Original article

Adiposity Indicators, Cardiometabolic Parameters and Critical Size of Adipocytes in Premenopausal Women

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Abstract. *Background and aim:* Adipocyte hypertrophy is an indicator of adipose tissue dysfunction that precedes the development of obesity comorbidities. The aim of this study was to analyze relationship between adiposity indicators, cardiometabolic parameters and the size of abdominal adipocytes in premenopausal women, and to develop cut-off levels for anthropometric indicators based on the critical size (100 μm) of visceral adipocytes. *Methods:* Study group consisted of 50 premenopausal women aged 42.88±7.17y. Subcutaneous and visceral (omental) adipose tissue samples were taken during laparotomy, and adipocyte size was analysed. Prior surgery all subjects underwent body composition analysis, anthropometric mesurements, and cardiometabolic risk assessment. *Results:* The size of subcutaneous and visceral adipocytes correlated significantly with all indicators of overall and regional adiposity, except thigh skinfold thickness, proximal and distal thigh circumferences. Indicators of upper body adiposity had better correlation with the size of visceral adipocytes comparing to subcutaneous adipocytes. Blood pressure and leptin levels had stronger correlation with the size of subcutaneous, while tryglicerides, HDL-cholesterol, uric acid, glycaemia and HOMA showed better correlation with the size of visceral adipocytes. After adjustment for overall and regional adiposity significant correlation only remained between subcutaneous adipocyte size and diastolic blood pressure ($r=352$, $p<0.05$) and visceral adipocyte size and glycaemia ($r=0.346$, $p<0.05$), while correlation between LDL-cholesterol and size of visceral adipocytes became significant ($r=0.294$, $p<0.05$). Among all anthropometric parameters highest predictive ability for critical size of visceral adipocytes showed waist-to-height ratio and body fat percent (AUC: 0.879 and 0.878, respectively). Specific cut-off values were obtained for following anthropometric parameters: waist-to-height ratio (0.51), body fat (39.65%), sagittal abdominal diameter-to-height ratio (0.16), waist-to-tight ratio (1.48), abdominal skinfold thickness (41.60 mm), abdominal diameter index (0.58), waist circumference (86.90 cm), waist-to-hip ratio (0.85), conicity index (1.19), trunk fat (34.00%), sagittal abdominal diameter (26.25 cm) and chest skinfold thickness (28.20 mm). *Conclusions:* These results imply to a fine interplay between cellular-to-whole body level morphology and functionality.

Key words: adipose tissue, obesity, anthropometry, waist circumference, sagittal abdominal diameter, waist-to-height ratio

Introduction

Obesity, particularly of abdominal, or visceral type is known to be associated with insulin resistance, cardiometabolic disturbances and type 2 diabetes. Visceral depot of abdominal adipose tissue has specific histoanatomical characteristics and physiological properties that favor the development of obesity associated

hyperinsulinemia and metabolic alterations, while subcutaneous depot represents the site of effective energy deposition having the protecting role against cardiometabolic outcomes (1,2). There is a wide range of body fat distribution in both normal-weight and obese subjects of both genders which determines the cardiometabolic risk. Women are particularly characterized by dynamic overtime changes in body fat distribution. Premenopausal women are mainly characterized by peripheral fat accumulation while menopausal transition pronounces central fat accumulation independently of age and overall adiposity thus playing a pivotal role in developing cardiometabolic abnormalities after menopause (3).

The enlargement of the adipose tissue mass is the result of adipocyte hypertrophy and/or hyperplasia. The finding of hypertrophic adipocytes indicates hypoxic changes and dysfunctionality of adipose tissue which are closely connected with the development of obesity complications (4-6). Hypertrophy of adipocytes has been shown to be related with insulin resistance and metabolic disturbances (7-9). The adipocyte diameter over 100 μm has been assigned as the critical size which corresponds with the limited diffusion of oxygen (10,11).

Anthropometric indicators of overall and regional adiposity, like body mass index, body fat percent, waist circumference, sagittal abdominal diameter or related indices, are simple and easily applicable in routine clinical practice and identifying of persons at higher risk (11-15). For the most often used indicators cut-offs have been proposed in the literature. Most of them are based on their ability to predict cardiovascular events, hyperinsulinemia and metabolic disturbances or to predict the size of visceral fat (15,16). There are only few data on their ability to predict the hypertrophy of visceral adipocytes (17,18). This study was designed with an aim to analyze relationship between adiposity indicators, cardiometabolic parameters and the size of abdominal subcutaneous and visceral adipocytes in premenopausal women, and to develop cut-off levels for anthropometric indicators based on the critical size (100 μm) of visceral adipocytes.

Material and Methods

Study group included 50 premenopausal women who underwent elective surgery at following departments Department of Abdominal, Endocrine and Transplantation Surgery and Department of Gynecology and Obstetrics of the Clinical Centre Vojvodina, and Clinic of Operative Oncology of the Oncology Institute of Vojvodina. Patients were diagnosed with cholelythiasis (n=12), ovarian cysts (n=5) and uterine myomas (n=33). Subjects were non-diabetic, free of major organ disease and with stable body mass for the past six months. The study was approved by Ethical committies of Clinical centre Vojvodina and Oncology Institute of Vojvodina and all subjects signed informed consent. Before surgery subjects underwent clinical evaluation including medical history, blood pressure measurements, blood sample collecting and anthropometric measurements.

Anthropometric measurements and body composition analysis were done a day before surgery. Anthropometric measurements included body mass, body height, skinfold thicknesses (chest, midaxillary, subscapular, biceps, triceps, abdominal, suprailiac, supraspinal, thigh, and calf), body circumferences (upper arm, forearm, chest, waist, hip, proximal, mid- and distal thigh, and calf), and sagittal abdominal diameter. Body height was measured using Harpenden anthropometer (Holtain Ltd, Croswell, UK) to the nearest 0.1 cm. Body weight was obtained within body composition assessment. Body mass and body height values were used in order to obtain body mass index (BMI=body mass (kg) / body height $(m)^2$). Study group included 20 normal-weight patients (BMI: 18.5-24.9 kg/m^2) and 30 overweight or obese (BMI≥25 kg/m^2) patiens.

All circumferences were measured using Holtain flexible tape (Holtain Ltd, Croswell, UK) with the precision 0.1 cm. Upper arm circumference was measured at the level of the midway between acromion process of scapula and olecranon of ulna. Forearm circumference was measured as the maximum circumference of the proximal part of the forearm. Chest circumference was measured at the level of the fourth costochondral joint, at the end of normal expiration. Waist circumference was measured at the level of the midway between the inferior margin of the last rib and the iliac crest, in a horizontal plane. Hip circumference was measured at the point of maximal protrusion over the greater trochanters. Thigh circumference was measured at three levels: proximal thigh circumference was measured just below the gluteal fold, mid-thigh circumference was measured at the level midway between the inguinal

crease and proximal border of patella, while the distal thigh circumference was measured proximal to femoral epicondyles. Calf circumference was measured as the maximum circumference of the calf (19).

Sagittal abdominal diameter (SAD) was measured in the supine position at the level of the highest point of the iliac crest using Holtain Kahn abdominal caliper (Holtain Ltd, Crymych, United Kingdom) (20).

Skinfold thicknesses were measured using Harpenden caliper (Holtain Ltd, Croswell, UK) to the nearest 0.2 mm (19). Three measurements were performed and the average value was used for the analyses. Chest skinfold thickness was measured diagonally, between anterior axillary fold and nipple. Midaxillary skinfold thickness was measured horizontally on the midaxillary line at the level of the xiphisternal junction. Subscapular skinfold thickness was measured below the inferior angle of the scapula in an oblique direction downwards and laterally at 45 degrees. Triceps skinfold thickness was measured on the posterior side of the upper arm in the vertical direction at the level halfway between the acromion and olecranon, while the biceps skinfold thickness was measured vertically at the same level on the anterior side. Abdominal skinfold thickness was measured in a horizontal direction 3 cm lateral and 1 cm inferior to the umbilicus. Suprailiac skinfold thickness was measured above the iliac crest posteriorly to the midaxillary line, in a downward direction, following natural fold lines of the skin. Supraspinal skinfold thickness was measured above the anterior superior iliac spine on a line to the anterior axillary border and on a diagonal line going downwards and medially at 45 degrees. Thigh skinfold thickness was measured vertically on the anterior aspect of thigh at the midway between inguinal crease and base of patella. Calf skinfold thickness was measured in the vertical direction on the medial side of the leg, at the level of the maximum calf girth.

On the base of the measured parameters following fat distribution indices were calculated: waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), waist-to-thigh ratio (WTR), conicity index (CI), sagittal abdominal diameter-to-height ratio (SADH), sagittal abdominal diameter-to-mid-thigh circumference (abdominal diameter index, ADI), body shape index (BSI) and body adiposity index (BAI) (19,21,22). WHR, WHtR and WTR were calculated by dividing the waist circumference by the hip circumference, body height and thigh circumference, respectively. SADH and ADI were calculated by dividing SAD by the body height and mid-thigh circumference, respectively. CI, BSI and BAI were calculated using following formulas:

$$CI = \frac{\text{waist circumference (m)}}{0.109 \times \sqrt{\frac{\text{weight (kg)}}{\text{height (m)}}}}$$

$$BSI = \frac{\text{waist circumference (m)}}{\text{BMI (kg/m}^2)^{\frac{2}{3}} \times \text{body height (m)}^{\frac{1}{2}}}$$

$$BAI = \frac{\text{hip circumference (cm)}}{\text{body height (m)}^{1.5}} - 18$$

Overall and regional body composition was assessed using bioelectrical impedance analysis (Tanita Body Composition Analyzer BC-418 MA III, Tanita Corporation, Tokyo, Japan). Total body fat mass, total body fat percentage, fat free mass, trunk fat mass and trunk fat percentage were assessed, and the ratio of trunk/limb fat mass was calculated.

Blood pressure was measured by an aneroid sphygmomanometer using the auscultatory method. Blood samples were taken after an overnight fast of at least 12 hours. Biochemical measurements included total cholesterol, tryglicerides, LDL- and HDL-cholesterol, fasting blood glucose, uric acid, fibrinogen, insulin and leptin. The total cholesterol and trygliceride levels were determined by an enzyme-based method, HDL-cholesterol levels were determined by the precipitation method with sodium phospho-wolframate, and LDL-cholesterol levels were calculated using Friedwald's equation (23). Index of atherosclerosis was calculated as the ratio between LDL- and HDL-cholesterol. Fasting glucose levels were determined by Dialab glucose GOD-PAP method, and serum insulin levels were determined by ELISA. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting glucose and insulin levels (24). Serum uric acid was measured by modified PAP method, the concentration of fibronogen was determined by a turbidimetry, while the leptin concentration was measured by enzyme immunoassay (ELISA). Baseline characteristics of the study group are given in the Table 1.

Table 1. Characteristics of the examined subjects

	Mean±SD	**Min-Max**
Body height (cm)	166.38±6.19	152.50-178.00
Body mass (kg)	74.14±15.64	44.20-115.50
BMI (kg/m^2)	26.87±5.97	16.60-42.42
Body composition parameters		
Total body fat (%)	26.43±10.88	6.40-55.50
Total body fat mass (kg)	34.24±7.99	14.50-48.10
Fat free mass (kg)	47.71±5.64	37.50-60.00
Trunk fat percentage (%)	31.30±8.99	6.00-46.40
Trunk fat mass (kg)	13.10±5.62	1.40-25.30
Trunk/limb fat mass	0.96±0.18	0.28-1.26
Skinfold thicknesses		
Chest (mm)	28.39±10.28	4.60-47.40
Midaxillary (mm)	31.38±9.33	6.40-47.20
Subscapular (mm)	30.42±13.54	9.10-64.50
Biceps (mm)	17.24±7.51	4.40-36.00
Triceps (mm)	30.28±9.54	6.80-49.00
Abdominal (mm)	38.76±13.99	6.80-77.30
Suprailiac (mm)	30.60±11.85	6.60-64.40
Supraspinal (mm)	21.73±9.30	4.60-39.20
Thigh (mm)	46.32±14.25	16.80-69.30
Calf (mm)	30.92±8.80	8.20-48.40
Circumferences		
Upper arm (cm)	28.27±3.38	28.27-35.60
Forearm (cm)	25.64±2.38	21.00-31.40
Chest (cm)	93.42±9.93	76.00-124.60
Waist (cm)	86.34±14.90	62.60-127.10
Hip (cm)	104.05±10.85	81.80-130.80
Proximal thigh (cm)	57.20±6.14	43.80-72.20
Mid thigh (cm)	52.14±5.63	40.80-64.70
Distal thigh (cm)	43.41±4.92	33.60-54.10
Calf (cm)	36.62±3.60	27.90-45.20
Sagittal abdominal diameter (cm)	24.96±5.54	10.20-36.00
Fat distribution indices		
WHR	0.83±0.08	0.69-0.97
WHtR	0.52±0.09	0.36-0.77
WTR	1.51±0.20	1.11-1.93
CI	1.19±0.09	1.02-1.39
SADH	0.15±0.03	0.06-0.22
ADI	0.48±0.08	0.25-0.62
BSI	0.075±0.005	0.063-0.087

	Mean±SD	Min-Max
BAI	30.60±5.72	20.35-43.71
Blood pressure		
Systolic (mmHg)	116.30±18.01	80.00-180.00
Diastolic (mmHg)	76.60±12.18	50.00-100.00
Biochemical parameters		
Total cholesterol	5.44±1.16	3.53-8.80
Tryglicerides	1.44±0.74	0.59-3.23
HDL-cholesterol	1.43±0.34	0.82-2.00
LDL-cholesterol	3.34±1.12	0.46-6.63
Index of atherosclerosis	2.63±1.33	0.95-7.36
Uric acid	261.38±84.90	107.00-451.00
Fasting glucose	4.50±0.91	3.40-8.30
Fibrinogen	3.54±1.14	2.00-6.30
Insulin	10.22±7.58	1.29-42.27
HOMA	11.16±11.66	0.15-56.15
Leptin	210.86±165.44	26.00-864.00

Adipose tissue samples (1x1x1 cm) were obtained from the subcutaneous and visceral fat depots of abdomen at the site of the surgical incision, and at the edge of the greater omentum, respectively, and fixed in 10% neutral buffered formalin. Samples were cut to 5 μm thick sections and stained with haematoxylin-eosin. Photographs were captured at 400 magnification using DP 70 digital camera with Olympus BX51 microscope (M/S – Japan). The images were processed by Image J software (http://rsbweb.nih.gov/ij/). Cross-sectional surface area (A) of at least 120 adipocytes of each patient was analyzed and adipocyte diameter (d) was derived as $d=\sqrt{4A/\pi}$. Adipose tissue characteristics are presented in the Table 2.

Statistical analysis was performed using IBM SPSS Statistics Version 22.0 (SPSS Inc, Chicago, IL). Values are represented as the mean ± standard deviation (X±SD), minimal (Min) and maximal values (Max). Adipocyte surface area was correlated with adiposity indicators, blood pressure and biochemical parameters using Pearson's correlation test. Correlation between adipocyte surface area, blood pressure and biochemical parameters was calculated controlling for the effect of overall and abdominal adiposity (BMI, BF% and waist circumference). Level of significant was set at $p=0.05$. Using the critical size of adipocytes of 100 μm, receiver operating characteristic (ROC) curve analysis was used to identify thresholds for adiposity indicators that showed strongest correlation with the size of visceral adipocytes.

Results

Adipocytes from subcutaneous fat depot were larger than those from visceral depot. Mean size of subcutaneous and visceral adipocytes was higher in overweight and obese women, and percent of hypertrophied adipocytes (diameter ≥100μm) in both depots was also higher in obese and overweight subjects (Table 2). Overweight and obese subjects had more than twice higher percentage of hypertrophied adipocytes in the visceral compartment comparing to the normal-weight subjects (27.26 vs. 12.85%).

The size of subcutaneous and visceral adipocytes correlated significantly with body mass and all indicators of overall and regional adiposity, except thigh skinfold thickness, proximal and distal thigh circumference (Table 3). Strongest relationship with the adipocyte size showed body fat percent and indicators of

Table 2. Adipose tissue characteristics

	Subcutaneous	Visceral
Adipocyte surface area (μm^2)		
Total	10232.04±7277.61	5478.28±4394.65
Normal weight	8004.20±5707.69	4358.88±3460.39
Overweight and obese	11817.35±7838.14	6247.75±4786.23
Adipocyte diameter (μm)		
Total	107.55±38.21	78.02±29.79
Normal weight	95.10±33.88	69.83±25.95
Overweight and obese	116.42±38.64	83.66±30.93
% of adipocytes with diameter ≥100μm		
Total	54.63	21.39
Normal weight	41.08	12.85
Overweight and obese	64.25	27.26

Table 3. Correlation between adiposity parameters and adipocyte surface area

	Adipocyte size	
	Subcutaneous	Visceral
Body height	-0.287*	-0.282*
Body mass	0.553**	0.499**
BMI	0.612**	0.567**
Body fat percent	0.734**	0.684**
Total body fat	0.652**	0.611**
Fat free mass	0.277	0.207
Trunk fat mass	0.712**	0.666**
Trunk fat percent	0.666**	0.615**
Trunk/limb fat mass	0.347*	0.326*
Chest skinfold thickness	0.617**	0.654**
Midaxillary skinfold thickness	0.578**	0.597**
Subscapular skinfold thickness	0.607**	0.558**
Triceps skinfold thickness	0.448**	0.373**
Biceps skinfold thickness	0.458**	0.376**
Abdominal skinfold thickness	0.602**	0.678**
Suprailiac skinfold thickness	0.544**	0.487**
Supraspinal skinfold thickness	0.599**	0.583**
Thigh skinfold thickness	0.266	0.177
Calf skinfold thickness	0.417**	0.361**
Upper arm circumference	0.501**	0.414**
Forearm circumference	0.416**	0.325*
Chest circumference	0.634**	0.639**
Waist circumference	0.672**	0.654**

	Adipocyte size	
	Subcutaneous	**Visceral**
Hip circumference	0.489**	0.465**
Proximal thigh circumference	0.275	0.190
Mid thigh circumference	0.337*	0.207
Distal thigh circumference	0.243	0.123
Calf circumference	0.411**	0.406**
SAD	0.708**	0.646**
WHR	0.701**	0.686**
WHtR	0.688**	0.675**
WTR	0.666**	0.713**
CI	0.653**	0.684**
SADH	0.731**	0.672**
ADI	0.730**	0.726**
BSI	0.469**	0.542**
BAI	0.561**	0.544**

Table 4. Correlation of blood pressure and biochemical parameters with adipocyte surface area

	Adipocyte size			
	Subcutaneous	**Adjusted for BMI, BF% and waist circumference**	**Visceral**	**Adjusted for BMI, BF% and waist circumference**
Systolic blood pressure	0.523**	0.286	0.404**	0.096
Diastolic blood pressure	0.535**	0.352*	0.407**	0.172
Total cholesterol	0.137	0.203	0.208	0.275
Tryglicerides	0.345*	0.168	0.420**	0.278
HDL-cholesterol	-0.181	0.150	-0.280*	-0.010
LDL-cholesterol	0.065	0.131	0.195	0.294*
Index of atherosclerosis	0.068	-0.061	0.238	0.179
Uric acid	0.287*	0.127	0.382**	0.266
Fasting glucose	0.286*	0.182	0.409**	0.346*
Fibrinogen	0.259	0.033	0.235	-0.025
Insulin	0.314*	-0.004	0.380**	0.108
HOMA	0.367**	-0.204	0.464**	-0.223
Leptin	0.384**	0.066	0.361*	0.224

*p<0.05; **p<0.01

central adiposity (trunk fat, SAD, SADH, ADI, WTR, WHR, WHtR, CI, waist circumference, chest circumference). Most anthropometric measures showed stronger correlation with the size of subcutaneous adipocytes, except indicators of upper body adiposity (chest circumference, chest, midaxillary and abdominal skinfold thicknesses, WTR, CI and BSI) that had better correlation with the size of visceral adipocytes.

Blood pressure, tryglicerides, uric acid, glycaemia, insulin, HOMA and leptin correlated significantly with the size of both, subcutaneous and visceral adipocytes (Table 4). Among them blood pressure and leptin

Table 5. Area under the curve

Variable	Cut-off	AUC (95% Confidence Interval)	Sensitivity	Specifity	p
WHtR	0.51	0.879 (0.780-0.977)	1.000	0.650	0.000
Body fat%	39.65	0.878 (0.756-0.999)	0.800	0.850	0.000
SADH	0.16	0.874 (0.756-0.991)	0.900	0.650	0.000
WTR	1.48	0.872 (0.769-0.976)	1.000	0.650	0.000
Abdominal skinfold thickness	41.60	0.868 (0.761-0.974)	1.000	0.675	0.000
ADI	0.58	0.856 (0.732-0.980)	0.600	0.950	0.001
Waist circumference	86.90	0.850 (0.735-0.965)	0.900	0.775	0.001
WHR	0.85	0.848 (0.737-0.958)	0.900	0.725	0.001
CI	1.19	0.847 (0.721-0.974)	1.000	0.605	0.001
Trunk fat%	34.00	0.841 (0.718-0.964)	0.900	0.675	0.001
SAD	26.25	0.834 (0.700-0.968)	0.900	0.700	0.001
Chest skinfold thickness	28.20	0.815 (0.692-0.938)	1.000	0.575	0.002

level had stronger correlation with the size of subcutaneous, while other metabolic parameters showed better correlation with the size of visceral adipocytes. HDL-cholesterol significantly inversly correlated only with the size of visceral adipocytes. The strongest correlation was observed between the size of visceral adipocytes and HOMA. After adjustment for BMI, body fat percent and waist circumference most significant correlations disappeared; significant correlation only remained between subcutaneous adipocyte size and diastolic blood pressure ($r=0.352$, $p<0.05$), and visceral adipocyte size and fasting glucose level ($r=0.346$, $p<0.05$), while correlation between LDL-cholesterol and size of visceral adipocytes became significant after adjustment for BMI, body fat percent and waist circumference ($r=0.294$, $p<0.05$).

Anthropometric indicators that showed the strongest association with the size of visceral adipocytes were subtracted in order to test their ability to predict critical size of visceral adipocytes. Highest predictive value was found for the WHtR (0.879) and body fat percent (0.878). Specific cut-off values were obtained for the each anthropometric parameter (Table 5): 0.51 for WHtR, 39.65% for body fat, 0.16 for SADH, 1.48 for WTR, 41.60 mm for abdominal skinfold thickness, 0.58 for ADI, 86.90 cm for waist circumference, 0.85 for WHR, 1.19 for CI, 34.00% for trunk fat, 26.25 cm for SAD and 28.20 mm for chest skinfold thickness.

Discussion

This study was conducted with an aim of analyzing the relationship between the size of subcutaneous and visceral adipocytes and simple adiposity indicators, and cardiometabolic parameters. We also aimed to develop cut-off levels for anthropometric indicators based on the critical size (100 μm) of visceral adipocytes. Our results showed that among all analyzed anthropometric parameters total body fat and abdominal adiposity indicators have strongest association with the size of both, subcutaneous and visceral abdominal adipocytes. The best predictors of the hypertrophy of adipocytes in visceral fat depot were WHtR and body fat percent, with the estimated cut-offs of 0.51 and 39.65%, respectively. Among cardiometabolic parameters glycaemia and LDL-cholesterol were independently associated with the size of visceral adipocytes.

Obesity is characterized by the enlargement of adipose tissue due to hypertrophy and/or hyperplasia of adipocytes. Excess caloric intake leads to adipose tissue expansion and remodeling. "Healthy" expansion of adipose tissue includes angiogenesis and adipocyte proliferation resulting in smaller adipocytes (25). On the other hand, enlargement of adipose tissue in a hypertrophic manner results in reaching their storage capacity and inability to respond properly to a higher demands which leads to an ectopic fat deposition and

metabolic disturbances (25). Adipocyte hypertrophy primary indicates increased fat load, reduced capacity to store fat, and failure of adipocytes to proliferate (26). Hypertrophy of adipocytes combined with a limited growth of blood vessels leads to hypoxic stress and inflammation (27). It is suggested that adipocytes have a critical volume (diameter over 80-100 μm) that cannot be further expanded reducing capacity to storage fat (28-31). The presence of larger adipocytes expresses exhaustion of adipose tissue fat storage potential and correlates with lipid accumulation in non-adipose tissues, adipocyte dysfunction, hypoxic changes, decreased production of adiponectin and increased secretion of adipokines with proinflammatory, diabetogenic and proatherogenic properties, and development of insulin resistance (7,32-38).

Adipose tissue depots differ in their metabolic activity, storage capacity and capacity of proliferation. According to "expandability hypothesis" individuals who have higher capacity to store fat in more hyperplastic, subcutaneous depots remain metabolically healthy (39). On the other hand, visceral adipocyte hypertrophy has been found to be related with markers of processes of triglyceride storage, hypertrygliceridemia, hypercholesterolemia, higher LDL-cholesterol and apolipoprotein B, and lower HDL-cholesterol (40-46). It is also associated with hypertension (47) and insulin resistance (46,48). Our previous study reported finding of significantly larger adipocytes in visceral adipose tissue of metabolically obese women comparing to metabolically healthy controls of the same nutrition level (49). Current study shows that blood pressure and leptin levels have stronger correlation with the size of subcutaneous, while tryglicerides, HDL-cholesterol, uric acid, glycaemia and HOMA show better correlation with the size of visceral adipocytes. The size of visceral adipocytes correlated with LDL-cholesterol and glucose level, independently of overall and regional fat mass. When the effects of overall and abdominal adiposity were excluded, size of subcutaneous adipocytes showed significant correlation only with diastolic blood pressure. The size of subcutaneous adipocytes stronger correlated with leptin levels which was expected knowing that subcutaneous adipose tissue is the main source of leptin (50,51). However, this correlation became insignificant after adjusting for overall and regional adiposity (BMI, body fat percent and waist circumference). Generally, overweight and obese women had higher percent of hypertrophied adipocytes (with diameter >100 μm) than normal-weight subjects in both adipose tissue depots. This was particularly pronounced in the visceral adipose tissue of overweight and obese women which contained more than twice higher percent of hypertophied adipocytes suggesting overloading of this adipose compartment. Also, as expected, enlarged visceral adipocytes even smaller than subcutaneous, showed stronger correlation with the biochemical indicators of obesity related metabolic disturbances. Although it is well known that adipose tissue has the ability to respond on increased nutrient intake with adipocyte hyperthropia or hyperplasia, the right mechanisms that determine the patterns of adipocyte enlargement are not fully investigated yet and some studies even reported different reply in regards to adipose tissue localisation. Investigating the changes in the number and the size of adipocytes of different adipose tissue depots in respons to weight gain, Tchoukalova et al. showed that excess energy intake for eight weeks leads to hypertpohy of abdominal subcutaneous adipocytes as well as hyperplasia of subcutaneous adipocytes located in femoral region (52). In our study, we demonstrated that the size of both subcutaneous and visceral adipocytes correlated with almost all indicators of overall and regional adiposity except the thigh region, especially with the indicators of central adiposity, that might be the consequence of femoral adipocyte hyperplasia instead of hypertrophy. Moreover, correlation was stronger between the size of subcutaneous adipocytes and most of anthropometric indicators except the indicators of upper body adiposity that correlated better with the size of visceral adipocytes. This finding might speak in favor of the necessity to distinguish the visceral, hypertrophic obesity in the upper parts and hyperplastic obesity in the lower parts of the body that some authors cited (53-55).

There is a number of anthropometric measures that are good predictors of cardiometabolic outcomes, like waist circumference, SAD and their ratios with body height (15,35,56). Cut-off values of most of anthropometric indicators of abdominal obesity have been defined according to their ability to predict the

cardiometabolic morbidity and mortality, or the size of abdominal visceral fat mass. To the best of our knowledge there are no suggested cut-offs based on the ability to predict hypertrophy of visceral adipocytes. The most widely used indicator is waist circumference. According to WHO recommendations waist circumference values over 80 and 88 cm correspond with higher and extremely high health risk in women, respectively (57). Our results correspond within above proposed range pointing to cut-off value of 86.9 cm. WHR has been proved as a good predictor of cardiovascular diseases showing the size of abdominal fat relative to peripheral ones (58). According to Lemieux et al. (59) WHR values of 0.88 correspond to a critical accumulation of visceral adipose tissue in women, while Dobbelsteyn et al. (60) defined predictive values between 0.76 and 0.80 for women according to its relationship with the various risk factors. WHR values over 0.85 are used as diagnostic criterion of adiposopathy (61), which correspond to our results. Putting the body height in the ratio with waist circumference has been showed to increase the predictive ability of waist circumference. WHtR has been shown as the even better marker because it correlates highly with cardiometabolic risk factors (56,58). Considering proposed values in the literature, lowest cut-off values of WHtR for women found Lin et al. (62) - 0.48, while Rodgrigues et al. (63) and Carneiro Roriz et al. (64) suggest higher predictive values in women: 0.54 and 0.59, respectively. According to our results WHtR value that correspond with the critical size od adipocytes was 0.51 which is in the line with the most studies that suggest 0.5 as the predictive value (14,56,58,65,66). At the same time WHtR appeared to have the highest predicitive value among all examined anthropometric parameters. Furthermore, our study showed that besides WHtR, body fat percent might be used as a strong predictor of visceral adipocite hypertrophy. While Li et al. in their study on Chinese population reported that having body fat percent over 34.95% and 36.55% carried a risk of metabolic syndrome and type 2 diabetes mellitus development (67), our cut-off value was slightly higher (39.65%). However, studies on Korean and Indian Asian population showed slightly different result since their body percent cut-off values related to cardiovascular risk were 37% and 38%, respectively (68,69). Moreover, our study determined cut-off values of trunk fat percent as well as of abdominal and chest skinfold thicknesses but we could not find any data of these cut-off values in the literature to compare with. WTR has been shown as a good predictor of ishaemic heart disease (11), peripheral vascular disease (35) and diabetes (39). According to Li et al. (39) optimal cut-off values of WTR for predicting diabetes were between 1.81 an 1.99, depending on the ethnicity and age. In our study cut-off for WTR was lower (1.48) which is closer to those reported by Carneiro Roriz et al. (64) - they defined cut-off value according to ability of WTR to predict visceral adipose tissue area and it was 1.57 for women. SAD (or abdominal height) has been proved as a good predictor of visceral adipose tissue area, atherogenic lipid profile, hypertension, glucose intolerance and insulin resistance in both genders and in both, normal-weight and obese subjects (13,25,26,39,60). According to the results of previous studies cut-off values for SAD were defined using different criteria. Most of these studies suggest cut-off values for women between 20 and 25 cm, depending on the criteria used. According to our results upper limit for SAD is higher than those proposed in the literature (26.25 cm). Our previous results, based on the relationship between SAD and cardiovascular risk in Serbian population showed also slightly higher cut-off value of SAD (24.3 cm) which could be population-specific result that also explains higher values in the current study (70). Some studies showed ADI and SADH as a slightly better predictors of cardiovascular risk than SAD alone (26,36,39), which is in line with our results. Comparing to cut-off points in detection of the excess in visceral adipose tissue in women reported by Carneiro Roriz et al. (64), our results are similar for SADH (0.13 vs. 0.155) and higher for ADI (0.38 vs. 0.495). Considering cut-offs for body fat percent our results correspond with results given by Joseph et al. (68) and Kim et al. (69) that are based to ability to identify cardiovascular risk (38% and 37%, respectively). Lahmann et al. (71) proposed lower cut-off based on the association between body fat percent and causes of mortality (35%), while Macias et al. reported higher cut-offs for women (44%) based on the ability to detect metabolic risk (72). Finally, conicity index was proposed as an indicator of abdominal

obesity based on the assumption that higher abdominal fat deposition changes the body shape into the double cone. Some studies showed its high discriminatory power in prediction of cardiovascular risk and diabetes (73,74). Pitanga and Lessa (75) and Cho et al. (76) proposed the same cut-off value for women (1.18) based on its ability to predict coronary risk and metabolic abnormalities, respectively. Our optimal cut-off value is in line with their results (1.19).

Several limitations of the study should be acknowledged. The first one is the sample population that included only premenopausal women. Recruitment of postmenopausal women and men of different ages would provide defining age- and gender-specific cut-offs. The small size of the sample should be mentioned, too. There are some suggestions that abdominal subcutaneous adipose tissue behaves as the one between visceral and peripheral adipose tissue (77). According to those speculations it would be better if we could compare size between visceral adipocytes and "real" peripheral adipocytes.

Conclusions

Our results showed significant correlation of the adipocyte size with anthropometric indicators of abdominal adipose tissue mass, especially ratios that include another one dimension (body height or peripheral adiposity, i.e. WHtR, ADI, CI and WTR). The most of obtained predictive values for anthropometric parameters is in accordance with values that predict cardiometabolic risk or visceral adipose tissue area, which represents a new dimension to validation of suggested cut-off values and imply to a fine interplay between cellular-to-whole body level morphology and functionality.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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