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Adipose Tissue Composition and Distribution Differences in Predicting Metabolic Disorders in Obese Patients

SUMMARY OF DOCTORAL DISSERTATION

Biomedical Sciences,
Medicine [06B]

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This dissertation was written during 2013–2018 at Vilnius University.

Academic supervisor:

Prof. Dr. Gintautas Brimas (Vilnius University, Biomedical Sciences, Medicine 06B)

Academic consultant:
Prof. Dr. Janina Tutkuvienė (Vilnius University, Biomedical Sciences, Medicine 06B)

This doctoral dissertation will be defended at a public meeting of the Dissertation Defense Panel:

Chairman – Prof. Dr. Tomas Poškus (Vilnius University, Biomedical Sciences, Medicine 06B).
Members:
Prof. Dr. Arvydas Kaminskas Vilnius University, Biomedical Sciences, Medicine 06B).
Prof. Dr. Sylvia Kirchengast (University of Vienna, Austria, Biomedical Sciences, Biology 01B)
Prof. Dr. Artūras Razbadauskas (Klaipėda University, Biomedical Sciences, Medicine 06B)
Prof. Dr. Violeta Žalgevičienė (Vilnius University, Biomedical Sciences, Medicine 06B)

The dissertation will be defended during a public meeting of the Dissertation Defence Panel at 4.00 p.m. on December 19, 2018 in the Red Hall of Vilnius University Hospital Santaros Klinikos.

Address: 2 Santariškių Str., 08661 Vilnius, Lithuania.

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Riebalinio audinio pasiskirstymo ir riebalų sudėties skirtumai tarp metabolinių sutrikimų turinčių ir neturinčių nutukusių pacientų

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Mokslinis vadovas:
prof. dr. (HP) Gintautas Brimas [Vilniaus universitetas, Biomedicinos mokslai, medicina 06B]
Mokslinis konsultantas:
prof. dr. (HP) Janina Tutkuvienė [Vilniaus universitetas, Biomedicinos mokslai, medicina 06B]

Gynimo taryba:
Pirmininkas – prof. dr. Tomas Poškus [Vilniaus universitetas, Biomedicinos mokslai, medicina 06B]
Nariai:
prof. dr. (HP) Arvydas Kaminskas [Vilniaus universitetas, Biomedicinos mokslai, medicina 06B]
prof. dr. Sylvia Kirchengast [Vienos universitetas, Austrija, Biomedicinos mokslai, biologija 01B]
prof. dr. Artūras Razbadauskas [Klaipėdos universitetas, Biomedicinos mokslai, medicina 06B]
prof. dr. Violeta Žalgevičienė [Vilniaus universitetas, Biomedicinos mokslai, medicina 06B]

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ABBREVIATIONS

CI	–	confidence interval
CVD	–	cardiovascular diseases
DBP	–	diastolic blood preassure
HDL	–	high-density lipoprotein cholesterol
HOMA-IR	–	a homeostasis model assessment for insulin resistance
^{1}H-MRS	–	hydrogen-1 magnetic resonance spectroscopy
^{1}H-NMR	–	hydrogen-1 nuclear magnetic resonance
MAO	–	metabolically abnormal obese
MHO	–	metabolically healthy obese
MS	–	metabolic syndrome
MUFA	–	monounsaturrated fatty acid
nonMS	–	metabolic syndrome is absent
LDL	–	low-density lipoprotein cholesterol
PAT	–	preperitoneal adipose tissue
PUFA	–	polyunsaturrated fatty acid
SAT	–	subcutaneous adipose tissue
SBP	–	systolic blood preassure
SFA	–	saturated fatty acid
TG	–	triglycerides
UA	–	uric acid
VAT	–	visceral adipose tissue

SUMMARY

1. INTRODUCTION

The prevalence of obesity is increasing worldwide, and more than 20% of all human population are obese. Obesity's prevalence has tripled during the last three decades (WHO 2017). There has been an increase of 28.3% in the rate of deaths related to high BMI globally since 1990 (Collaborators 2017). Each 5 kg/m^2 higher than one's recommended BMI is associated with a 30% higher overall mortality. Cardiovascular disease was the leading cause of death, diabetes was the second one, accompanied by chronic kidney, hepatic diseases and cancer (MacMahon et al. 2009). Metabolic syndrome is a risk factor for CVD, type 2 diabetes and is diagnosed in 60% of obese patients (Park et al. 2003).

It has been shown that there exists a subset of the obese population without any metabolic abnormalities. This phenotype of obesity is termed as metabolically healthy obesity. The overall MHO prevalence ranges from 6% to 75% (Rey-López et al. 2014); thus, MHO patients might be at a lower risk of developing cardiovascular events or all-cause mortality (Lassale et al. 2017; Eckel et al. 2016). Despite the excessive BMI or total amount of adipose tissue, these patients remain insulin-sensitive and have a normal lipid profile and blood pressure. It was determined that MHO has a distinct fat distribution pattern, a favorable inflammatory profile as well as different adipose tissue metabolism and composition (Mathew et al. 2016).

Until the 1950s adipose tissue was characterized as a connective tissue that contained lipid droplets (Rosen & Spiegelman 2014). Over the past decade and a half, adipose tissue became to be considered as an endocrine organ that plays a critical role in the maintenance of energy homeostasis in the autocrine, paracrine and endocrine levels (Harwood 2012; Wozniak et al. 2009; Galic et al. 2010; Esteve Ràfols 2014).

Obesity is characterized by an excessive storage of fatty acids in an expanding adipose tissue mass. In the situation of overfeeding,

individual adipose tissue has an increased demand for lipid storage. It was shown that a healthy adipose tissue storage capacity involves adipocyte hyperplasia, and dysfunctional remodeling involves hypertrophy. White adipose tissue expansion through hyperthrophy is associated with insulin resistance and cardiometabolic complications (Engin & Engin 2017). Studies revealed that the SAT has a finite capacity to expand, which is called *adipose expandability hypothesis*. When the personal fat threshold is reached, the lipid excess is deposited as an ectopic fat (Gesta & Kahn 2017; Cuthbertson et al. 2017; Dobson et al. 2016).

Visceral fat is a strong, independent predictor of all-cause mortality in men (Kuk et al. 2006). Recent studies demonstrated that it has a strong correlation with insulin resistance, type 2 diabetes, CVD, metabolic syndrome and cancer (Preis et al. 2011; Fox et al. 2007; Neeland et al. 2013; Liu et al. 2010; Britton et al. 2014; Smith et al. 2012; Oka et al. 2010; Shiina & Homma 2013; Gletsu-Miller et al. 2013). Nevertheless, it is still unknown what is the critical VAT threshold for the development of metabolic disturbances and a transition from the MHO to the MAO phenotype.

It is possible to quantify the amount of adipose tissue by various techniques, while anthropometry, ultrasonography, CT and MRT are used the most. It is possible to estimate the obesity by skinfold measurements, BMI or WHR; however, it is impossible to distinguish the different fat depots by these determinants. CT and MRI are the standard techniques for determining the distribution of adipose tissue. However, their limited availability, price and time required to perform the examination, the possible contraindications and radiation exposure during a CT scan are limiting the usage of these research tools in large epidemiologic studies. Meanwhile, the ultrasonography is easily performed, widespread, patients are not exposed to radiation during it and its results are comparable with those obtained by CT and MRI (Fox et al. 2007; Kim et al. 2004; Leite et al. 2002; Ribeiro-Filho et al. 2001; Bazzocchi et al. 2016) and between different examiners (Gouvea et al. 2013; Stoner et al. 2015; Philipsen et al. 2013). An

ultrasonography can measure intra-abdominal fat more accurately than anthropometric measurements (Stolk et al. 2003; Bertoli et al. 2015; Meriño-Ibarra et al. 2005) and can be used in the obese population (Pontiroli et al. 2002; Sabir et al. 2001; Philipsen et al. 2015). Visceral fat thickness, measured by ultrasonography, is strongly associated with all MS components (Kim et al. 2004; Guldiken et al. 2006; Sogabe et al. 2012; Miranda Prado 2012; Soattin et al. 2013; Roever et al. 2016) and it is proposed that it could be used for the diagnosis of MS (Ribeiro-Filho et al. 2001; Meriño-Ibarra et al. 2005; Chiba et al. 2007; Vasilescu et al. 2011).

Needle aspiration biopsy was the preferable method for obtaining adipose tissue samples in most of the human adipose tissue fatty acid composition studies. Recently, a non-invasive research tool was developed for measuring adipose tissue unsaturation *in vivo* – magnetic resonance spectroscopy. It is possible to distinguish different fat locations during the examination. ^{1}H-MRS (1.5 or 3 Tesla) used *in vivo* reduces the spectral dispersion of lipids and limits the usage of this tool and is not capable of distinguishing individual fatty acids. The low magnetic field 7 Tesla ^{1}H-MRS was introduced recently, but its clinical usage is still limited in clinical practice. However, ^{1}H-MRS allows to perform a repeated sampling of the same adipose tissue location, determine fatty acid composition (MUFA, PUFA and SFA ratios) and estimate its metabolic activity (Lundbom et al. 2016). Thus, it is possible to measure the total amount of lipids in various depots and its saturation ratio (Calderan et al. 2006; Velan et al. 2008; Lundbom et al. 2011; Naukkarinen et al. 2014; Lundbom et al. 2016). A recent study has shown that adipocyte insulin sensitivity correlates positively with their saturated fat content, and that the fat unsaturation degree is different in various fat localizations (Lundbom et al. 2013). It was performed with ^{1}H-MRS, but the results were not validated by the analysis of adipose tissue biopsies.

Nuclear magnetic resonance spectroscopy is widely used as a method in lipid analysis *in vitro*. It allows for structure elucidation as well as a qualitative and quantitative analysis of lipid molecules. NMR has

several advantages compared to the commonly used chromatographic analysis. It is a non-destructive method, and, for quantification, no specific standards are necessary. For lipid investigation, ^{1}H, ^{13}C and ^{31}P nuclei are used for routine NMR. The ^{1}H nucleus with a spin quantum number I=1/2, a high gyromagnetic ratio and a natural abundance of 99.985% is the most sensitive NMR probe and, thus, appropriate for investigating even minor unsaturated lipids within a short experimental time (Alexandri et al. 2017; Knothe & Kenar 2004).

This study uses anthropometric, ultrasonographic and ^{1}H-MRS tools to determine whether superficial and deep subcutaneous, preperitoneal and visceral adipose tissue depots differ in their distribution and fatty acid composition in metabolically healthy and unhealthy obese populations.

2. THE AIM OF THE STUDY

The aim of this study was to determine the distribution and composition of adipose tissue and its predictive value for metabolic disorders in obese patients.

3. OBJECTIVES

1. To evaluate the distribution of adipose tissue by anthropometric and ultrasonographic methods in obese patients with and without metabolic syndrome
2. To determine the composition of superficial and deep subcutaneous, preperitoneal and visceral adipose tissues by ^{1}H NMR in obese patients with and without metabolic syndrome.
3. To evaluate the influence of superficial and deep subcutaneous, preperitoneal and visceral adipose tissue distributions and compositions on the emergence of metabolic disturbances in obese patients.

4. SCIENTIFIC NOVELTY OF THE STUDY

1. The present study is the first prospective study determining the distribution of superficial, preperitoneal and visceral adipose tissues using ultrasonography and determining the composition of these tissues with ^{1}H NMR in obese patients.
2. The composition of preperitoneal adipose tissue was determined by ^{1}H NMR spectroscopy in obese patients for the first time.
3. This is the first prospective study evaluating the impact of preperitoneal adipose tissue ^{1}H NMR composition on metabolic disturbances in obese patients.
4. This study has identified the independent prognostic factors determining the occurrence of metabolic disturbances in obese patients.

5. PRACTICAL SIGNIFICANCE

1. The present study demonstrates that waist circumference should be measured as the narrowest waist circumference in obese patients.
2. The data of this study provides anthropometric measurement thresholds for metabolic syndrome in obese patients: the cutoff value for weight is 123.90 kg, and the cutoff value for waist circumference at midpoint is 123.40 cm, and the cutoff value for the narrowest waist circumference is 117.60 cm (calculated for an average man's height of 1.79 m and woman's height of 1.65 cm).
3. This study demonstrates that visceral adipose tissue thickness should be measured up to the lumbar vertebra using an ultrasonography in obese patients.
4. The data of this study provides ultrasonographic thresholds for metabolic syndrome in obese patients: the cutoff value for adipose tissue thickness up to the aorta is 8.93 cm, and the cutoff value for adipose tissue thickness up to the lumbar vertebra is 11.53 cm.
5. The present study demonstrates that the composition of superficial and deep subcutaneous adipose tissue should be evaluated separately in obese patients.

6. The present study demonstrates that preperitoneal adipose tissue should be distinguished from visceral adipose tissue in studies concerned with visceral adipose tissue.
7. The data of this study enabled us to build a prognostic model for distinguishing metabolic disturbances in obese patients.

6. STUDY HYPOTHESES

1. There is no essential difference between skin thickness measurements in obese patients with and without metabolic syndrome.
2. Ultrasonography is an effective method for distinguishing obese patients with and without metabolic syndromes.
3. The ^{1}H NMR composition of adipose tissue is different between obese patients with and without metabolic syndrome.

7. MATERIAL AND METHODS

7.1 Subjects and Study Design

The prospective cross-sectional study was approved by the Lithuanian Bioethics Committee on March 12, 2014.

7.2 Recruitment of Subjects

All the subjects included in our study were recruited at the Department of General Surgery of the Republican Vilnius University Hospital, where they were referred for surgical treatment. Inclusion criteria were as follows: aged between 18 and 65 years with the BMI more than 30 kg/m^2. The exclusion criteria for the study were pregnancy, mental diseases, contraindications for operative treatment. All participants signed a form of informed consent.

7.3 Assessment of the Subjects

All the participants underwent the standard examination, which included anthropometric measurements, blood tests, an ultrasonography of

adipose tissue and an ^{1}H NMR of adipose tissue samples according to the study protocol.

The standard anthropometric measurements were those of height and weight, waist measurements (narrowest waist, midpoint between the lowest rib and the iliac crest and above the uppermost border of the iliac crest), hip circumference and skinfolds. The body mass index (BMI) was calculated as an individual's weight (kg) divided by height squared (m^2).

Blood samples for laboratory analyses were taken after a 12 h fasting. Laboratory tests included an assessment of fasting plasma glucose, total cholesterol, HDL, LDL, TG, UA, insulin, leptin, adiponectin concentrations. Blood tests were performed at the Centers of Laboratory Diagnostics of the Republican Vilnius University Hospital and Vilnius University Hospital Santaros Klinikos using standard laboratory methods. A homeostasis model assessment for insulin resistance (HOMA-IR) was used as an indicator for insulin resistance.

All ultrasonographic examinations were performed by a single investigator. Ultrasonography was performed with the Aloka ultrasonography machine (Japan). A modified method of Stolk was used to assess the subcutaneous, preperitoneal and visceral adipose tissue thickness (Figure 1). All adipose tissue measurements were performed on a supine subject following a strict protocol. All measurements were performed three times at the end of the quiet expiration without compression applied to the transducer. The mean values were taken for analysis.

Adipose tissue biopsies were taken at the beginning of surgery from superficial and deep subcutaneous (separated by subsutaneous fascial plane), preperitoneal (located between parietal peritoneum and the transversal fascia) and visceral (omental) adipose tissues, which, in turn, were washed out in a normal saline solution and frozen immediately. Adipose tissue samples were stored in –70°C temperature before the chemical analyses were performed. The adipose tissue samples were homogenized and extracted using a modified Folch

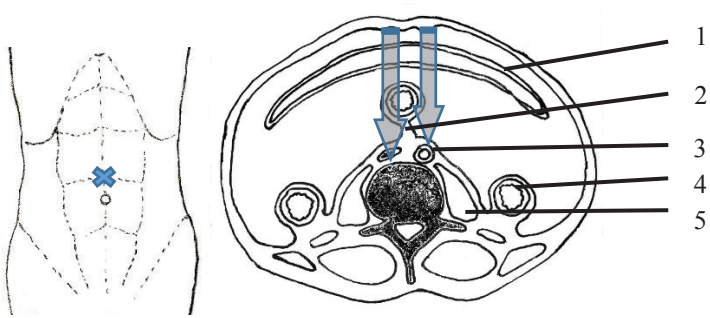

Fig. 1. Visceral adipose tissue thickness measurements by modified method of Stolk. X – position of the ultrasound probe – 2 cm above umbilicus. 1. *omentum majus* 2. *mesenterium* 3. *aorta abdominalis* 4. *colon descendens* 5. *m. psoas major*

extraction procedure. ^{1}H NMR spectra were recorded on a Bruker Ascend 400 spectrometer operating at 9.4 Tesla, corresponding to the resonance frequency of 400 MHz for the ^{1}H nucleus, equipped with a direct detection four-nuclei probe head and field gradients on axis z.

The subjects were classified according to the NCEP:ATPIII criteria into two groups, namely a group with metabolic syndrome and one without metabolic syndrome. High blood pressure was defined as SBP≥130 mmHg and/or DBP≥85 mmHg or higher and/or a patient using antihypertensive drugs; hypertriglyceridemia was defined as TG≥1,7 mmol/l; HDL cholesterolemia was defined as <1,03 mmol/l for men and <1,29 mmol/l for women and/or a patient using anticholesteremic drugs; high fasting plasma glucose was defined as ≥5,6 mmol/l; waist circumference was defined as abnormal >102 cm for men and >88 cm for women. MS was diagnosed for those who had 3 or more of the above criteria.

7.4 Statistical Analysis

The primary effect variable used for power and sample size calculation analysis was the thickness of visceral adipose tissue.

Assuming the mean difference to be 2.3, the SD of 0.3 for groups, and aiming for the power of 0.90 and the type 1 error of 0.05, 29 patients were required in each group.

The Shapiro-Wilk test was used to examine the normality of data. The central tendency and dispersion of normally distributed data were described by mean and standard deviations. Student *t* and Mann-Whitney-Wilcoxon tests were used to compare parametric and nonparametric data, respectively. Pearson or Spearman correlations were computed among all measurements. Multivariate linear regression was used to evaluate the associations of the factors with the MS. Cutoff thresholds were obtained using a univariate analysis with receiver operating characteristic curves (ROC). Multiple logistic regression was used to determine the variables with a major effect on the MS. The odds ratio and 95% CI were calculated using the β coefficient from the logistic regression models.

The statistical software R-commander (version 3.2.4) and Excel (Microsoft Office 365) were used for data analysis. A p value of <0.05 was considered statistically significant.

8. RESULTS

70 patients were recruited in the study between March 2014 and January 2018. Fourty eight participants (68.57%) were female. The mean age of the study population was 42.7±11.56 years. The mean BMI was 41.47±8.42 kg/m^2(Tables 1, 2). In the MS group, participants were heavier and had higher BMIs than in the nonMS group.

Table 1. Baseline characteristics of the study population.

	Men (n=22)	Women (n=48)	*p* value
Age (years)	45.36±9.54	41.47±12.28	0.16
Height (m)	1.79±0.06	1.65±0.05	**<0.001**
Weight (kg)	139.83±22.54	109.66±23.77	**<0.001**
BMI (kg/m^2)	43.79±7.88	40.41±8.53	0.07

BMI – body mass index.

Table 2. Baseline characteristics of the MS and nonMS obese study subjects.

	MS (n=40)	nonMS (n=30)	*p* value
Age (years)	44.0±11.56	40.96±11.54	0.28
Height (m)	1.70±0.09	1.68±0.08	0.28
Weight (kg)	127.71±26.87	107.71±23.44	**0.001**
BMI (kg/m^2)	43.98±8.81	38.12±6.63	**0.002**

MS – metabolic syndrome is present; nonMS – metabolic syndrome is absent; BMI – body mass index.

All three waist circumferences were wider between MS and nonMS groups. The waist-to-hip ratio was significantly higher in the MS group. No difference was observed in skinfold thickness measurements between these groups (Table 3).

Table 3. Anthropometric characteristics of the MS and nonMS obese study subjects.

	MS (n=40)	nonMS (n=30)	*p* value
WC 1 (cm)	124.81±16.20	110.47±13.38	**<0.001**
WC 2 (cm)	132.88±17.13	116.62±15.47	**<0.001**
WC 3 (cm)	133.86±16.93	121.66±13.92	**0.001**
Hip circumference (mm)	125.97±12.80	120.33±12.50	0.07
Waist hip ratio	1.06±0.09	0.97±0.09	**<0.001**
Biceps skinfold thickness (mm)	21.71±9.39	24.10±12.24	0.59
Triceps skinfold thickness (mm)	30.43±13.07	31.61±11.11	0.69
Subscapular skinfold thickness (mm)	41.10±13.38	44.77±15.72	0.48
Suprailiac skinfold thickness (mm)	31.65±12.70	29.84±12.40	0.42
Abdominal skinfold thickness (mm)	45.86±14.04	41.81±12.54	0.23
Mid-thight skinfold thickness (mm)	44.69±21.97	55.98±18.41	0.07

MS – metabolic syndrome is present; nonMS – metabolic syndrome is absent; WC 1 – narrowest waist circumference; WC 2 – waist circumference at the midpoint between the lowest rib and the iliac crest; WC 3 – waist circumference above the uppermost border of the iliac crest.

No difference was found in the ultrasonographic measurements of subcutaneous and preperitoneal adipose tissues between MS and nonMS groups; however, visceral fat thickness was significantly higher in the MS group (Table 4).

Table 4. Ultrasonographic characteristics of the MS and nonMS obese study subjects.

	MS (n=40)	nonMS (n=30)	*p* value
SAT_{epi} (cm)	3.76±1.30	3.55±1.19	0.42
SAT_{umb} (cm)	4.77±1.49	4.52±1.31	0.47
PAT (cm)	2.25±0.77	1.96±0.78	0.13
VAT_{ao} (cm)	10.03±3.68	7.01±2.72	**<0.001**
VAT_{vert} (cm)	12.45±3.96	9.23±2.86	**<0.001**

MS – metabolic syndrome is present; nonMS – metabolic syndrome is absent; SAT_{epi} – subcutaneous adipose tissue thickness in epigastrium; SAT_{umb} – subcutaneous adipose tissue thickness in the paraumbilical area; PAT – preperitoneal adipose tissue thickness; VAT_{ao} – visceral adipose tissue thickness up to the superior wall of the aorta; VAT_{vert} – visceral adipose tissue thickness up to the upper border of the vertebral body.

As subjects were classified using the NCEP:ATPIII criteria into two groups, the significant differences in fasting plasma glucose, TG, HDL, SBP and DBP were as expected. The UA, insulin concentration and HOMA-IR were significantly higher in the MS group. Adiponectin concentration was higher in the nonMS group (Table 5).

Fat tissue samples obtained during the surgery were examined using the ^{1}H NMR. The amount of monounsaturated fatty acids in superficial subcutaneous adipose tissue was significantly higher in the nonMS group. The amount of polyunsaturated fatty acid composition of superficial and preperitoneal subcutaneous adipose tissue was significantly higher in the nonMS group. There was no difference in saturated fatty acid composition between the MS and nonMS groups (Tables 6, 7 and 8).

Table 5. Clinical and laboratory data of the MS and nonMS obese study subjects.

	MS (n=40)	nonMS (n=30)	*p* value
Glu (mmol/l)	6.28±1.36	5.41±0.59	**<0.001**
TG (mmol/l)	2.77±1.31	1.41±0.65	**<0.001**
HDL (mmol/l)	1.11±0.28	1.30±0.28	**0.004**
LDL (mmol/l)	3.67±0.78	3.74±0.80	0.72
Chol (mmol/l)	5.74±1.08	5.71±0.95	0.91
Uric acid (μmol/l)	378.88±95.58	329.33±80.59	**0.021**
Adiponectin (μg/ml)	5.87±2.34	9.39±6.09	**0.002**
Leptin (ng/ml)	43.79±28.42	42.69±31.30	0.70
Insulin (pmol/l)	121.67±59.66	82.17±33.25	**0.003**
HOMA-IR	2.36±1.14	1.55±0.63	**0.001**
SBP (mmHg)	141.27±20.84	125.5±13.73	**<0.001**
DBP (mmHg)	85.41±9.8	79.07±8.26	**0.003**

MS – metabolic syndrome is present; nonMS – metabolic syndrome is absent; Glu – fasting plasma glucose; TG – triglycerides; HDL – high density lipoprotein cholesterol; LDL – low density lipoprotein cholesterol; Chol – total cholesterol; HOMA-IR – a homeostasis model assessment for insulin resistance; SBP – systolic blood pressure; DBP – diastolic blood pressure.

Table 6. The ^{1}H NMR monounsaturated fatty acid composition of adipose tissue triglycerides of the MS and nonMS obese study subjects.

	MS (n=40)	nonMS (n=30)	*p* value
MUFA SAT 1 (%)	48.52±8.41	53.88±7.97	**0.009**
MUFA SAT 2 (%)	50.58±8.58	54.23±6.69	0.11
MUFA PAT (%)	47.58±9.50	52.18±8.84	0.15
MUFA VAT (%)	52.32±8.74	54.56±6.84	0.77

MS – metabolic syndrome is present; nonMS – metabolic syndrome is absent; MUFA – monounsaturated fatty acids; SAT 1 – superficial subcutaneous adipose tissue; SAT 2 – deep subcutaneous adipose tissue; PAT – preperitoneal adipose tissue; VAT – visceral adipose tissue.

Table 7. ^{1}H NMR polyunsaturated fatty acid composition of adipose tissue triglycerides of the MS and nonMS obese study subjects.

	MS (n=40)	nonMS (n=30)	*p* value
PUFA SAT 1 (%)	20.37±6.89	17.26±5.65	**0.025**
PUFA SAT 2 (%)	17.34±6.18	15.92±5.61	0.25
PUFA PAT (%)	20.40±6.65	15.91±6.39	**0.014**
PUFA VAT (%)	17.53±5.40	16.45±4.25	0.37

MS – metabolic syndrome is present; nonMS – metabolic syndrome is absent; PUFA – polyunsaturated fatty acids; SAT 1 – superficial subcutaneous adipose tissue; SAT 2 – deep subcutaneous adipose tissue; PAT – preperitoneal adipose tissue; VAT – visceral adipose tissue.

Table 8. ^{1}H NMR saturated fatty acid composition of adipose tissue triglycerides of the MS and nonMS obese study subjects.

	MS (n=40)	nonMS (n=30)	*p* value
SFA SAT 1 (%)	31.08±5.04	28.98±4.83	0.18
SFA SAT 2 (%)	32.08±7.90	30.31±5.53	0.55
SFA PAT (%)	32.05±5.67	32.01±5.74	0.97
SFA VAT (%)	30.21±6.93	29.04±3.99	0.83

MS – metabolic syndrome is present; nonMS – metabolic syndrome is absent; SFA – saturated fatty acids; SAT 1 – superficial subcutaneous adipose tissue; SAT 2 – deep subcutaneous adipose tissue; PAT – preperitoneal adipose tissue; VAT – visceral adipose tissue.

VAT thickness, measured with ultrasonography in the MS group, showed a statistically significant linear correlation with height, weight, BMI, the narrowest waist circumference, waist circumference at the midpoint, waist circumference above the uppermost border of the iliac crest, hip circumference, waist-hip ratio, suprailiac and abdominal skinfold thicknesses, SBP and DBP, glucose and UA concentrations in the blood, pancreatic β-cell function (r=0.32–0.81). VAT thickness negatively correlated with SFA concentration in PAT and VAT (r=-0.53–-0.39).

SAT thickness in the epigastrium, measured with ultrasonography in the MS group, showed a statistically significant linear correlation

with BMI, waist circumference above the uppermost border of the iliac crest, the triceps, subscapular, abdominal and mid-thigh skinfold thicknesses, HDL, leptin concentration, pancreatic β-cell function (r=0.33–0.61) and had a negative correlation with height and TG (r=-0.47–-0.39). SAT thickness in the epigastrium, measured using ultrasonography in the nonMS group, showed a statistically significant linear correlation with BMI, the narrowest waist circumference, hip circumference, biceps, suprailiac and mid-thigh skinfold thicknesses, leptin and insulin concentrations (r=0.39–0.62) and showed a negative correlation with LDL and total cholesterol concentration in blood (r=-0.40–-0.39).

SAT thickness in the supraumbilical region, measured using ultrasonography in the MS group, showed a statistically significant linear correlation with hip circumference, subscapular, iliac and mid-thigh skinfold thicknesses, leptin concentration in the blood (r=0.39–0.79) and showed a negative correlation with age, height, glucose and TG concentrations in the blood (r=-0.43–-0.34). SAT thickness in the supraumbilical region, measured using ultrasonography in the nonMS group, showed a statistically significant negative linear correlation with deep SAT SFA concentration (r=-0.41)

PAT thickness, measured using ultrasonography in the MS group, showed a statistically significant linear correlation with waist circumference and UA concentration in the blood (r=0.32–0.40). PAT thickness, measured using ultrasonography in the nonMS group, showed a statistically significant linear correlation with weight, triceps, subscapular, suprailiac, abdominal and mid-thigh skinfold thicknesses, leptin and insulin concentrations and HOMA-IR (r=0.38–0.46). It showed a negative correlation in the same group with age (r=-0.48).

A fatty acid concentration in the adipose tissue showed multiple statistically significant linear correlations with anthropometric, blood test and clinical determinants in the group with MS (Table 9). SFA concentration in deep SAT showed a negative correlation with almost all of them except the HDL, UA and insulin concentrations in the blood.

Table 9. Linear correlations of fatty acid ^{1}H-NMR composition with anthropometric, blood test and clinical determinants in the group with MS.

Determinant	Fatty acids	r	*p* value
Weight	MUFA PAT	0.33	0.042
	SFA PAT	-0.38	0.017
	SFA VAT	-0.36	0.025
BMI	SFA SAT 2	-0.38	0.018
	SFA PAT	-0.39	0.019
	SFA VAT	-0.38	0.017
WC1	SFA SAT 2	-0.35	0.034
	SFA PAT	-0.37	0.019
	SFA VAT	-0.38	0.016
WC2	SFA SAT 1	-0.37	0.02
	SFA SAT 2	-0.41	0.011
	SFA PAT	-0.41	0.009
	SFA VAT	-0.47	0.002
WC3	SFA SAT 2	-0.35	0.034
	SFA PAT	-0.37	0.019
	SFA VAT	-0.38	0.016
Hip circumference	SFA SAT 2	-0.35	0.032
Waist-hip ratio	MUFA VAT	0.32	0.046
	SFA PAT	-0.35	0.028
	SFA VAT	-0.34	0.034
Glucose	MUFA SAT 2	0.34	0.035
	SFA SAT 2	-0.34	0.038
HDL	MUFA SAT 2	-0.34	0.037
Uric acid	MUFA SAT 1	0.36	0.025
	MUFA SAT 2	0.44	0.005
Insulin	MUFA PAT	0.37	0.019
	SFA VAT	-0.33	0.039
HOMA-IR	MUFA PAT	0.37	0.022
	SFA SAT 2	-0.34	0.038
	SFA PAT	-0.33	0.038

WC 1 – narrowest waist circumference; WC 2 – waist circumference at the midpoint between the lowest rib and the iliac crest; WC 3 – waist circumference above the uppermost border of the iliac crest; MUFA – monounsaturated fatty acids; SFA – saturated fatty acids; SAT 1 – superficial subcutaneous adipose tissue; SAT 2 – deep subcutaneous adipose tissue; PAT – preperitoneal adipose tissue; VAT – visceral adipose tissue; HDL – high density lipoprotein cholesterol; HOMA-IR – a homeostasis model assessment for insulin resistance.

SFA in all adipose tissue layers showed a strong linear correlation with waist circumference at the midpoint. SFA concentration in the PAT layer showed a negative correlation with weight, BMI, the narrowest waist circumference, waist circumference at the midpoint, waist circumference above the uppermost border of the iliac crest, waist-hip ratio, insulin concentration in the blood and HOMA-IR. There were no statistically significant correlations between the studied determinants and PUFA concentration in the adipose tissue layers.

The fatty acid concentration in the adipose tissue showed multiple statistically significant linear correlations with anthropometric, blood test and clinical determinants in the nonMS group (Table 10). MUFA and PUFA in the layers of adipose tissue showed a correlation with the triceps, subscapular and mid-thigh skinfold thicknesses. Truncal skinfold thicknesses showed a positive correlation with MUFA and negative concentration with PUFA concentrations in superficial SAT. Peripheral adipose tissue in the extremities showed a positive correlation with PUFA concentration in deep SAT. The triceps and mid-thigh skinfold thicknesses showed a positive correlation with PUFA concentration in VAT. SFA concentration in the deep SAT, PAT and VAT showed a negative correlation with mid-thigh skinfold thickness.

PUFA concentration in the deep SAT showed a positive correlation with adiponectin and leptin concentration in the blood.

SFA concentration in deep SAT showed a negative correlation with insulin concentration in the blood, HOMA-IR and pancreatic β-cell function.

In a ROC analysis, we further defined the anthropometric, ultrasonographic, adipose tissue ^{1}H NMR and blood test determinants, which were statistically significant for the MS prediction in obese patients and determined the optimal cutoff values (Table 11).

Table 10. Linear correlations of fatty acid ^{1}H-NMR composition with anthropometric, blood test and clinical determinants in the group without MS.

Determinant	Fatty acids	R	*p* value
Age	MUFA SAT 1	-0.38	0.039
	MUFA SAT 2	-0.47	0.009
	SFA SAT 2	0.46	0.011
Weight	SFA SAT 2	-0.43	0.018
BMI	PUFA SAT 2	0.43	0.018
WC1	MUFA SAT 1	0.41	0.025
	SFA SAT 1	-0.37	0.045
	SFA PAT	-0.39	0.034
WC2	MUFA SAT 1	0.47	0.008
	SFA SAT1	-0.40	0.027
Biceps skinfold thickness	PUFA SAT 2	0.38	0.036
Triceps skinfold thickness	PUFA SAT 2	0.40	0.03
	PUFA VAT	0.43	0.02
Subscapular skinfold thickness	MUFA SAT 1	0.51	0.004
	PUFA SAT 1	-0.38	0.038
Mid-thigh skinfold thickness	MUFA SAT 2	-0.47	0.048
	MUFA PAT	-0.44	0.035
	MUFA VAT	-0.44	0.038
	PUFA SAT 2	0.57	0.005
	PUFA VAT	0.44	0.034
Adiponectin	PUFA SAT 1	0.50	0.005
	PUFA SAT 2	0.42	0.022
Leptin	PUFA SAT 2	0.54	0.002
Insulin	SFA SAT 2	-0.43	0.017
HOMA-IR	SFA SAT 2	-0.41	0.024
%B	SFA SAT 2	-0.45	0.013

WC 1 – narrowest waist circumference; WC 2 – waist circumference at the midpoint between the lowest rib and the iliac crest; MUFA – monounsaturated fatty acids; PUFA – polyunsaturated fatty acids; SFA – saturated fatty acids; SAT 1 – superficial subcutaneous adipose tissue; SAT 2 – deep subcutaneous adipose tissue; PAT – preperitoneal adipose tissue; VAT – visceral adipose tissue; HOMA IR – a homeostasis model assessment for insulin resistance.

Table 11. An ROC analysis on anthropometric, ultrasonographic, adipose tissue fatty acid composition and blood test data to predict metabolic syndrome in obese patients.

Determinant	AUC (CI)	Cutoff values (AUC CI)
Weight (kg)	0.73 (0.60, 0.90)	123.90 (0.60, 0.90)
BMI (kg/m^2)	0.71 (0.59, 0.84)	43.86 (0.59, 0.84)
WC 1 (cm)	0.75 (0.64, 0.87)	117.60 (0.70, 0.80)
WC 2 (cm)	0.76 (0.64, 0.88)	123.40 (0.72, 0.77)
VRA_{ao} (cm)	0.74 (0.62, 0.86)	8.93 (0.62, 0.77)
VRA_{vert} (cm)	0.74 (0.63, 0.86)	11.53 (0.60, 0.80)
Insulin (pmol/l)	0.71 (0.59, 0.83)	-
HOMA-IR	0.73 (0.61, 0.85)	-
MUFA SAT 1 (%)	0.67 (0.54, 0.80)	52 (0.62, 0.70)
PUFA PAT (%)	0.67 (0.55, 0.80)	20 (0.51, 0.77)

AUC – area under the curve; CI – confidence interval; BMI – body mass index; WC 1 – narrowest waist circumference; WC 2 – waist circumference at the midpoint between the lowest rib and the iliac crest; VAT_{ao} – visceral adipose tissue thickness up to superior wall of aorta; VAT_{vert} – visceral adipose tissue thickness up to the upper border of vertebral body; HOMA-IR – a homeostasis model assessment for insulin resistance; MUFA – monounsaturated fatty acids; PUFA – polyunsaturated fatty acids; SAT 1 – superficial subcutaneous adipose tissue; PAT – preperitoneal adipose tissue; "-" – non significant.

In order to predict MS, we measured its correlation with multiple anthropometric, ultrasonographic, adipose tissue ^{1}H NMR data and blood test determinants. The parameters that had strong correlation with MS and uncorrelated with each other were used to build an MS-predicting multiple linear regression model. Our study showed that in all obese patients under the study adiponectin, VAT thickness measured using ultrasonography up to the upper border of the vertebral body and MUFA concentration in superficial SAT are independent determinants of MS (Table 12). The odds ratio was also calculated (Table 13).

Table 12. Indices in the MS predicting model in obese patients

Predicting parameter	*B*	*p*	R^2
Adiponectin	-0.27±0.11	**0.02**	0.34
VAT_{vert}	0.29±0.1	**0.004**	
MUFA SAT 1	-1.48±0.5	**0.004**	

VAT_{vert} – visceral adipose tissue thickness up to the upper border of vertebral body; MUFA – monounsaturated fatty acids; SAT 1 – superficial subcutaneous adipose tissue; β – beta coefficient; R^2 – determination coefficient.

Table 13. The odds ratio for adiponectin, VAT thickness measured using ultrasonography up to the upper border of the vertebral body and MUFA concentration in superficial SAT to predict MS in obese patients.

Predicting parameter	Odds ratio	95% CI
Adiponectin	0.76	0.59, 0.92
VAT_{vert}	1.34	1.12, 1.68
MUFA SAT 1	0.24	0.08, 0.57

VAT_{vert} – visceral adipose tissue thickness up to the upper border of vertebral body; MUFA – monounsaturated fatty acids; SAT 1 – superficial subcutaneous adipose tissue; CI – confidence interval.

The final regression model was:

$$P\,(MS=1)=\frac{e^{6{,}53-0{,}27*Adiponektinas\ (\mu g/ml)+0{,}29*VRA_{sl}\ (cm)-1{,}43*MNRR\ PRA1\ (\%)}}{1+e^{6{,}53-0{,}27*Adiponektinas\ (\mu g/ml)+0{,}29*VRA_{sl}\ (cm)-1{,}43*MNRR\ PRA1\ (\%)}}$$

The regression model predicted MS in 85.5 % of all patients. An ROC curve analysis on the regression model to predict MS reached the sensitivity and specificity of 87.2% and 83.3%. The area under the ROC curve was 0.88 (95% CI 0.79, 0.97).

9. STUDY LIMITATIONS

Our study has limitations that need to be mentioned. First, our findings are limited by the small sample size, especially in the nonMS men's group. A greater number of samples could lead to a higher generalization of our results in the obese population. Second, the BMI and weight were different in the MS and nonMS groups in the study. However, after data correction for these variables and in regression models, the BMI and weight did not have any significant impact on the determinants of metabolic health or the prediction of MS. Third, we studied only the Lithuanian obese population. Thus, population-based studies are therefore required to generalize our findings.

10. DISCUSSION

One of the main goals of this research was an attempt to find a way to predict metabolic disturbances in obese individuals. While not all results were significant, the overall direction of results showed trends that could be helpful in learning about who is more likely to be metabolically healthy or unhealthy if obese. To the best of our knowledge, this study is the first that complexisively examined the distribution of subcutaneous, preperitoneal and visceral adipose tissue by means of an ultrasonography and its composition using ^{1}H-NMR in the obese population. To date, no work was published on the ^{1}H-NMR composition of preperitoneal adipose tissue or its impact on metabolic disturbances in obese individuals.

Our data suggests that the MS group has a lower BMI, WC and WHR than nonMS individuals. Schröder (Schröder et al. 2014) found that the MHO were younger, more highly educated, smoked more, adhered to a less healthy diet, possessed lower BMIs and lower WCs than the MAO phenotype group. However, there is no direct link between BMI and metabolic disturbances. Our study contributes that weight and BMI did not have any direct impact on the emergence of MS.

WC has a strong correlation with cardiometabolic disturbances and is an accurate surrogate marker for visceral adiposity (Borruel & Molto 2014). In our study, the WCs of all men were more than 102 cm, and for women – more than 88 cm. Furthermore, WHR exceeded the WHO recommended values (1,11±0,06 in men and 0,98±0,09 in women). We can conclude that all participants in our study had central adiposity. However, the metabolic activity of SAT and VAT is different. WC and WHR cannot differentiate between these two fat depots in the abdominal area; hence, more accurate markers should be used.

Our present results indicate that there is no difference between skinfolds in the MS and nonMS groups in the obese population. However, the triceps and mid-thigh skinfolds were thicker in women in comparison with men in both the MS and nonMS groups. We have faced the same technical problems as Gray (Gray et al. 1990) did while performing anthropometric measurements. It was impossible to measure abdominal (BMI $\geq$35 kg/m^2) and thigh (BMI $\geq$40 kg/m^2) skinfold thickness in some study participants. On the one hand, it was difficult to raise an adequate skinfold for measurement, and on another – the used caliper could not accommodate some skinfolds in obese individuals.

In our study, glucose, TG and insulin concentrations were higher, and HDL was lower in the MS group. Our data was in agreement with the NCEP-ATPIII recommended values for MS evaluation. Several studies have shown that MHO individuals have lower TG and higher HDL concentrations (Brochu et al. 2001; Karelis et al. 2005; Kim et al. 2013; Manu et al. 2012) and that they have better insulin sensitivity; therefore, lower glucose and insulin concentrations in serum (Brochu et al. 2001; Karelis et al. 2005; Stefan et al. 2008). We observed that adiponectin serum concentration was higher in the nonMS group and there were no differences in leptin serum concentration between MS and nonMS groups. These findings are consistent with the data of various authors who had previously conducted metabolical health research in obesity (Alfadda 2014; Eglit et al. 2013). Our study suggests that patients with MS have a higher UA concentration in the

serum than nonMS individuals. It is in consistency with the previous report of Mangge (Mangge et al. 2013). He found that the UA levels in serum was a significant predictor of obesity with metabolic disturbances in juveniles and adults. It was shown in other studies that the UA concentration in serum was independently associated with the presence of metabolic and proinflammative disorders in MS (Tamba et al. 2008; Nagahama et al. 2015; Li et al. 2015; Chen et al. 2017). There was no difference in serum UA concentration between MS and nonMS groups in men, although it almost reached statistical significance between MS and nonMS women ($p=0.052$) in our study. Iacobellis et al. (Iacobellis et al. 2005) suggested a UA concentration in serum <333 μmol/l in women and <416 μmol/l in men as a threshold for differentiating MHO and MAO phenotypes. Primeau et al. (Primeau et al. 2011) reviewed 15 studies that report MHO prevalence and the UA concentration in serum as the predicting factors of metabolic health were used only in the study of Iacobellis et al. HOMA-IR was statistically different in our study groups and reached the mean of 2.36±1.14 in the group with MS. Qu (Qu et al. 2011) suggested HOMA-IR <2.6 as a normal range, HOMA-IR 2.6-3.8 as a transitional range without insulin resistance and HOMA-IR >3.8 as the best cutoff value for the definition of insulin resistance. However, these reference values are calculated for Mexican Americans. In fact, there are other HOMA-IR thresholds suggested: ≤1,95 (Karelis et al. 2004; Shin et al. 2006; Jennings et al. 2008), ≤2,5 (Kuk & Ardern 2009), ≤2,7 (Karelis et al. 2005), <2,8 (Bonora et al. 1998), <5,1 (Wildman et al. 2008; Messier et al. 2010). The lack of standardized reference range for the HOMA-IR, adipokines and UA shows that more prospective population-based studies should be conducted in the future.

We used a modified method of Stolk to assess subcutaneous, preperitoneal and visceral adipose tissue thickness by ultrasonography. In our systematic literature review we concluded that SAT and VAT should be measured 1-2 cm above the umbilicus and VAT should be measured up to the anterior wall of aorta or up to the lumbar vertebra in obese patients (Buckus & Brimas 2018). SAT and PAT thickness in

epigastrium were measured 2 cm below the xiphoid process. PAT was measured as a distance between *linea alba* and the peritoneum of the liver. Kim et al. (Kim et al. 2004) reported that the measurements of PAT thickness are unreliable because of the irreproducibility or from differences in measuring sites. Even though it is difficult to evaluate the exact ultrasound probe placement site, our study shows that PAT is involved in the change of metabolic health in obesity. We believe more prospective studies should be done to find the best measurement site for PAT and to verify it using CT or MRT.

Our data suggests that SAT was thicker in women and VAT was thicker in men. In the nonMS group, VAT thickness measured using ultrasonorgaphy was less than in the MS group. This was still the case after correcting the data for sex, body weight and BMI (VAT_{ao} $p<0.039$, VAT_{vert} $p=0.042$). Therefore, we suggest that VAT plays a significant role in the evaluation of MS in obese population.

In the present study, pancreatic β-cell function had a significant negative correlation with VAT thickness and positive correlation with SAT thickness in obese individuals with MS. Therefore, this data suggests that SAT has a protective role against the evaluation of carbohydrate metabolism disturbances.

Our research proved that VAT thickness measured using ultrasonography has a strong correlation with the determinants of metabolic health, such as WC, WHR, abdominal and suprailiac skinfolds, SBP and DBP, glucose and UR concentrations in serum in obese individuals. The same correlations were observed in both sexes with MS. Our data agreed with the previous reports where VAT thickness correlated with all components of MS (Kim et al. 2004; Guldiken et al. 2006; Sogabe et al. 2012; Miranda Prado 2012; Soattin et al. 2013; Roever et al. 2016) and ultrasonography was suggested as a diagnostic tool for MS diagnosis (Ribeiro-Filho et al. 2001; Meriño-Ibarra et al. 2005; Chiba et al. 2007; Vasilescu et al. 2011). Our present study suggests that VAT thickness measurements, taken using ultrasonography, are a useful tool for the evaluation of VAT distribution and accompanied metabolic disturbances in the obese population.

The overall sensitivity of an ultrasonography up to the aorta to detect MS was 78%, specificity 60%, and the summary area under the ROC curve was 0,74 (95% CI 0.62-0.86) and sensitivity up to the lumbar vertebra to detect MS was 60%, specificity 80%, and the summary under the ROC curve was 0,69 (95% CI 0.63-0.86). We further examined the lower cutoffs for the detection of MS and found that VAT thickness up to the aorta and VAT thickness up to the lumbar vertebra measured using ultrasonography was 8.93 cm and 11.53 cm, respectively.

VAT thickness was measured using various techniques in other studies. Therefore, it is very difficult to compare the results, as measurements are performed in different ethnical populations and in the groups with different weight or BMI values. Kim et al. (Kim et al. 2004) suggested the cutoff value of VAT for predicting the presence of MS to be 4.76 cm and 3.55 cm in men and women, respectively. However, the study was performed only within the Korean population. Leite et al. (Leite et al. 2002) suggested the cutoff value of intra-abdominal thickness to predict risk factors for CVD to be 7 cm for moderate risk group and 9 cm for men and 8 cm for women in high-risk groups. Thus, the exact cutoff values for predicting metabolic disturbances are warranted in longitudinal studies.

PAT thickness did not show significant difference between our study groups. However, it had a strong correlation with the triceps, subscapular, suprailiac, abdominal and mid-thight skinfold thicknesses in the nonMS women group and with the subscapular skinfold thickness in MS men group. Excessive energy is stored in SAT at first. When the personal fat threshold is reached, the lipid excess is deposited as an ectopic fat (Gesta & Kahn 2017; Cuthbertson et al. 2017; Dobson et al. 2016). PAT is analyzed as a part of VAT in the literature (Fukuda et al. 2015). Our data suggests that PAT is a distinctive fat depot with different metabolic activity and fat deposition pattern.

Needle aspiration biopsy was the preferable method for obtaining adipose tissue samples in most of the human adipose tissue fatty acid composition studies. However, adipose tissue samples were taken

from different sites, e.g., the thighs, buttocks, SAT from the abdominal wall, VAT as omental adipose tissue etc. (Malcom 1989; Calder et al. 1992; Tjønneland & Overvad 1993; Phinney et al. 1994; Thomas et al. 1998; Pedersen et al. 2000; Abraitienė et al. 2008; Lundbom et al. 2010; Giuliani et al. 2014). That is why the results could not be generalized in most cases. Diet, ethnicity, lifestyle, the region of residence and age of the individual could affect the composition of adipose tissue fatty acids. To our best knowledge, this is the first study where adipose tissue fatty acid composition from four depots (superficial SAT, deep SAT, PAT and VAT) in the obese population is examined. There is a lack of information about the exact fatty acid composition in these specific depots. Some studies have compared the fatty acid composition of the superficial and deep SAT (Lundbom et al. 2013); however, there is no such studies on the superficial or deep SAT and VAT composition differences. We did not find any studies on the fatty acid composition of PAT in our systematic review.

Our data suggests that the SAT and VAT fatty acid composition of MUFA, PUFA and SFA is in consistency with other authors' data (Garaulet et al. 2001). Men had more MUFA, and women had more SFA in PAT in our study. SFA concentration was bigger in PAT in comparison with superficial SAT (the difference was observed in all research participants and in the MS group), although the difference was not statistically significant. PAT has a significantly bigger concentration of SFA than VAT. It could be related to the differences of SFA/MUFA ratio, which, in turn, is related to *de novo* lipogenesis, desaturase activity and a turnover of fatty acids (Roberts et al. 2009; Sjögren et al. 2008; Votruba & Jensen 2007). However, it is still unknown how these processes impact the amount of SFA and MUFA in adipose tissue. Lundbom et all. (Lundbom et al. 2013) proposed that more saturated adipose tissue has a bigger metabolic activity. We observed a statistically significant difference in SFA concentration in superficial SAT, PAT and VAT in the nonMS group. It was proposed earlier that PAT has less-proinflammatory properties than SAT and VAT in obese individuals (Silva et al. 2017) and that PAT has a different lipolytic activity in comparison with superficial SAT and VAT (Enevoldsen et

al. 2001). Our research proved that PAT is a distinct fat depot with different metabolic activity and fatty acid composition, although it is an internal fat depot.

In the present study, we observed a statistically significant difference in superficial SAT MUFA (p=0.009), PUFA (p=0.025) and PAT PUFA (p=0.014) concentrations between MS and nonMS groups. The same significance was observed after correcting the data for sex, age, weight, height and WC at the midpoint between the lowest rib and the iliac crest (superficial SAT MUFA p=0.003 and PUFA p=0.03, PAT PUFA p=0.046). Therefore, we suggest that the composition of fatty acids in superficial SAT and PAT is suitable for studying metabolic health in the obese population.

In the present study, we observed a statistically significant difference in superficial SAT MUFA (p=0.005), PUFA (p=0.004) and PAT MUFA (p=0.0046), PUFA (p=0.011) concentrations between MS and nonMS groups in women. The same significance was observed after correcting the data for age, weight, height, BMI and WC at the midpoint between the lowest rib and the iliac crest (superficial SAT MUFA p=0.0046, PUFA p=0.008 and PAT MUFA p=0.031, PUFA p=0.027). Therefore, we suggest that the composition of fatty acids in superficial SAT and PAT is suitable for studying metabolic health in the obese women population.

In the present study, we found that deep SAT SFA and MUFA concentrations have a significant relationship with the MS determinants in MS group. We did not find the same correlation with superficial SAT or PUFA concentrations in different fat depots. However, SFA, MUFA and PUFA concentrations in superficial and deep SAT depots significantly correlate with anthropometric and laboratory data in the nonMS group. PUFA concentration in the superficial SAT correlates with leptin and adiponectin concentrations in serum. SFA concentration in deep SAT has a negative correlation with insulin concentration in the serum, HOMA-IR and β-cell function. The thickness of different skinfolds positively correlated with MUFA and PUFA concentrations in the superficial and deep SATs in the nonMS group. Enevoldsen et al. (Enevoldsen et al. 2001) suggest that superficial and deep SATs *in*

vivo have different lipolytic activities in humans. Kim et al. propose that deep SAT is closely related with obesity-induced metabolic complications (Kim et al. 2016). However, Walker et al. (Walker et al. 2014) suggested that superficial SAT has independent effects that associate with the metabolic complications of obesity. Therefore, the exact association between SAT layers and the complications of obesity is still unclear. Our data suggests that deep SAT correlates with the determinants of the adverse effects of obesity. We suggest that more prospective studies should be conducted to evaluate the impact of SAT layers on metabolic health in the obese population.

In the present study, UA concentration in serum had a positive correlation with MUFA and a negative correlation with SFA concentrations in deep SAT and VAT in the women's group with MS. The opposite was observed in the nonMS women's group – a positive correlation with PUFA and SFA concentrations in VAT and a negative correlation with MUFA concentration in deep SAT and VAT. UA concentration in the serum has an association with the adverse effects of central adiposity; therefore, its relations with fatty acid patterns in fat depots suggests that adipose tissue composition plays a significant role in the metabolic health of the obese population.

Adiponectin, insulin and UA concentrations in the serum, HOMA-IR, BMI, weight, MUFA or PUFA concentrations in superficial SAT, PUFA concentration in PAT, VAT thickness measured using ultrasonography up to the aorta or VAT thickness up to the lumbar vertebra were found as variables that had a strong correlation with MS and uncorrelated with each other. The variables used for the diagnosis of MS were not included in the analysis. Based on P values, four linear regression models with MS as a dependent variable in the studied population were performed. The linear regression models showed that in all obese patients under the study, adiponectin concentration in serum, VAT thickness measured using ultrasonography up to the upper border of the vertebral body and MUFA concentration in superficial SAT are independent determinants of MS. The best regression model predicted MS in 85.5% of all patients. An ROC curve analysis on the regression model to predict MS reached the sensitivity and specificity

of 87.2% and 83.3%, AUC 0,88 (CI 95% 0.79, 0.97). For every 1 cm increase in VAT thickness measured with an ultrasonoraphy up to the upper border of the vertebral body, the obese patient had a 1.34-fold (95% CI, 1.12, 1.68) greater MS risk. For every 1 μg/ml increase in adiponectin concentration, the obese patient had a 1.3-fold (95% CI, 0.59, 0.92), and for every 0.1% increase in MUFA concentration in superficial SAT – a 4.17-fold (95% CI, 0.08, 0.57) lower MS risk.

In the final linear regression model, weight and BMI did not have a significant impact on the prediction of MS. We believe these two variables do not have any essential impact on the evaluation of MS in the obese population. However, larger population-based studies are required to confirm our findings.

Despite the increased interest in the metabolically normal obesity, there are no unique criteria to define metabolic health (Primeau et al. 2011; Roberson et al. 2014). A lack of knowledge of the determinants and molecular mechanisms associated with MHO indicates the need to investigate the composition and distribution of adipose tissue and its association with metabolic disturbances. A better understanding of the underlying causes of metabolic health would help to distinguish the obesity phenotypes, aid in the development of new preventive strategies for those who are at a greater risk of developing metabolic abnormalities and prevent any excessive dieting, pharmacological and surgical treatments in healthy obese individuals. Future population-based studies should be performed to consolidate the adiponectin concentration in serum, VAT thickness measured using ultrasonography up to the upper border of the lumbar vertebra and the MUFA concentration in superficial SAT as the relevant predictors of metabolic syndrome in the obese population.

11. CONCLUSIONS

1. The thickness of the visceral adipose tissue measured using ultrasonographic and anthropometric determinants (waist circumference and waist hip ratio) were significantly higher in the group of obese patients with metabolic syndrome.
2. The amount of polyunsaturated fatty acids in superficial subcutaneous adipose tissue and in preperitoneal adipose tissue were significantly higher, while that of monounsaturated fatty acids in superficial subcutaneous tissue was significantly lower in the group of obese patients with metabolic syndrome.
3. Adiponectin concentration, visceral adipose tissue thickness measured using ultrasonography up to the lumbar vertebra and monounsaturated fatty acid concentration in superficial subcutaneous adipose tissue are independent prognostic factors in metabolic syndrome determination in obese patients.

12. FURTHER DIRECTIONS

Adipose tissue fatty acid composition and its relationship with adipose tissue metabolism will be evaluated in further studies.

The morphological structure of adipose tissue will be identified by running electron microscopy scans, conducting genetic research and carrying out studies of proinflammatory determinants.

Further population studies should be done to evaluate the significance of the prognostic model and the thresholds of its determinants.

Patients without metabolic disturbances should be evaluated in long-term follow-up studies so as to determine their metabolic health changes.

13. REFERENCES

A list of references is provided in the manuscript of the Dissertation.

BRIEF INFORMATION ABOUT THE AUTHOR

Name	Bronius Buckus
Date of birth	1982.10.31
Email	buckus.bronius@gmail.com

PROFESSIONAL POSITION, WORKPLACE, WORK EXPERIENCE

Since 2017	Endoscopy doctor, Republican Vilnius University Hospital, 29 Šiltnamių Str., Vilnius, Lithuania
Since 2015	Echoscopy doctor, Republican Vilnius University Hospital, 29 Šiltnamių Str., Vilnius, Lithuania
Since 2013	General surgeon, Republican Vilnius University Hospital, 29 Šiltnamių Str., Vilnius, Lithuania
Since 2012	Lecturer, Clinic of Gastroenterology, Nephro-Urology and Surgery, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University
2009–2013	Medical doctor, Republican Vilnius University Hospital, 29 Šiltnamių Str., Vilnius, Lithuania
2008–2011	Lecturer, Department of Anatomy, Histology and Anthropology, Faculty of Medicine, Vilnius University
2004–2008	Laboratory technician, Department of Anatomy, Histology and Anthropology, Faculty of Medicine, Vilnius University

EDUCATION

2017.05	Introductory courses "Endoscopy of the Gastrointestinal Tract," Vilnius University, Faculty of Medicine
2013.06	Professional qualification of a general surgeon, Vilnius University, Faculty of Medicine
2013.05	Introductory courses "Abdominal Ultrasound," Vilnius University, Faculty of Medicine
2008.06	Professional qualification of a medical doctor, Vilnius University, Faculty of Medicine
2007.06	Master's degree in Medicine, Vilnius University, Faculty of Medicine

PUBLICATIONS ON THE SUBJECT OF THE DOCTORAL DISSERTATION

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3. Aurelija Smalenskaitė, Bronius Buckus, Stasys Tautkus, Aldona Beganskienė, Gintautas Brimas, Aivaras Kareiva. Determination of fatty acid composition of adipose tissue by ^{1}H NMR spectroscopy.

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4. Bronius Buckus, Gintautas Brimas, Aurelija Smalenskaitė, Aldona Beganskienė, Aivaras Kareiva. Evaluation of adipose tissue composition by ^{1}H NMR and it's relationship to ultrasonoscopic measurements in obese patients.

The 8th Congress of the Baltic Association of Surgeons, 2015.09.10–12, Tallinn, Estonia

5. Bronius Buckus, Gintautas Brimas, Žygimantas Juodeikis, Aurelija Smalenskaitė, Aldona Beganskienė, Aivaras Kareiva. Evaluation of adipose tissue composition by ^{1}H NMR and it's relationship with ultrasonoscopic measurements in obese patients.

The 3rd International Conference "Evolutionary Medicine: Prie-existing Mechanisms and Patterns of Current Health Issues," 2016.06.14–19, Vilnius, Lithuania

6. Bronius Buckus, Gintautas Brimas, Aivaras Kareiva. Evaluation of adipose tissue distribution by ultrasonography and it's relationship to metabolic disturbances in obese patients.

The 18th International EFSUMB Congress, 2016.10.26–29 Leipzig, Germany

7. Bronius Buckus, Gintautas Brimas, Aivaras Kareiva. Evaluation of adipose tissue distribution by ultrasonography and it's relationship to metabolic disturbances in obese patients.

SUMMARY OF THE DISSERTATION IN LITHUANIAN

SUTRUMPINIMAI

AKS – arterinis kraujo spaudimas
CD – cukrinis diabetas
DTL-ch – didelio tankio lipoproteinų cholesterolis
IR – rezistentiškumas insulinui
JA – juosmens apimtis
JKS – juosmens klubų santykis
KM – kūno masė
KMI – kūno masės indeksas
KT – kompiuterinė tomografija
^{1}H-MBR – vandenilio jonų magnetinių branduolių rezonansas
MetS – metabolinis sindromas
MNRR – mononesočiosios riebalų rūgštys
MTL-ch – mažo tankio lipoproteinų cholesterolis
PNRR – polinesočios riebalų rūgštys
PRA – poodinis riebalinis audinys
PreRA – preperitoninis riebalinis audinys
RA – riebalinis audinys
RR – riebalų rūgštys
SRR – sočiosios riebalų rūgštys
ŠR – šlapimo rūgštis
TAG – trigliceridai
UGT – ultragarsinis tyrimas
VRA – visceralinis riebalinis audinys

1. DARBO TIKSLAS

Nustatyti riebalinio audinio pasiskirstymo ir sudėties ypatumus, leidžiančius prognozuoti metabolinius sutrikimus nutukusiems pacientams.

2. DARBO UŽDAVINIAI

1. Tiriant antropometriniais ir ultragarsiniais metodais, nustatyti metaboliniu sindromu sergančių ir juo nesergančių nutukusių pacientų riebalinio audinio (poodinio paviršinio, poodinio giliojo, preperitoninio ir centrinio) pasiskirstymo skirtumus.
2. Tiriant ^{1}H-MBR spektroskopijos metodu, nustatyti metaboliniu sindromu sergančių ir juo nesergančių nutukusių pacientų riebalinio audinio (poodinio paviršinio, poodinio giliojo, preperitoninio ir centrinio) sudėties skirtumus.
3. Įvertinti riebalinio audinio pasiskirstymo ir sudėties ypatumų ryšį su metaboliniu sindromu ir nustatyti nepriklausomus prognostinius veiksnius, lemiančius metabolinių sutrikimų atsiradimą nutukusiems pacientams.

3. DARBO NAUJUMAS

1. Nutukusių ligonių periferinio, preperitoninio ir centrinio riebalinio audinio pasiskirstymas, nustatomas ultragarsiniu metodu, šių riebalinio audinio sričių riebalų rūgščių sudėties tyrimas ^{1}H-MBR spektroskopijos metodu ir jų sąsajos su metaboliniais sutrikimais kompleksiškai nebuvo tirta ne tik Lietuvoje, bet ir tarptautiniu mastu.
2. Pirmą kartą ^{1}H-MBR spektroskopijos metodu tiriama nutukusių ligonių preperitoninio riebalinio audinio sudėtis. Taip pat pirmą kartą įvertinta preperitoninio riebalinio audinio sudėties įtaka nutukusių asmenų metaboliniams sutrikimams atsirasti.
3. Nustatyti nepriklausomi prognostiniai veiksniai, lemiantys metabolinių sutrikimų atsiradimą nutukusiems pacientams.

4. PRAKTINĖ REIKŠMĖ

1. Nutukusių asmenų juosmens apimtį geriausia matuoti siauriausioje juosmens vietoje tarp apatinių šonkaulių ir klubinių skiauterių.
2. Metabolinio sindromo diagnostikos nutukusiems ligoniams kūno masės slenkstinė riba – 123,90 kg, juosmens apimties vidurio taške slenkstinė riba – 123,40 cm, siauriausio juosmens matmens slenkstinė riba – 117,60 cm (apskaičiuota pagal vidutinį vyrų (1,79 m) ir moterų (1,65 m) ūgį).
3. Nutukusių asmenų visceralinį riebalinį audinį UGT metu reikia matuoti iki juosmeninio slankstelio viršutinio krašto.
4. Metabolinio sindromo diagnostikos nutukusiems ligoniams ultragarsinio tyrimo metu išmatuoto visceralinio riebalinio audinio iki aortos priekinės sienelės slenkstinė riba – 8,93 cm, visceralinio riebalinio audinio iki juosmens slankstelio viršutinio krašto – 11,53 cm.
5. Atliekant nutukusių asmenų poodinio riebalinio audinio tyrimus, reikia atskirai tirti paviršinį ir gilųjį sluoksnius.
6. Tiriant nutukusių asmenų visceralinį riebalinį audinį, turi būti išskiriamas ir preperitoninis riebalinis audinys bei jo įtaka metabolinei sveikatai.
7. Prognostiniu modeliu galima išskirti nutukusių asmenų rizikos grupes ir joms pritaikyti individualius diagnostikos ir nutukimo gydymo algoritmus.

5. GINAMIEJI DISERTACIJOS TEIGINIAI

1. Metaboliniu sindromu sergančių ir juo nesergančių nutukusių asmenų odos klosčių matavimai nesiskiria.
2. Ultragarsiniai riebalinio audinio matavimai yra efektyvus būdas atskirti metaboliniu sindromu sergančius ir juo nesergančius nutukusius asmenis.
3. Metaboliniu sindromu sergančių ir šiuo sindromu nesergančių nutukusių asmenų ^{1}H-MBR riebalinio audinio sudėtis skiriasi.

6. DARBO METODOLOGIJA

6.1 Tyrimo modelis

Šis darbas yra perspektyvusis skerspjūvio tipo biomedicininis tyrimas, kuriame tiriami MetS rizikos veiksniai nutukusių ligonių populiacijoje, naudojant antropometrines, ultragarsines ir ^{1}H-MBR vaizdinimo priemones. Tyrimą 2014 m. kovo 12 d. patvirtino Lietuvos bioetikos komitetas.

6.2 Tiriamųjų atranka

Tyrime dalyvavo VšĮ Respublikinės Vilniaus universitetinės ligoninės Bendrosios chirurgijos centro ligoniai. Nuo 2014 m. kovo 12 d. iki 2018 m. sausio 1 d. tyrime buvo siūloma dalyvauti pacientams, kuriems buvo numatytas operacinis gydymas Bendrosios chirurgijos centre ir jie atitiko atrankos kriterijus.

Ligonių įtraukimo kriterijai:
1. Ligonis yra nutukęs (KMI >30 kg/m^2)
2. Ligoniui 18-65 metai
3. Ligoniui atliekama planinė pilvo ertmės operacija
4. Ligonis pasirašė asmens informavimo ir informuoto asmens sutikimo formą.

Ligonių atmetimo kriterijai:
1. Ligonis jaunesnis nei 18 ir vyresnis nei 65 metų amžiaus
2. Ligonis serga psichikos liga
3. Ligoniui kontraindikuotinas operacinis gydymas
4. Ligonis nepasirašė informuoto asmens sutikimo formos.

Visiems biomedicininio tyrimo dalyviams buvo pateiktos Lietuvos bioetikos komiteto patvirtintos asmens informavimo formos, atsakyta į visus klausimus ir jie pasirašė informuoto asmens sutikimo formas. Kiekvienam ligoniui suteiktas kodas, naudojant sugeneruotą atsitiktinių skaičių seką.

6.3 Tyrimo eiga

1. Pacientui sutikus dalyvauti tyrime, prieš operaciją buvo surenkami reikalingi duomenys (amžius, ūgis, svoris, KMI, juosmens, klubų apimtys ir odos klosčių apimtys) ir užpildoma duomenų anketa.
2. Atliekami paciento kraujo tyrimai – nustatoma lipidograma, TAG, insulinas, gliukozė, ŠR, leptinas, adiponektinas.
3. Atliekamas RA ultragarsinis tyrimas, kurio metu nustatomas PRA, PreRA ir VRA pasiskirstymas.
4. Operacijos metu, nenaudojant papildomų pjūvių, ligoniams paimta po gabalėlį RA (~5 g iš priekinės pilvo sienos paviršinio ir giliojo sluoksnių, preperitoninio bei visceralinio RA).
5. Dalis kraujo tyrimų atlikta VšĮ Respublikinės Vilniaus universitetinės ligoninės laboratorinės diagnostikos skyriuje, kita dalis kraujo ir RA audinys buvo užšaldyti esant –70 ^{o}C temperatūrai. Sukaupus pakankamą tiriamosios medžiagos kiekį, ji transportuota į VšĮ Vilniaus universiteto ligoninės Santaros klinikų Laboratorinės diagnostikos centrą atlikti likusių kraujo rodiklių tyrimų, o RA – į Vilniaus universiteto Chemijos fakultetą, kur atlikta jo homogenizacija ir riebalų ekstrakcija. RA ^{1}H-MBR tyrimas atliktas pagal Vilniaus universiteto Chemijos fakultete priimtas metodikas.

6.4 Statistinė analizė

Statistinė duomenų analizė atlikta naudojant „Excel“ (Microsoft Office 365) ir „R-commander“ (versija 3.2.4) [329] standartinių programų paketus. Atlikta aprašomoji statistika: apskaičiuoti kiekybinių kintamųjų rodiklių vidurkiai, vidurkių standartinės paklaidos ir pasikliautiniai intervalai, standartiniai nuokrypiai, duomenų aibių pločiai (min–max). Apskaičiuotos kokybinių kintamųjų absoliučios ir procentinės vertės. Kintamųjų pasiskirstymas pagal normalųjį dėsnį tikrintas pritaikius Šapiro ir Vilko normalumo testą. Nepriklausomų imčių, kurių intervaliniai kintamieji buvo su normaliuoju pasiskirstymu, vidurkių lygybės hipotezei tikrinti naudotas Stjudento t testas, kai

buvo lyginami dviejų grupių vidurkiai, ir vienfaktorinės dispersinės analizės (ANOVA) metodas, kai buvo lyginami kelių grupių vidurkiai. Nepriklausomų imčių, kurių intervaliniai kintamieji buvo su nenormaliuoju pasiskirstymu, vidurkių lygybės hipotezei tikrinti naudotas Mano, Vitnio ir Vilkoksono kriterijus. Tiesinei priklausomybei tarp kintamųjų įvertinti buvo naudojamas Pirsono koreliacijos koeficientas, jei duomenys buvo pasiskirstę pagal normalųjį dėsnį, ir Spirmeno, jei ne. Koreliuojančių veiksnių įtakos vertinimui naudota tiesinė ir logaritminė regresija. Prognostinių veiksnių, turinčių įtakos MetS, paieškai sukurtas regresijos modelis, jame paliekant reikšmingus ir tarpusavyje nekoreliuojančius kintamuosius. Skirtumas tarp dviejų imčių laikytas statistiškai reikšmingu, kai $p < 0,05$.

7. TYRIMŲ REZULTATAI

Nuo 2014 m. kovo 3 d. iki 2018 m. sausio 1 d. į biomedicininį tyrimą įtraukta 70 ligonių – 48 (68,57 %) moterys ir 22 (31,43 %) vyrai. Vidutinis amžius buvo 42,7±11,56 metai (nuo 18 iki 63), vidutinė KM – 119,14±27,18 kg (nuo 74 iki 185,55). Tiriamųjų demografiniai rodikliai pateikiami 10 ir 11 lentelėse. Vyrų ūgis ir KM buvo didesni negu moterų. Pagal amžių ir KMI vyrų ir moterų grupės nesiskyrė.

Nutukusiųjų, kurie serga MetS, kūno masė ir KMI buvo didesni negu nesergančiųjų MetS.

Visos trys JA (siauriausias juosmens matmuo, JA vidurio taške, JA virš klubinių skiauterių) ir JKS statistiškai reikšmingai buvo didesni pacientų, kuriems diagnozuotas MetS, grupėje, palyginti su pacientų, kurie nesirgo MetS, grupe. Odos klosčių matmenys tarp sergančiųjų ir nesergančiųjų MetS statistiškai reikšmingai nesiskyrė. Nors šlaunies odos klostės nesergančiųjų MetS buvo storesnės, tačiau reikšmingo skirtumo negavome.

Ligonių, kuriems diagnozuotas MetS, kraujo gliukozės, TAG, ŠR, insulino, HOMA IR rodikliai ir SAKS bei DAKS buvo statistiškai reikšmingai didesni negu ligonių, kuriems nepasireiškė MetS. Ligo-

nių, kurie neserga MetS, adiponektino ir DTL-ch koncentracija buvo statistiškai reikšmingai didesnė negu ligonių, kurie serga MetS

Tiriamųjų, sergančių MetS, VRA buvo statistiškai reikšmingai didesnis negu ligonių, nesergančių MetS, tačiau nei PRA, nei PrePRA storiai, matuojant UGT, tarp šių grupių nesiskyrė.

Sergančiųjų MetS ir nesergančiųjų šiuo sindromu grupėse statistiškai reikšmingai skyrėsi paviršinio PRA MNRR ir PNRR bei preperitoninio RA PNRR kiekis. Lyginant nutukusių ligonių RR sudėtį RA sluoksniuose, nustatyta, kad paviršinio PRA sluoksnio PNRR kiekis didesnis negu giliajame PRA ir VRA, SRR kiekis mažesnis negu PreRA, o MNRR kiekis mažesnis negu VRA. Giliojo PRA MNRR kiekis mažesnis, o SRR kiekis didesnis negu VRA. PreRA MNRR kiekis mažesnis negu VRA, o PNRR ir SRR kiekis didesnis negu VRA.

VRA UGT matavimai iki aortos ir iki juosmeninio slankstelio sergančiųjų MetS grupėje statistiškai reikšmingai koreliavo su ūgiu, KM, KMI, siauriausiu juosmens matmeniu, JA vidurio taške, JA virš klubinių skiauterių, klubų apimtimi, JKS, klubo ir pilvo odos klostėmis, SAKS ir DAKS, gliukozės ir ŠR kiekiu kraujyje, kasos β ląstelių funkcija ($r = 0,32–0,81$). Abu centrinio riebalinio audinio UGT matmenys neigiamai koreliavo su PreRA ir VRA SRR kiekiu nesergančiųjų MetS grupėje ($r = –0,53–0,39$).

UGT matavimai epigastriumo srityje sergančiųjų MetS grupėje statistiškai reikšmingai koreliavo su ūgiu, KMI, JA virš klubinių skiauterių, užpakaline žasto, pomentine, pilvo ir šlaunies odos klostėmis, DTL-ch, leptinu, kasos β ląstelių funkcija ($r = 0,33–0,61$) bei neigiamai koreliavo su ūgiu ir TAG ($r = –0,47–0,39$). PRA UGT matavimai epigastriumo srityje nesergančiųjų MetS grupėje statistiškai reikšmingai koreliavo su KMI, siauriausiu juosmens matmeniu, klubų apimtimi, žasto priekine, klubo ir šlaunies odos klostėmis, leptinu, insulinu ($r = 0,39–0,62$) bei neigiamai koreliavo su amžiumi, MTL-ch ir bendro cholesterolio kiekiu ($r = –0,40–0,39$).

PRA UGT matavimai virš bambos sergančiųjų MetS grupėje statistiškai reikšmingai koreliavo su klubų apimtimi, pomentine, klubo

odos, šlaunies odos klostėmis, leptinu (r = 0,39–0,79) bei neigiamai koreliavo su amžiumi, ūgiu, gliukozės ir TAG kiekiu (r = –0,43–0,34). PRA UGT matavimai virš bambos neigiamai koreliavo su giliojo PRA sočiųjų RR kiekiu nesergančiųjų MetS grupėje (r = –0,41).

PreRA UGT matavimai sergančiųjų MetS grupėje statistiškai reikšmingai koreliavo su klubų apimtimi ir ŠR kiekiu kraujyje (r = 0,32–0,40). PreRA UGT matavimai nesergančiųjų MetS grupėje statistiškai reikšmingai koreliavo su KM, žasto užpakaline, pomentine, klubo, pilvo ir šlaunies odos klostėmis, leptino, insulino kiekiu kraujyje ir HOMA IR (r = 0,38–0,46) bei neigiamai koreliavo su amžiumi (r = –0,48).

Apskaičiavus RA RR sudėties koreliacijas su antropometriniais, kraujo tyrimų ir klinikiniais rodikliais, tiriamųjų, kurie serga MetS, grupėje nustatyta, kad RR sudėtis statistiškai reikšmingai koreliuoja su KM, KMI, siauriausiu juosmens matmeniu, JA vidurio taške, JA virš klubinių skiauterių, klubų apimtimi, JKS, gliukozės, DTL-ch, ŠR ir insulino koncentracija kraujyje, jautrumu insulinui.

Giliojo PRA sluoksnio SRR kiekis neigiamai koreliavo beveik su visais išvardytais komponentais, išskyrus DTL-ch, ŠR ir insulino kiekiu kraujyje.

Tarp JA vidurio taške ir visų RA sluoksnių SRR kiekio pastebėta statistiškai reikšminga neigiama koreliacija.

PreRA SRR sudėtis statistiškai reikšmingai neigiamai koreliavo su KM, KMI, siauriausiu juosmens matmeniu, JA vidurio taške, JA virš klubinių skiauterių, JKS ir insulino koncentracija bei jautrumu insulinui.

Tiriamųjų, kurie serga MetS, grupėje statistiškai reikšmingų koreliacijų tarp tiriamų rodiklių ir PNRR skirtingose RA srityse nepastebėta.

Apskaičiavus RA RR sudėties koreliacijas su demografiniais, antropometriniais, kraujo tyrimų ir klinikiniais rodikliais, tiriamųjų, kurie neserga MetS, grupėje nustatyta, kad RR sudėtis statistiškai reikšmingai koreliuoja su amžiumi, KM, KMI, siauriausiu juosmens matmeniu, JA vidurio taške, žasto užpakaline, žasto priekine, pomentine

ir šlaunies odos klostėmis, adiponektino, leptino ir insulino koncentracija kraujyje, jautrumu insulinui ir kasos β ląstelių funkcija.

Amžius reikšmingai neigiamai koreliuoja su paviršinio ir giliojo PRA sluoksnių MNRR ir teigiamai su SRR kiekiu giliajame PRA.

Skirtingai negu sergančiųjų MetS grupėje, nesergančių MetS tiriamųjų grupėje stebima RA MNRR bei PNRR koreliacija su žasto užpakalinės, žasto priekinės, pomentinės ir šlaunies odos klosčių storiu. Liemens odos klostės storis reikšmingai teigiamai koreliuoja su paviršinio PRA MNRR ir neigiamai – su PNRR kiekiu, o galūnių odos klostės reikšmingai teigiamai koreliuoja su giliojo PRA PNRR. Žasto užpakalinės ir šlaunies odos klosčių storis reikšmingai teigiamai koreliuoja su VRA PNRR sudėtimi, o šlaunies odos klostės storis reikšmingai neigiamai koreliuoja su giliojo PRA, PreRA ir VRA SRR kiekiu.

Adiponektino ir leptino koncentracijos kraujyje reikšmingai teigiamai koreliuoja su giliojo PRA PNRR, o adiponektino koncentracija dar ir su paviršinio PRA PNRR kiekiu.

Insulino koncentracija kraujyje, jautrumo insulinui modelis HOMA IR ir kasos β ląstelių funkcija reikšmingai neigiamai koreliuoja su giliojo PRA SRR kiekiu.

ROC kreivių analizė parodė, kad nutukusių ligonių KM, KMI, siauriausio juosmens matmens, JA vidurio taške, UGT iki aortos ir juosmeninio slankstelio, insulino koncentracija kraujyje ir jautrumas insulinui, paviršinio PRA MNRR bei PreRA PNRR kiekių plotų po kreive (angl. *area under the curve*, AUC) reikšmės statistiškai reikšmingai skyrėsi nuo atskaitos linijos ir yra tinkamos prognozuoti MetS pasireiškimą. Taip pat išskirtos nutukusių asmenų MetS prognozavimo rodiklių slenkstinės reikšmės.

Rodikliai, reikšmingai koreliuojantys su MetS, toliau panaudoti sudarant prognostinius regresijos modelius:

$$P\,(MS=1)=\frac{e^{6{,}53-0{,}27*Adiponektinas\ (\mu g/ml)+0{,}29*\mathrm{VRA}_{sl}\ (cm)-1{,}43*MNRR\ PRA1\ (\%)}}{1+e^{6{,}53-0{,}27*Adiponektinas\ (\mu g/ml)+0{,}29*\mathrm{VRA}_{sl}\ (cm)-1{,}43*MNRR\ PRA1\ (\%)}}$$

Regresijos modelio bendras teisingai suklasifikuotų pacientų procentas sudarė 85,5 proc. ROC kreivės analizė parodė, jog šio regresinio modelio plotas po kreive yra statistiškai reikšmingas (AUC = 0,88, PI 0,79–0,97), jo specifiškumas siekia 83,3 proc., jautrumas – 87,2 proc.

Nustatyta, kad 1 cm ultragarsu išmatuoto VRA storio iki juosmeninio slankstelio padidėjimas metabolinio sindromo išsivystymo tikimybę nutukusiam ligoniui padidina 1,34 (95 % PI, 1,12–1,68) karto, o 1 µg/ml adiponektino koncentracijos bei 0,1 proc. mononesočiųjų riebalų rūgščių koncentracijos padidėjimas metabolinio sindromo išsivystymo tikimybę nutukusiam ligoniui sumažina 1,3 (95 % PI, 0,59–0,92) ir 4,17 (95 % PI, 0,08–0,57) karto.

8. IŠVADOS

1. Metabolinį sindromą turinčių nutukusių ligonių grupėje centrinio riebalinio audinio storis, matuojant ultragarsu, ir antropometrinių tyrimų rodikliai (juosmens apimtis bei juosmens ir klubų santykis) yra statistiškai reikšmingai didesni negu nutukusių ligonių, neturinčių metabolinio sindromo.

2. Tiriant ^{1}H-MBR spektroskopijos metodu, nustatyta, kad metabolinį sindromą turinčių nutukusių ligonių grupėje mononesočių riebalų rūgščių kiekis paviršiniame poodiniame audinyje yra statistiškai reikšmingai mažesnis, o polinesočių riebalų rūgščių kiekis paviršiniame poodiniame bei preperitoniniame riebaliniame audiniuose didesnis negu metabolinio sindromo neturinčių ligonių grupės.

3. Adiponektinas, visceralinio riebalinio audinio storis iki juosmeninio slankstelio viršutinio krašto ir mononesočiųjų riebalų rūgščių kiekis paviršiniame poodiniame riebaliniame audinyje yra nepriklausomi prognostiniai veiksniai, turintys didžiausią įtaką nutukusių asmenų metaboliniams sutrikimams atsirasti.

9. DARBO TĄSOS KRYPTYS

1. Tikslingi nutukusių asmenų riebalinio audinio riebalų rūgščių sudėties ir metabolizmo sąsajų su metaboliniais sutrikimais tolesni tyrimai.
2. Reikalingas riebalinio audinio morfologinės sandaros nustatymas moderniomis vaizdinimo priemonėmis, svarbu genetiniai tyrimai ir uždegiminių rodiklių paieška.
3. Tikslingi tolesni populiaciniai tyrimai prognostinės formulės reikšmingumo lygmeniui ir prognostinių veiksnių ribinėms reikšmėms nustatyti.
4. Reikalingas metabolinių sutrikimų neturinčių ligonių ilgalaikis sekimas, vertinant šių ligonių metabolinės sveikatos pokyčius.

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XIX tarptautinė konferencija „EcoBalt 2014“, 2014 m. spalio 8–10 d. Ryga, Latvija

2. Aurelija Smalenskaitė, Bronius Buckus, Stasys Tautkus, Aldona Beganskienė, Gintautas Brimas, Aivaras Kareiva. Analytical characterisation of adipose structure and composition: a novel approach towards diagnostics and therapeutics.

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XX IFSO Pasaulinis kongresas, 2015 m. rugpjūčio 26–29 d. Viena, Austrija

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VIII Baltijos chirurgų asociacijos kongresas, 2015 m. rugsėjo 10–12 d. Talinas, Estija

5. Bronius Buckus, Gintautas Brimas, Žygimantas Juodeikis, Aurelija Smalenskaitė, Aldona Beganskienė, Aivaras Kareiva. Evaluation of adipose tissue composition by ^{1}H NMR and it's relationship with ultrasonoscopic measurements in obese patients.

Trečioji tarptautinė konferencija „Evoliucinė medicina: šiuolaikinių sveikatos problemų evoliuciniai mechanizmai ir dėsningumai", 2016 m. birželio 14–19 d. Vilnius, Lietuva

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XVIII EFSUMB tarptautinis kongresas, 2016 m. spalio 26–29 d. Leipcigas, Vokietija

7. Bronius Buckus, Gintautas Brimas, Aivaras Kareiva. Evaluation of adipose tissue distribution by ultrasonography and it's relationship to metabolic disturbances in obese patients.

TRUMPOS ŽINIOS APIE DISERTANTĄ

Vardas, pavardė	Bronius Buckus
Gimimo data	1982.10.31
E-meilas	buckus.bronius@gmail.com

PROFESINĖ PATIRTIS, DARBOVIETĖS

Nuo 2017	Gydytojas endoskopuotojas, Respublikinė Vilniaus universitetinė ligoninė, Šiltnamių g. 29, Vilnius, Lietuva
Nuo 2015	Gydytojas echoskopuotojas, Respublikinė Vilniaus universitetinė ligoninė, Šiltnamių g. 29, Vilnius, Lietuva
Nuo 2013	Gydytojas chirurgas, Respublikinė Vilniaus universitetinė ligoninė, Šiltnamių g. 29, Vilnius, Lietuva
Nuo 2012	Lektorius, Gastroenterologijos, nefrourologijos ir chirurgijos klinika, Klinikinės medicinos institutas, Medicinos fakultetas, Vilniaus universitetas
2009-2013	Medicinos gydytojas, Respublikinė Vilniaus universitetinė ligoninė, Šiltnamių g. 29, Vilnius, Lietuva
2008-2011	Asistentas, Anatomijos, histologijos ir antropologijos katedra, Medicinos fakultetas, Vilniaus universitetas
2004-2008	Laborantas, Anatomijos, histologijos ir antropologijos katedra, Medicinos fakultetas, Vilniaus universitetas

IŠSILAVINIMAS

2017.05	Įvadiniai kursai „Endoskopija: ezofagogastroduodenoskopijos įvadinis kursas“, Vilniaus universitetas, Medicinos fakultetas
2013.06	Gydytojo chirurgo profesinė kvalifikacija, Vilniaus universitetas, Medicinos fakultetas
2013.06	Įvadiniai kursai „Pilvo organų echoskopijos įvadinis kursas“, Vilniaus universitetas, Medicinos fakultetas
2008.06	Medicinos gydytojo profesinė kvalifikacija, Vilniaus universitetas, Medicinos fakultetas
2007.06	Gydytojo profesinė kvalifikacija, Vilniaus universitetas, Medicinos fakultetas

Anglų kalbos redaktorius Markas Aurelijus Piesinas
Vilniaus universiteto leidykla
Universiteto g. 1, LT-01513 Vilnius
El. p. info@leidykla.vu.lt,
www.leidykla.vu.lt
Tiražas 35 egz.