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Differences in body composition between metabolically healthy and unhealthy midlife women with respect to obesity status

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ABSTRACT: Body composition (BC) characteristics across metabolic health-by-body mass index categories were examined. Metabolic health (MH) was defined by five biomarkers: waist circumference, blood pressure, levels of triglycerides, high density lipoprotein cholesterol, and fasting glucose. Potential differences in BC characteristics between metabolically healthy obese (MH-O) and metabolically unhealthy obese (MUH-O) women, and between MH normal weight (MH-NW) and MUH normal weight (MUH-NW) women were explored in 276 Slovak midlife women (39-65 years). Body composition parameters were measured with bioimpedance analyzer (BIA 101, Akern, S. r. l.). A simple comparison of the BC data between the subgroups showed significant differences in resistance (Rz, ohm) (p=0.035), muscle mass (MM, kg) (p=0.044), and total body water (TBW, kg) (p=0.047) between MH-O and MUH-O women. However, we did not observe any significant differences in BC characteristics between MH-NW and MUH-NW. Specific logistic regression models were used to determine differences in BC characteristics between various obesity phenotypes, with controlling for age, menopausal status, smoking status and sport activity. Our results indicated that increasing age and decreasing Rz were statistically significantly associated with an increased likelihood of exhibiting MUH-O (p=0.031 for age; p=0.032 for Rz). Moreover, other logistic models which included age, menopausal status, biochemical variables and life style factors such as covariates, showed that increasing alanine aminotransferase (ALT) and uric acid (UA) were statistically significantly associated with an increased likelihood of exhibiting MUH-O (p=0.023 for ALT, p=0.010 for UA). In conclusion, MUH-O and MH-O cardiometabolic profiles are characterized by differences in the value of resistance and plasma levels of ALT and UA.

KEY WORDS: metabolic abnormalities, body mass index, bioimpedance analysis

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Introduction

Obesity is a major contributor to the global burden of chronic diseases and disabilities, and has been increasing globally over the past 40 years (NCD Risk Factor Collaboration 2016). In Europe, the prevalence of obesity, defined as body mass index (BMI)≥30 kg/m^2, varies between 6% and 20%, with higher prevalence in Central and Eastern European countries (Rabin et al. 2007; Berghofer et al. 2008; Peralta et al. 2018).

Obese individuals may be protected from obesity-related cardiometabolic diseases (Camhi and Katzmarzyk 2014) or may be at a significantly lower risk than estimated from the positive association between body mass index (BMI) and cardiometabolic risk. This subphenotype has been described as metabolically healthy obese (MH-O) and is characterized by the absence of cardiometabolic abnormalities (Primeau et al. 2011; Blüher 2020), lower risk for cardiovascular disease (CVD), hypertension (Eckel et al. 2018; Mongraw-Chaffin et al. 2018; Kouvari et al. 2019), diabetes (Meigs et al. 2006; Aung et al. 2014; Kim et al. 2016), dyslipidemia and mortality (Durward et al. 2012; Izumida, Nakamura and Ishikawa 2019), despite excessive body fat accumulation, when compared with their metabolically unhealthy obese (MUH-O) counterparts. However, individuals that are within a normal BMI range may also be predisposed to similar adverse health outcomes as those observed in obese patients (Choi et al. 2013). Lean individuals with abnormal metabolic profiles have been defined as "metabolically unhealthy normal-weight" (MUH-NW). Many studies showed that MUH-NW adults exhibited increased risk in developing atherosclerosis (Yoo et al. 2014), CVD and all-cause mortality compared to MH-O (Choi et al. 2013; Schulze 2019).

Bioelectrical impedance analysis (BIA) is a non-invasive method to assess body composition (BC) and is applicable in estimating many potential health risks (Visser et al. 2012; Sergi et al. 2017). Bioelectrical impedance analysis measures the opposition to an alternating current through body compartments (resistance, Rz) and the delay in conduction by cell membranes (reactance, Xc). Rz is the pure opposition offered by the body to the flow of an alternating electric current, related to extra- and intracellular fluid located primarily within lean mass. Xc is the opposition offered by electric flow due to capacitance produced by tissue interfaces and cell membranes, and reflects the ability of cell membranes to act as capacitors, offering reactance. Rz is inversely proportional to body water content and Xc is related to extra- and intracellular water balance, which is dependent on cell membrane integrity (Oliveira, Santos and Mello 2012). The composite marker phase angle (arc tangent of Xc/Rz) reflects the amount and integrity of body cells, predicts patient outcomes in a variety of diseases (Kyle et al. 2004; Norman et al. 2010) and identifies patients with nutritional risk (Kyle et al. 2012). Previous studies revealed that the evaluation of important indicators of nutritional status, such as phase angle, fat free mass, muscle mass, and fat mass, can be useful for predicting metabolic and CVD in all BMI categories (Aleman-Mateo et al. 2010; Lang et al. 2015).

The aim of this cross-sectional study was to evaluate BC characteristics in several metabolic phenotypes in a population of normal weight and obese Slovak

midlife women and to identify the most important BC determinants of these phenotypes, in addition to anthropometric, and biochemical characteristics.

Subjects and methods

This study was based on data collected during cross-sectional surveys in Slovakia between 2013–2017 in order to analyse the associations of various biological, environmental, and clinical determinants of menopause in Slovak women ranging in age from 39 to 65 years. Three sub-groups were compared and analysed during these projects: late premenopausal, perimenopausal and early postmenopausal. A total of 276 Caucasian women were suitable and subsequently included in this study. Women were recruited from different localities in the western and middle regions of Slovakia via an invitation letter regarding the study, which was distributed prior to data collection with the associated of local physicians. Participants were then interviewed during a medical examination in the morning and were investigated with respect to their medical, anthropometrical and lifestyle aspects at local Health Centres. Women recovering from acute disorders such as cancer, myocardial infarction or stroke were excluded from the survey. The participants were mostly married (72.5%), originated from towns (53.1%), and gained secondary education level (67%). Additional baseline description of the study sample is presented in Table 1. Each woman provided written informed consent for the study which adhered to the Declaration of Helsinki Principles.

The entire sample was divided into four sub-groups; MH normal weight (BMI<25 kg/m^2), MUH normal weight (BMI<25 kg/m^2), MH obese (BMI≥30 kg/m^2) and MUH obese (BMI≥30 kg/m^2). Because of the small number of overweight (BMI≥25 and <30 kg/m^2) women suitable for this study, this sub-group was not the subject of this analysis. Women were classified as MUH (≥2 metabolic risk factors: blood pressure≥130/85 mmHg or diagnosis of hypertension; triglycerides≥1,7 mmol/l; high-density lipoprotein cholesterol<1,3 mmol/l; fasting glucose≥5,55 mmol/l or diagnosis of diabetes mellitus; waist circumference≥88 cm) or MH (<2 risk metabolic factors) (Camhi and Katzmarzyk 2014).

Biochemical analysis

Venous blood was collected following overnight fasting. Plasma was then separated and biochemical analysis of alanine aminotransferase (ALT), gamma-glutamyltransferase (GMT), uric acid (UA), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose were conducted by routine laboratory methods in the Department of Clinical Laboratories of the Bratislava Alpha Medical. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula (Friedewald et al. 1972).

Anthropometric, body composition and blood pressure measurements

All anthropometrical parameters were measured by professional anthropologists and the same instruments were used on all women. Anthropometric measurements were taken using the standard anthropometric technique. Body height was measured by anthropometer (Sieber and Hegner) at the head level with the women standing barefoot and with feet together with accuracy of 0.5 cm. Body

Table 1. Demographic characteristics and cardiometabolic risk factors in Slovak women[a]

	Total	MH-NW	MUH-NW	MH-O	MUH-O
n (%)	276	121 (44)	24 (9)	17 (6)	114 (41)
Age (years)	49.8±6.5	47.2±5.3[b]	52.7±6.6	48.6±4.0[b]	52.2±6.8
Height (cm)	163.4±5.7	164.1±5.7	162.4±5.7	162.8±4.5[b]	162.9±5.8
Weight (kg)	75.5±18.8	59.7±5.9	60.8±7.5	87.9±7.2	93.5±11.8
WC (cm)	87.8±17.2	73.0±6.8[b]	79.4±8.5	94.6±9.1[b]	104.4±10.5
HC (cm)	105.5±13.4	95.2±5.1	95.8±4.5	113.0±10.6	117.3±10.2
BMI (kg/m^2)	28.3±7.1	22.2±1.7[b]	23.0±2.0	33.2±2.4	35.3±4.4
WHR	0.83±0.09	0.77±0.06[b]	0.83±0.08	0.84±0.1[b]	0.89±0.1
Systolic BP (mmHg)	126.0±17.8	118.7±16.0[b]	126.3±22.8	120.3±10.2[b]	134.5±15.6
Diastolic BP (mmHg)	78.9±11.4	75.1±9.6[b]	78.6±9.4	77.9±6.1[b]	83.2±12.5
Glucose (mmol/l)	5.13±1.51	4.59±0.48[b]	5.24±0.99	4.83±0.65[b]	5.72±2.10
Triglycerides (mmol/l)	1.35±1.09	0.90±0.33[b]	2.22±2.73	0.91±0.29[b]	1.72±0.82
HDL-cholesterol (mmol/l)	1.56±0.46	1.85±0.44[b]	1.34±0.42	1.62±0.19[b]	1.29±0.30
TC (mmol/l)	5.37±0.98	5.29±1.02	5.57±0.87	5.03±0.85	5.47±0.97
LDL-cholesterol (mmol/l)	3.28±0.95	3.08±0.92	3.47±1.19	3.03±0.84	3.49±0.90
n (%)	220	109 (49)	18 (8)	17 (8)	76 (35)
ALT (μkat/l)	0.33±0.20	0.26±0.08[b]	0.33±0.17	0.29±0.10[b]	0.44±0.27
GMT (μkat/l)	0.42±0.43	0.29±0.17	0.35±0.24	0.43±0.44[b]	0.62±0.61
Uric acid (μmol/l)	253.6±68.6	222.4±50.7	241.8±60.5	251.5±49.0[b]	301.7±70.2
n (%)	276	121 (44)	24 (9)	17 (6)	114 (41)
Smoking status					
Regular smokers	43 (16)	20 (16)	4 (17)	3 (18)	16 (14)
Occasional smokers	31 (11)	13 (11)	1 (4)	4 (23)	13 (11)
Non-smokers	202 (73)	88 (73)	19 (79)	10 (59)	85 (75)
Sport activity					
Regularly	32 (11)	24 (20)	4 (17)	1 (6)	3 (3)
Occasionally	198 (72)	89 (73)	18 (75)	13 (76)	78 (68)
Never	46 (17)	8 (7)	2 (8)	3 (18)	33 (29)
Menopausal status					
Late premenopausal	124 (45)	73 (60)	7 (29)	9 (53)	35 (31)
Perimenopausal	19 (7)	8 (7)	2 (8)	1 (6)	8 (7)
Early postmenopausal	133 (48)	40 (33)	15 (63)	7 (41)	71 (62)
Abdominal obesity WHR > 0.89	62 (23)	3 (5)	5 (8)	4 (6)	50 (81)
Hypertension	88 (32)	23 (26)	8 (9)	1 (1)	56 (64)
Diabetes mellitus or hyperglycemia	49 (18)	2 (4)	9 (18)	2 (4)	36 (74)
Hypertriglyceridemia	61 (22)	2 (3)	8 (13)	0 (0)	51 (84)
Low HDL-cholesterol	90 (33)	9 (10)	17 (19)	0 (0)	64 (71)
Hypercholesterolaemia LDL-cholesterol > 3.00	168 (61)	60 (36)	17 (10)	9 (5)	82 (49)

Abbreviations: MH-NW, metabolically healthy normal weight; MUH-NW, metabolically unhealthy normal weight; MH-O, metabolically healthy obese; MUH-O metabolically unhealthy obese; WC, waist circumference; HC, hip circumference; BMI, body mass index; WHR, waist to hip ratio; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; GMT, gamma-glutamyltransferase, [a]Data presented as mean ± SD; [b]Significant difference in the means between MH-NW and MUH-NW, and between MH-O and MUH-O. All continuous data were tested by Mann-Whitney U-test or Independent Samples T-test.

weight was measured on a personal balance scale with the woman being barefoot and in underwear only, with an accuracy of 0.1 kg. Waist and hip circumferences were measured to the nearest 0.5 cm using a non-elastic tape, with the woman standing. Waist circumference (WC) was measured at the level of the umbilicus, and the hip circumference (HC) was measured at the maximum posterior protrusion of the buttocks. Inter- and intra-observer variability in the measurements were conducted before the investigations. The value of the inter and intra-observer variability was less than 0.5 cm. Body mass index was calculated as body weight divided by height squared. Waist-to-hip ratio (WHR) was calculated as the circumference of the waist divided by the circumference of the hips.

Body composition variables were obtained with a bioelectric impedance analyzer (BIA 101, Akern S.r.l., Florence, Italy). This apparatus generates a constant excitation current at 800 μA at a signal frequency of 50 kHz with a four-electrode arrangement. The BIA measurements were carried out in the morning, with the woman lying supine on a bed after overnight fasting and at least 12 hours after physical training or vigorous exercise. We obtained the two specific measurements of resistance (Rz), which arises from intracellular and extracellular fluids, and reactance (Xc), which is related to the capacitance of the cell membrane. Resistance is typically reduced by body fluids, which are proportional to lean body mass and is increased by body fat, through which a current is not readily conducted. Resistance and reactance are vectors that are related by phase angle, for which a larger value reflects increased body cell mass (Barbosa-Silva et al. 2003, Kyle et al. 2004). We also obtained data on fat mass (FM), fat free mass (FFM), muscle mass (MM), body cell mass (BCM), total body water (TBW), extra- and intracellular water (ECW, ICW).

Systolic and diastolic blood pressure (sBP, dBP) were measured in the morning during medical examination, in the sitting position using a digital sphygmomanometer.

Data analysis

The assumption of normal distribution was tested by the one-sample Kolmogorov-Smirnov test. A comparison between the subgroups was analyzed using the Mann-Whitney U-test in case of not normal distribution and the t-test fro independent sample, in case of normally distributed data. A discriminant stepwise analysis model was used to determine the BC variables which best identify MUH-NW, and MUH-O. All the measured BC variables and also BMI were included in discriminant analysis. A stepwise logistic regression analysis (likelihood ratio) was carried out, with the presence of MUH-O as dependent variable and progressive elimination of covariates (age, menopausal status, sport, smoking, BC parameters, and biochemical health factors). Only those continuous variables with values of $p<0.05$ in the T-test or U-test were included in the logistic regression as covariates. Statistical computations were performed by the SPSS 17.0 software programme (SPSS Inc., Chicago, IL). A *p*-value less than 0.05 was considered significant.

Results

The anthropometric, biochemical, and life style characteristics of studied women in obese and normal weight sub-

groups are summarized in Table 1. The MH-NW and MUH-NW women differed significantly in their mean values of age, WC, BMI, WHR, sBP, dBP, glucose, TG, HDL-C, ALT liver enzyme. The MH-O and MUH-O women differed significantly in their mean values of age, WC, WHR, sBP, dBP, glucose, TG, HDL-C, UA, ALT, and GMT liver enzymes. According to the defined criteria, the prevalence of MUH status in the entire study sample was 50%. After dividing the entire sample into four cohorts based on BMI category and metabolic health, the following prevalences were recorded; MH-NW 44 %, MUH-NW 9%, MH-O 6% and MUH-O 41% (as in Table 1).

The prevalences among different BMI subgroups were as follows: MUH-NW women accounted for 16% among normal-weight midlife women and MUH-O women accounted for 87% among obese midlife women.

We compared the BC characteristics between MH-NW and MUH-NW in Figure 1 and no significant difference was established for any BC parameter ($p>0.05$). Additionally, the relationship between MUH-NW presence, BMI and all BC parameters was tested by stepwise discriminant analysis (data not shown). The BMI was selected as the best predictor of MUH-NW (Exact F=4.59, $p=0.034$). This documents that MH-NW and MUH-NW women differed mainly in BMI. Other investigated variables were excluded in the stepwise statistics.

Figure 2 highlights BC variables differences between MH-O and MUH-O women. Our results revealed that MUH-O women had statistically significantly lower Rz (508±13.1 vs. 477±5.2 ohm; $p=0.035$), more TBW (37.6±0.73 vs. 42.7±3.17 l; $p=0.047$) and more MM (27.6±0.51 vs. 29.5±0.36 kg; $p=0.044$) than MH-O women.

A logistic regression was performed to ascertain the effects of age, menopausal status, sport, smoking, Rz, TBW (kg), MM (kg) on the likelihood that women

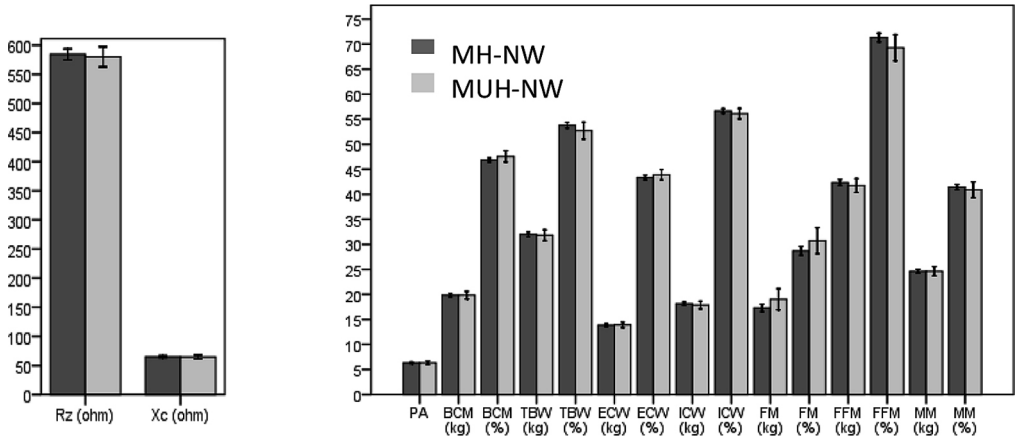

Fig. 1. Body composition comparisons between metabolically healthy and unhealthy normal weight women

Abbreviations: Mean ± SE; Error bars represent standard errors. MH-NW – metabolically healthy normal weight, MUH-NW – metabolically unhealthy normal weight, Rz – resistance, Xc – reactance, PA – phase angle, BCM – body cell mass, TBW – total body water, ECW – extracelullar water, ICW – intracelullar water, FM – fat mass, FFM – fat free mass, MM – muscle mass.

have MUH-O (as in Table 2). The logistic regression model indicated that increasing age and decreasing Rz were significantly associated with an increased likelihood of exhibiting MUH-O (p=0.031 for age; p=0.032 for Rz). This analysis also revealed that the effect of Rz on MHU-O was independent from age.

Furthermore, this analysis also revealed that the differences in TBW (kg) and MM (kg) between subgroups were not statistically significant when age, Rz and life style factors were used in the model.

Additionally, the relationship between MUH-O presence, BMI and all BC

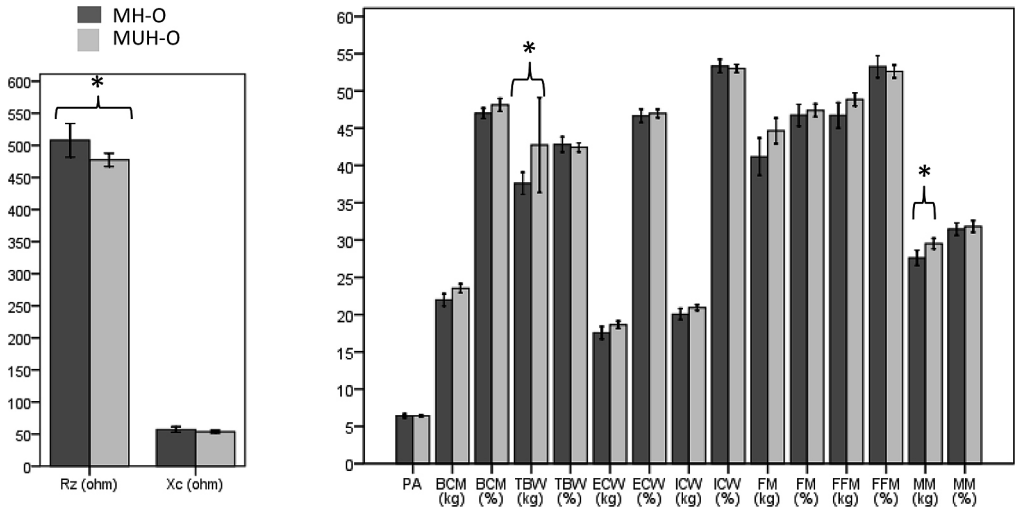

Fig. 2. Body composition comparisons between metabolically healthy and unhealthy obese women

Abbreviations: *p < 0.05; Mean ± SE; Error bars represent standard errors. MH-O – metabolically healthy obese, MUH-O – metabolically unhealthy obese, Rz – resistance, Xc – reactance, PA – phase angle, BCM – body cell mass, TBW – total body water, ECW – extracelullar water, ICW – intracelullar water, FM – fat mass, FFM – fat free mass, MM – muscle mass.

Table 2. Binary logistic regression, the effect of selected risk factors in metabolically unhealthy obesity

MUH-O vs. MH-O	Covariates	B	SE	p	Exp (B)	95% CI	
Model 1	Age	0.097	0.045	0.031	1.102	1.009	1.203
	Rz	−0.011	0.005	0.032	0.989	0.980	0.999
	Excluded variables (p>0.05): menopausal status, sport, smoking, TBW (kg), MM (kg)						
Model 2	ALT	5.328	2.352	0.023	206	2.1	20 695
	Excluded variables (p>0.05): age, menopausal status, sport, smoking, GMT						
Model 3	UA	0.013	0.005	0.010	1.013	1.003	1.023
	Excluded variables (p>0.05): age, menopausal status, sport, smoking						

Abbreviations: MH-O – metabolically healthy obese, MUH-O – metabolically unhealthy obese, Rz – resistance, TBW – total body water, MM – muscle mass, ALT – alanine aminotransferase, GMT – gamma-glutamyltransferase, UA – uric acid.

parameters was tested by stepwise discriminant analysis (data not shown). The Rz was selected as the best predictor of MUH-O (Exact F=4.55, p=0.035). This identified that MH-NW and MUH-NW women differed mainly in Rz. Other investigated variables were excluded in the stepwise statistics.

Moreover, other logistic models based on age, menopausal status, biochemical variables and life style factors as covariates, showed that increasing ALT and UA were statistically significantly associated with an increased likelihood of exhibiting MUH-O (p=0.023 for ALT, p=0.010 for UA, Table 2).

Discussion

The results from our study determined the prevalence of the unhealthy metabolic phenotype in obese (41% of the total sample) and normal-weight women (9% of the total sample). There have been several studies that attempted to estimate the prevalence of the MUH-O and MUH-NW phenotypes (Wildman et al. 2008; Vliet-Ostaptchouk et al. 2014; Jung et al. 2015). due to different criteria used to define metabolic health, prevalence can be quite heterogeneous. Philips et al. (2013) demonstrated considerable variation in the prevalence of MH-O (2.2% to 11.9%), MUH-O (20.6% to 30.1%), MH-non obese (8.8% to 52.7%), and MUH-non obese (14.7% to 59%).

In the current study, MUH-O and MH-O cardiometabolic profiles were characterized by differences in BC. MUH-O and MH-O women differed significantly in the value of Rz. We found that women with the MUH-O phenotype had lower Rz in comparison to their MH-O counterparts utilizing our cardiometabolic clustering definition. Currently, we do not know of other studies which had exclusively documented differences in Rz values between MH-O and MUH-O women. However, some studies identified, for example, that the main impedance characteristics (Rz and/or Xc) of women suffering from CVD (Drozdova et al. 2016), chronic kidney disease (Bellizzi et al. 2006) or lung cancer (Toso et al. 2000) were significantly lower than of those who did not havementioned diseases. Despite the fact that PA seems to be a good prognostic marker for mortality in many clinical conditions, such as cancer, kidney and cardiac diseases (Garlini et al. 2019), and identifies patients with nutritional risk independently of body weight (Looijaard et al. 2020), we did not determine the association neither between MUH-O and MH-O, nor between MUH-NW and MH-NW.

BIA is based on the relationship between the volume of a conductor and its electrical Rz. Since MM is the largest tissue in the body and is also an electrolyte-rich tissue with a low Rz, muscle is a dominant conductor. Previous studies have shown that there is a strong correlation between Rz and MM measurements (Petrobelli et al. 1998; Nunez et al. 1999; Janssen et al. 2000). In our study, we measured less MM (kg) in MH-O than in MUH-O women. However, the difference was not statistically significant when Rz was used in the regression model in obese women. Some studies have demonstrated the importance of MM in metabolic health. For example, Lee et al. (2018) indicated that greater MM at baseline is significantly associated with maintenance of metabolically healthy status, especially in nonobese individuals. Furthermore, Xia et al. (2017) found that abnormal metabolism in normal weight Chinese adults is associated with lower MM (%) along

with lower TBW (%), and higher FM (%). However, based on our results, we hypothesize that the raw BIA measurement, such as Rz, is a more important indicator in metabolic health prediction than MM itself, especially in obese midlife women.

Previous studies have also shown equivocal results in FM and FFM between any studied subgroups; some show significantly less FM (Ortega et al. 2013) and lower FFM (Brochu et al. 2008; Messier et al. 2010; Camhi and Katzmarzyk 2014) in MH-O, whereas others along with our study have not shown significant differences between MH-O and MUH-O phenotypes for FM (Stefan et al. 2008) and FFM (Succurro et al. 2008).

The MH-O women had significantly lower concentrations of ALT and GMT, as well as lower UA levels compared with at-risk women. Our results from logistic regression analysis with control for age, menopausal status, life style, confirmed the considerable contribution of ALT, and UA in MUH-O phenotype. Mangge et al. (2010) suggest that serum levels of UA are a significant predictor of MUH obesity in juveniles and adults. Our findings concur with the results of Messier et al. (2010). Therein, the authors indicated that postmenopausal women displaying the MH-O phenotype present favorable levels of ALT, AST (aspartate aminotransferase), and GMT. They suggest that lower concentrations of hepatic enzymes, in particular, lower circulating ALT levels, in MH-O individuals may reflect lower hepatic insulin resistance and lower liver fat content; and this could be involved, at least in part, in the protective profile of MH-O individuals.

In summary, our study provides evidence that Rz, plasma levels of ALT and UA should be evaluated as other biomarkers related to metabolic health in obese women. These biomarkers should serve as additional determinants in differentiating between MH-O and MUH-O women and to predict the metabolic health in obese Slovak midlife women.

However, there are also some limitations in this study. The cross-sectional nature of our study made it difficult to draw conclusions regarding causal pathways. Moreover, the study population was smaller when divided by BMI and metabolic abnormalities in various subgroups, and was also limited to the age range from 39 to 65 years. Considering these facts, our results and suggestions require confirmation by replicated investigation in a future independent cohort with a larger sample size and in various age categories. The risk of MUH-O is associated with many more biochemical factors, such as pro-inflammatory markers, along with life style of the women. Therefore, our findings should prompt further studies that consider some of the above mentioned variables.

Conclusion

In this pilot study, we have provided novel data that supports the significant association of Rz, plasma levels of ALT and UA with metabolic health in obese Slovak midlife women, with a decrease in Rz and higher ALT and UA levels indicating a worse prognosis and the presence of MUH-O.

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The Authors' contribution

LV contributed to the conception, design, and performance of the study, and the writing of the manuscript. DF participated in collection of data, analysis and interpretation of data, and the writing of the manuscript. DS was innovator for the project, participated in the conception, design, data collection, performance of the study.

Conflict of interest

The authors declare that there is no conflict of interest.

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