($p < 0.05$)
Tongue thickness	2	none
Tongue volume	10	−: mean IMT left ICA and CFA
Parapharyngeal wall thickness from pharynx	Left: 11, Right: 9	none
Parapharyngeal wall thickness from carotid artery	Left: 5, Right: 2	none
Parapharyngeal fat area	12	+: weight, waist circumference, metabolism −: mean and max CIMT right and left CCA, mean IMT CFA
Submental fat tissue thickness	6	−: muscle percentage, mean IMT right CCA
Posterior airway space occlusal width	16	−: mean IMT left ICA, CFA, left CCA EMT, BMI

IMT: intima-media thickness, CIMT: carotid intima-media thickness, CCA: common carotid artery, ICA: internal carotid artery, CFA: common femoral artery, EMT: extra-medial thickness, BMI: body-mass index.

4. Discussion

In the current study on discordant twins, we demonstrated that accumulated parapharyngeal fat tissue, independently of genetic background and common environmental factors, is associated with elevated body weight and waist circumference and higher metabolism which may further prove the role of central type obesity and upper airway narrowing. Higher submental fat tissue thickness was also associated with lower muscle percentage. We also found an interesting correlation between anatomic markers and decreased IMT values. The narrowest width of the posterior airway space showed a correlation with IMT and EMT thickness as well as elevated BMI values. To our knowledge, this is the first study on discordant monozygotic twins investigating the background of anatomic markers associated with upper airway narrowing.

Obesity is evidently a highly heritable condition which further leads to a higher genetic determination of upper airway narrowing and possible OSA development itself. The accumulation of parapharyngeal fat tissue induces the narrowing of the upper airways in obese subjects. During a weight reduction program, a decrease in parapharyngeal fatty tissue and improved OSA symptoms were reported [21]. Our study results suggested that patients with higher BMI had significantly narrower posterior airway space which further proves the effect of obesity on upper airway obstruction. BMI is a widely accepted rough screening method of body weight categorization; however, it does not take into consideration excess weight caused by increased muscularity and also does not provide information regarding obesity types. Whole body composition analysis scales, however, combined with hip and waist circumference registration give more detailed insight into the composition of the body thus providing additional information on overweight subjects' risk for OSA. Central-type obese patients have a higher risk of developing diseases associated with obesity compared to peripheral obesity [22]. The body type of the patient could easily be determined by the waist-to-hip ratio. In our study group, a higher amount of parapharyngeal fat tissue was associated with higher waist circumference and submental neck fat tissue thickening was correlated with lower body muscle percentage which further proves the importance of detailed body type and body composition analysis in obese patients. This method could be a helpful addition to the screening method for central obesity and risk for OSA development.

PVAT plays an important contributing role in the development of atherosclerosis [23,24]. Several papers showed the role of increased perivascular adipose tissue accumulation in coronary artery disease as a noninvasive imaging biomarker of coronary inflammation which associates with high-risk plaque features and independently predicts cardiac mortality [15,25]. However, there have been a few studies investigating the possible effects of PVAT surrounding the carotid arteries. Hu et al. found an elevated density of carotid artery PVAT on CT scans in patients with embolic stroke of unknown source [26]. Zhang et al. found an independent association between carotid artery PVAT density and intraplaque hemorrhage analyzing CT and MRI scans [27]. In another study, Zhang et al. also found a significant correlation between cerebrovascular symptoms and carotid PVAT density during a retrospective analysis of CT images [28]. Baradaran et al. also found an increased density of carotid PVAT on CT scans in patients with stroke or TIA compared to asymptomatic patients [29]. However, there are no data on the role of PVAT and carotid IMT itself. There have been studies on the role of EMT as a measure of adventitial structure and perivascular adiposity that found a significant correlation between EMT and metabolic syndrome. However, in this study, we only found a significant association between the narrowest point of the posterior airways and EMT on the left carotid artery. Interestingly, in our study, IMT of several arterial segments showed a negative association with higher parapharyngeal fat tissue accumulation. Meanwhile, several studies have investigated the association between OSA and CIMT. A meta-analysis of 16 studies found that individuals with severe OSA had a significantly higher CIMT compared to those without OSA, meanwhile, patients with mild-moderate OSA showed similar IMT values as the control group [30]. Another meta-analysis of 18 studies also found that severe OSA was positively correlated with CIMT thickening, meanwhile, patients with mild to moderate OSA showed similar CIMT values as the control group [31]. The controversy between our results and the current literature could be due to several reasons. First of all, the studies investigating PVAT and carotid artery atherosclerosis mentioned above assessed the density and inflammation of the fat tissue in the small range of the artery on CTA scans, meanwhile, we only measured the axial area of the whole parapharyngeal fat tissue on MRA images. Also, our study subjects were relatively young, in the meantime, CIMT thickening is mainly associated with aging [32]. Furthermore, our study group was relatively healthy based on average BMI, low rate of plaque burden, low number of patients who had hypertension, DM, or dyslipidemia and few subjects had a history of smoking. Therefore, even early atherosclerotic markers are less expected to be present in this study group. We could interpret that CIMT would not be an optimal marker in the early screening of OSA, rather it could be an effective screening method later on after the development and progression of the disease for the detection of resulting atherosclerosis. In conclusion, in the currently available literature, there are limited data regarding carotid and femoral IMT and EMT and their association with risk for cardiovascular events.

Our study had a few limitations such as it included a relatively small number of subjects which led to a low number of discordant pairs. Our study group had a 1:2 male-to-female ratio; meanwhile, OSA would be more common in the male population. In the absence of predetermined values in the literature, our statistical analysis was performed based on self-determined cut-off values for discordancy which could lead to miscalculations. Polysomnography or other OSA-related assessment methods were not performed during the current study; therefore, the contribution of the investigated factors to OSA development could not be determined.

5. Conclusions

In the current study, we found a significant association between elevated parapharyngeal fat tissue area and higher body weight, waist circumference and metabolism which further proves the possible role of central-type obesity in parapharyngeal adipose tissue accumulation which could lead to the development of OSA. Higher submental fat tissue thickness was also associated with lower body muscle percentage. We detected a significant association between the narrowest point of the upper airways and higher values of IMT, EMT and elevated BMI. We also reported an interesting negative association between OSA-related anatomic features and CIMT thickness, which suggests that CIMT might not be a strong marker in early atherosclerosis screening in OSA patients. Our study can contribute to a better understanding of the background of anatomic features associated with OSA. Further studies on this subject are needed on larger sample sizes and more diverse subject groups.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (TUKEB 30/2014 and 189/2014).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data supporting reported results can be provided upon request.

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Conflicts of Interest: The authors declare no conflict of interest.

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