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The relationship between total body fat and distribution of body fat mass and markers of insulin resistance in young women with normal weight — a pilot study

ABSTRACT

Introduction. Total body fat and body fat distribution are factors closely associated with development of insulin resistance, including subjects with normal body weight and BMI (body mass index).

Objectives. The objective of the study was to determine relation between insulin resistance index and selected parameters of body fat distribution in potentially healthy young females with body mass index below 25 kg/m^2.

Material and methods. Study group consisted of 36 women with a BMI < 25 kg/m^2, who underwent anthropometric measurements, i.e.: height, weight, waist circumference, hip circumference and blood pressure measurement. The segmental body composition was measured by of the use of the bioelectric impedance analysis (BIA). Moreover, oral glucose tolerance test (OGTT) was performed with blood collection in 0, 60 and 120 minute of the test. The fasting samples were used for determination of concentrations of glucose, insulin, C-peptide, a total cholesterol, triglycerides, HDL and LDL cholesterol. The following insulin resistance indices were calculated: HOMA-IR, HOMA2-IR, HOMA2-%B, HOMA2-%S and IRI/G.

Results. All the volunteers presented normal glucose tolerance in 120 minute of the OGTT test, as well as normal values of IRI/G index. Moreover, for such parameters as: total cholesterol, HDL and LDL cholesterol, triglycerides and CRP no values outside the reference range were found. C-peptide concentration was found to be significantly correlated with total body fat (r = 0.532; p = 0.001) and trunk fat mass (r = 0.471; p = 0.004).

Conclusions. In the young, non-obese women it seems to be justified to test concentration of glucose and C-peptide while assessing potential insulin resistance with simultaneous examination of the total and trunk body fat. (Clin Diabet 2016; 5, 2: 41–48)

Key words: insulin resistance, body fat weight, bioelectric impedance

Introduction

In the last several years there was a number of studies conducted to definee detailed criteria of cardiovascular disease, diabetes and metabolic syndrome probability [1–3]. The problem of these diseases is visible in the developed and developing countries, where the largest increase in new cases of the disease is observed and directly related to increasing number of obese people. Excessive body weight caused by

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increase in body fat — especially the abdomen one is the main cause of increasing tissue insulin resistance [4]. This relationship is also found in people with normal body weight and BMI (body mass index), which indicates that fat tissue distribution is a key factor in development of metabolic disorder [5–7], in increasingly younger people [8]. Insulin resistance seems to be one of the factors related to reproduction disorders, including risk of spontaneous abortion [9, 10]. Tissue insulin resistance is found not only in overweight or obese women, or ones suffering from polycystic ovary syndrome [11], but also in potentially healthy women with normal BMI [10].

The golden standard for determination of insulin resistance is euglycemic clamp, which is technically difficult and very burdensome for the body. In clinical conditions it is rarely used due to difficult procedure and high costs. In practice, indirect methods for assessment of insulin resistance are used the most often, which are either fasting glucose and insulin concentration or oral glucose tolerance test (OGTT). One of such indices is ratio of insulin to glucose concentration in fasting condition, i.e. IRI/G ratio. However, the most commonly HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index that is also calculated based on fasting concentration of insulin and glucose is used [4]. Moreover, one can use HOMA2-IR index and index of beta cell function β HOMA-%B (Homeostasis Model Assessment of β-cell Function) as well as insulin sensitivity index HOMA-%S (Homeostasis Model Assessment of Insulin Sensitivity) that can be calculated using generally available HOMA2 calculator. Additional parameter used for assessment of insulin resistance is C-peptide concentration and increasing number of researchers points to appropriateness of its determination especially in young people [12].

Testing body fat quantity and distribution has become such a clinically important parameter that the International Diabetes Federation (IDF), in their "Platinum Standard" of additional tests related to metabolic syndrome, recommends analysis of body composition and body fat distribution using Dual-energy X-ray absorptiometry (DEXA) or computer tomography/magnetic resonance imaging (CT/MRI) [13]. These methods, although very accurate, are not widely available andare related to high costs and expose patient to unnecessary radiation [14]. There are few others methods for the measurement of body composition and assessment of the amount of body fat, among which the most commonly used is bioelectrical impedance analysis (BIA). The body composition test using BIA method is safe and can be conducted virtually regardless of health, age or sex. The BIA is a simple and minimally invasive method with high repeatability. The methods involves flow of low-intensity electric current and assessment of resistance of individual tissues. From the clinical perspective, systematic control of body composition allows effective monitoring of physical activity, diet used or applied therapy [15–17]. Additional advantage of the BIA is a short time of analysis, as well as easy-to-use, usually portable equipment [15].

In Poland obesity is diagnosed already in one of five young people and the number is constantly increasing. This is mainly related to the change in lifestyle, high-calorie diet as well as social and economic development. Due to the global problem, preventive actions are underway all over the world in order to reduce the development of obesity, particularly among young people. However, the literature contains little data on insulin resistance markers in the group age of young people with normal body weight that could be useful information in prevention of civilisation disease resulting from increase of body fat [18].

Objective

The objective of the study was to determine relation between insulin resistance index and selected parameters of body fat distribution using BIA in potentially healthy young females of body mass index below 25 kg/m^2.

Material and methods

Characteristics of study group

The study group consisted of 36 young females, students of Wroclaw Medical University, aged 20 to 23 y.o. with BMI < 25, which did not report current health problems, chronic medication use and addictions. Additionally, none of the volunteers reported family history of metabolic diseases. The volunteers were informed about the purpose and the aim of the study and gave their written consent.

Physical examination

On the study day the volunteers came to the Teaching Medical Diagnostics Laboratory of the Wroclaw Medical University fasted, in early morning hours, i.e. between 7:30 and 8:30 AM. After completing the questionnaire, a physical examination was conducted involving height, weight, waist circumference, hip circumference and blood pressure measurement. Height, waist and hips circumference were measured with an accuracy of 0.5 cm. Waist circumference was measured in the midway between lower abdomen quadrant and lower rib edge, while hips circumference at the greatest circumference of the thigh. Body weight was measured using medical scales without footwear and

Table 1. Anthropometric characteristics and distribution of body mass of participants

Parameter	Median	Q1–Q3
Anthropometric data		
Height [cm]	165.0	163.5–175.5
Body weight [kg]	54.6	51.9–61.2
Age (years)	22	21–23
Systolic blood pressure [mm Hg]	110	105–117
Diastolic blood pressure [mm Hg]	70	67–75
Waist circumference [cm]	72.0	69.0–78.5
Hip circumference [cm]	93.2	89.5–97.5
BMI [kg/m^2]	20.2	19.3–21.9
WHR	0.78	0.76–0.82
Body composition parameters		
Total fat mass [kg]	12.3	10.4–16.6
Total fat mass (%)	23.0	20.6–27.2
Total body water [kg]	31.2	29.6–33.5
Total body water (%)	56.4	53.2–58.2
Muscle mass [kg]	40.4	38.2–43.5
Muscle mass (%)	73.2	68.8–75.4
Fat-free mass [kg]	42.6	40.3–45.8
Fat-free mass (%)	76.9	72.5–79.4
Trunk fat mass [kg]	5.8	4.4–8.5
Trunk fat mass (%)	10.6	8.8–13.9

BMI — body mass index, WHR — waist/hips ratio, Q1–Q3 — quartiles 1–3

outerwear. The blood pressure was measured twice using sphygmomanometer at rest; the statistical analysis was performed for averaged values. Moreover, for each person waste-hips ratio (WHR) and body mass index (BMI) were calculated.

Body composition analysis

Segmental body composition measurement was performed using the Tanita Model BC 418 MA analyser. The analyser, using 8 electrodes, allows precise estimation of body fat and body muscle in individual body segments, particularly of fat tissue located inside the abdominal cavity. The following values were used in statistical analysis: total fat mass (FM), trunk fat mass (TFM), total body water (TBW), muscle mass (MM) and fat free mass (FFM) (Tab. 1).

Laboratory tests

From all volunteers, in fasting conditions, venous blood was collected with K_3EDTA as an anticoagulant to obtain plasma and with coagulant activator in order to obtain serum. Then, among the volunteers, whose fasting glucose concentration in plasma was < 126 mg/dl, oral glucose tolerance test was performed for 75 g of glucose.

The fasting samples were used for determination of the concentrations of: glucose, insulin, C-peptide, total cholesterol, triglycerides, HDL and LDL cholesterol. In the samples collected in 60 and 120 minute of the OGTT, concentrations of glucose and insulin were determined.

Glucose concentration in venous plasma was determined using enzymatic colorimetric method GOD-POD (Glucose GOD-POD, Thermo Fisher Scientific Inc., Vantaa, Finland); enzymatic colorimetric method was also applied for determination of triglycerides (Triglycerides, Thermo Fisher Scientific Inc., Vantaa, Finland), total cholesterol (Thermo Fisher Scientific Inc., Vantaa, Finland) and HDL cholesterol (Thermo Fisher Scientific Inc., Vantaa, Finland), while LDL cholesterol was calculated using Friedewald equation. Insulin and C-peptide were determined using immunoenzymatic assay (DRG Insulin and C-Peptide ELISA Kit, DRG Instruments GmbH, Marburg, Germany). Metabolic characteristics of the study group is presented in Table 2.

For all the tests, appropriate control materials were used.

Insulin resistance indices

HOMA-IR index was calculated based on fasting concentrations of insulin and glucose using the formula:

$$\text{HOMA-IR} = \text{fasting glucose concentration [mmol/L]} \times \text{fasting insulin concentration [}\mu\text{IU/mL]}/22.5$$

The study used also indices, modified by Levy et al., i.e. HOMA2-IR and HOMA2-%B and HOMA2-%S which were calculated using HOMA2 calculator available at the website of the Oxford Centre for Diabetes, Endocrinology and Metabolism (https://www.dtu.ox.ac.uk/homacalculator/). Moreover, fasting insulin [μIU/mL] and glucose [mg/dL] ratio was determined — IRI/G.

Statistical analysis

The statistical analysis was performed using software called *Statistica 10* (StatSoft, Tulsa, USA). Distribution normality of the tested variables was verified by Shapiro-Wilk test and by using Levene's variance homogeneity test. In order to determine relation between analysed parameters, Pearson's linear correlation coefficient was applied — for parameters with normal distribution, or Spearman's ranks were applied — if variable distribution was not normal. For the verification procedures the assumed significance level was $p < 0.05$.

Due to the fact that the majority of parameters did not have normal distribution, the results are presented as median and range between first and third quartile (Q1–Q3).

Table 2. Metabolic characteristics of subjects

Parameter	Median	Q1–Q3
Carbohydrate metabolism parameters		
Fasting glucose [mmol/L]	5.1	4.9–5.4
Glucose 60′ [mmol/L]	5.3	4.6–6.4
Glucose 120′ [mmol/L]	5.1	4.4–5.9
Fasting insulin [μIU/mL]	10.8	9.2–14.0
[pmol/L]	65	55–84
Insulin 60′ [μIU/mL]	55.5	34.4–84.3
[pmol/L]	333	206–506
Insulin 120′ [μIU/mL]	44.3	28.5–67.6
[pmol/L]	266	171–406
C-peptide [nmol/L]	1.16	0.60–1.69
Indirect insulin resistance indices		
IRI/G	0.1	0.1–0.2
HOMA-IR	2.4	2.1–3.2
HOMA2-IR	1.4	1.2–1.8
HOMA2-%B	124.5	102.6–137.4
HOMA2-%S	72.1	55.2–84.6
Lipid metabolism parameters		
Total cholesterol [mmol/L]	4.30	3.78–4.87
HDL cholesterol [mmol/L]	1.53	1.42–1.71
LDL cholesterol [mmol/L]	2.49	1.94–2.74
Triglycerides [mmol/L]	0.70	0.60–1.17
C-reactive protein	0.7	0.2–1.7

CRP — C-reactive protein, HOMA-IR — Homeostasis Model Assessment of Insulin Resistance, HOMA2-IR — Homeostasis Model Assessment, version 2, HOMA2-%B — Homeostasis Model Assessment of β-cell Function, HOMA2-%S — Homeostasis Model Assessment of Insulin Sensitivity, IRI/G — insulin/glucose ratio, Q1–Q3 — quartiles 1 and 3

Results

Anthropometric characteristics and body mass distribution of tested volunteers are presented in Table 1. The total body fat mass for 25–75 percentile in the tested group was in the range of 10.4–16.6 [kg]. However, the relative body fat mass exceeding acceptable percentage for age and sex of > 30% was observed in 3 women (8.3%) despite correct values of BMI (median: 20.2 — with maximum: 24.6). Central obesity measured as waist circumference ≥ 80 cm was found in 22.2% women. All the parameters of body fat distribution (both absolute and relative values) were correlated with waist circumference significantly, while the most significant correlation coefficient was found for trunk fat mass (WC vs. TFM $r = 0.657$, $p < 0.001$).

Table 2 presents metabolic characteristics of the tested group and the most popular insulin resistance indices. Under the basic conditions, glucose and insulin concentration were in range of reference values, while for glucose those were so-called high normal values (> 4.9 mmol/L). 21 women (58.3%) presented an increased fasting concentration of C-peptide (1.05 nmol/L) whereas, over 3.31 nmol/L was found in three of them. In turn, for such parameters as: total cholesterol, HDL and LDL cholesterol, triglycerides and CRP, no values outside the allowable concentration range were found. In all tested volunteers normal glucose tolerance in 120 minute of the OGTT [19] and normal values of IRI/G ration were observed. Interestingly, in the tested group, a relatively high median of HOMA-IR index was found, equal to 2.4. At the same time it was found that the studied group had normal function of pancreas beta cells (HOMA2-%B), with median of insulin sensitivity index HOMA2-%S being 72.1.

It is surprising that fasting glucose concentration had negative correlation with total fat mass ($r = –0.404$; $p = 0.015$), and also with absolute trunk fat mass ($r = –0.417$; $p = 0.012$). C-peptide, however, was significantly correlated with total fat mass ($r = 0.532$; $p = 0.001$) and trunk fat mass ($r = 0.471$; $p = 0.004$) (Fig. 1). Moreover, relative value of FM was correlated with C-peptide ($r = 0.362$; $p = 0.030$) and similar significance was found for TFM percentage and HOMA2-%B ($r = 0.356$; $p = 0.033$). There was no correlation between insulin concentration in any point of OGTT, for both absolute and relative values, observed (Tab. 3).

Discussion

The World Health Organisation (WHO) places great emphasis on prevention of civilisation diseases, which are the consequence of development of tissue insulin resistance, including diabetes, cardiovascular diseases and metabolic syndrome [1, 2]. Despite that, in databases such as PubMed there is a rather small number of papers relating to young, potentially healthy people, for whom probability of insulin resistance was verified in correlation with selected parameters of fat tissue [20]. Moreover, in such health conditions as polycystic ovary syndrome, insulin resistance in slim women is observed in 30% of cases, while for obese women this value reaches up to 80%. Due to that, constant monitoring of fat mass and fat distribution in correlation with tissue insulin resistance indices seems to be crucial for women of childbearing age [9].

The recognised factor of development of insulin resistance is increase in total fat mass, especially in the abdomen part [21, 22]. In the last several years it was shown that central obesity is a better predictor of development of insulin resistance that commonly used body mass index. It is recommended that evaluation of central obesity, expressed as waist circumference, shall be used in clinical practice for assessment of risk of development of type 2 diabetes, even in people with BMI < 25 kg/m^2 [23]. Waist circumference measurement

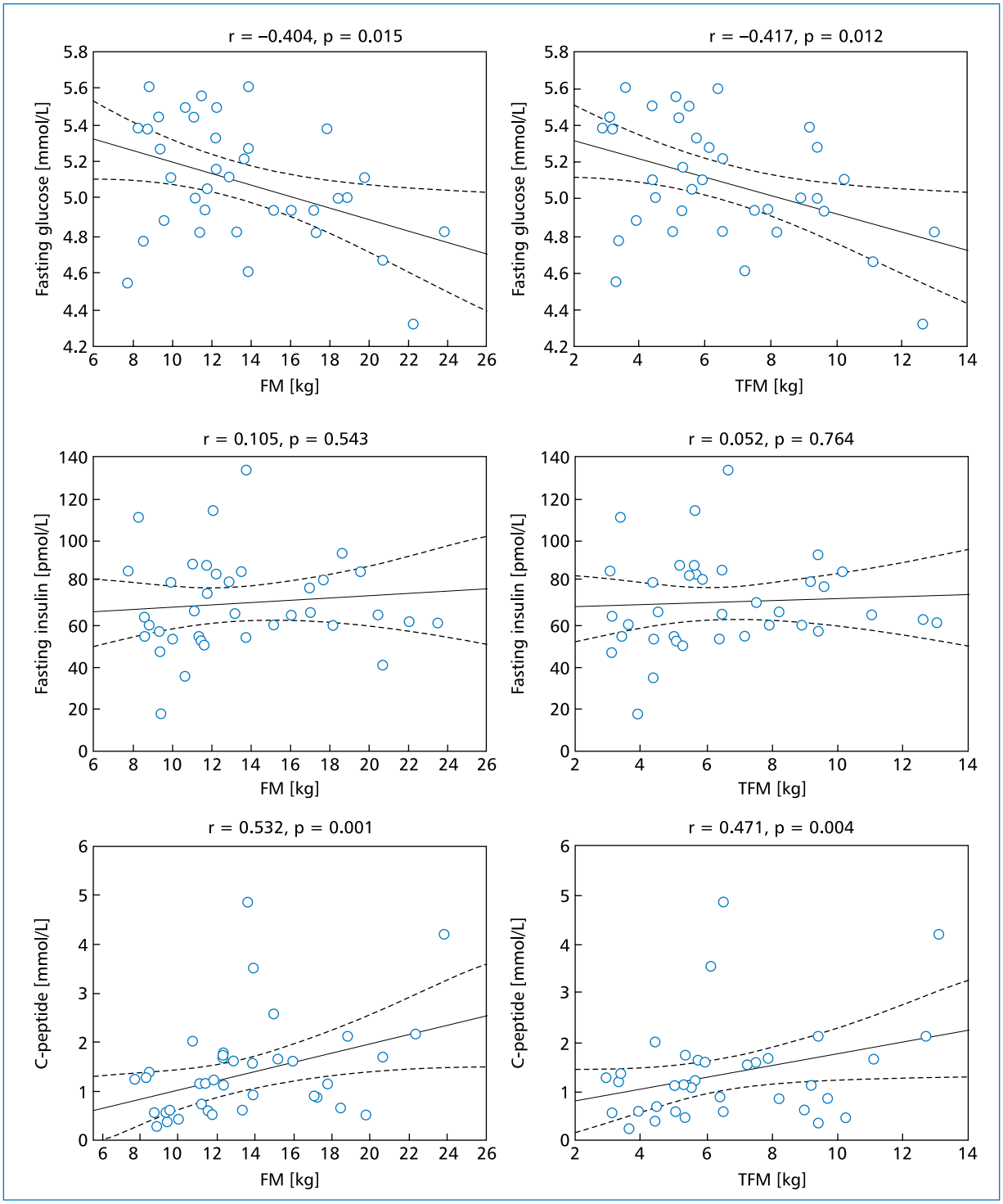

Figure 1. Plots of value scatter for fasting glucose, insulin and C-peptide in correlation with total fat mass [kg] and trunk fat mass [kg]

used for diagnosis of metabolic disease is continuously assessed, and becomes more and more rigorous parameter determined separately for each population. Currently, for the European women according to the IDF criteria, this value is ≥ 80 cm [1, 13]. In the examined group of volunteers, WC median was 72 cm, while central obesity measured according to waist circumference was found in 8 women (22.2%), whereas it must be noted that maximum WC was 89 cm. Despite the small group, the values are similar to the values obtained by Miazgowski et al. (26.2%), who studied a group of 145 young women from Polish population [22].

Table 3. Correlations of total fat mass (FM) and trunk fat mass (TFM) with indicators of insulin resistance. Correlations of total fat mass (FM) and trunk fat mass (TFM) with indicators of insulin resistance

Parameter	FM				TFM			
	[kg]		(%)		[kg]		(%)	
	r	p	r	p	r	p	r	p
Fasting glucose	**–0.404**	**0.015**	–0.236	0.166	**–0.417**	**0.012**	–0.322	0.055
Glucose 60′	–0.149	0.386	–0.184	0.282	–0.297	0.078	–0.262	0.123
Glucose 120′	–0.075	0.665	–0.127	0.459	–0.203	0.234	–0.193	0.260
Fasting insulin	0.105	0.543	0.187	0.275	0.052	0.764	0.187	0.276
Insulin 60′	–0.003	0.987	–0.027	0.874	–0.120	0.485	–0.085	0.622
Insulin 120′	–0.040	0.819	0.254	0.134	–0.136	0.431	0.267	0.116
IRI/G ratio	0.299	0.077	–0.048	0.780	0.270	0.111	–0.108	0.530
HOMA-IR	0.116	0.499	0.103	0.548	0.091	0.596	0.085	0.623
HOMA-%S	–0.203	0.234	–0.169	0.325	–0.167	0.332	–0.156	0.364
HOMA-%B	**0.396**	**0.017**	0.327	0.052	**0.363**	**0.029**	**0.356**	**0.033**
HOMA2-IR	0.219	0.199	0.175	0.307	0.170	0.323	0.166	0.335
C-Peptide	**0.532**	**0.001**	**0.362**	**0.030**	**0.471**	**0.004**	0.314	0.062

Pearson's linear correlation coefficients were used for parameters with normal distribution, while Spearman's ranks were applied, if variable distribution was not normal

In medical practice, BMI is still used for expressing estimated fat mass, despite its limitations. Its main limitation is the lack of distinction between fat mass and muscle mass [23, 24] as well as the fact that it gives no information on body fat distribution [25]. Therefore, there is an increasing trend of recommending body composition measurements, especially using generally available techniques such as BIA. In our studies we have also observed a strong correlation between BMI and FM ($r = 0.756$; $p < 0.001$) and a negative correlation between BMI and MM ($r = –0.764$; $p < 0.001$). Accurate estimation of fat and muscle mass in individual body segments, particularly visceral adipose tissue located inside the abdominal cavity, allows precise determination of health risks related to development of tissue insulin resistance.

In clinical practice, commonly used insulin resistance indices involve simultaneous determination of glucose and insulin concentration, in basic conditions or during functional tests (mainly OGTT). The determined values can be used for calculation of so-called indirect insulin resistance indices. The simplest one is a ratio of fasting blood concentration of insulin [mIU/L] and glucose [mg/dL] — IRI/G. The decisive value suggesting insulin resistance is > 0.3 [26]. All the tested volunteers presented normal values of IRI/G ratio. Moreover, in the tested group there was no significant correlation found for IRI/G ratio with the total or trunk fat mass.

Another indirect insulin resistance index is a mathematical model HOMA-IR, evaluating relation between generation of glucose in the liver and function of pancreas beta cells that regulate concentration of glucose and insulin. HOMA-IR reflects mainly insulin sensitivity in fasted conditions and, to a limited extent, a possibility of determination of insulin resistance after meal [27]. Matthews et al. [28] presented a strong correlation between HOMA-IR and insulin sensitivity index determined by means of hyperinsulinemic-euglycemic clamp, which is recognised as golden standard for assessment of insulin resistance. Due to the complexity and invasiveness of the method and high costs of the procedure, the technique is not appropriate for epidemiology studies, therefore routine diagnostics uses indirect insulin resistance indices, including HOMA-IR [29]. The value of HOMA-IR for young people with normal body mass in ideal conditions should be 1.0. However, this index depends on many factors, including age, sex, ethnicity or fat mass, therefore it is difficult to establish cutoff of HOMA-IR, which have to be determined separately for each population [30]. Moreover, this parameter has certain clinical limitations, especially for people with impaired glucose tolerance [27]. For Polish population cutoff of HOMA-IR was determined among others by Szurkowska et al. They determined its value, for which insulin resistance can be diagnosed, as the upper quartile of distribution in population of normal glucose tolerance and normal body weight, i.e. HOMA-IR > 2.1 [31] while Żyła [30] has adopted value ≥ 2.5. By cutoff value of HOMA-IR ≥ 2.5, insulin resistance could be diagnosed in over 47% of tested volunteers. However, assuming that the study group consisted of

potentially healthy people of normal body weight and adopting insulin resistance diagnosis cutoff based on HOMA-IR — upper quartile, the value would be ≥ 3.2. This is a value close to Q3 of the entire group tested by Szurkowska et al., which greatly shifts the cutoff value for insulin resistance diagnosis in our population.

All the tested women had normal fat mass for their sex, age and ethnicity. The body fat mass increases with age. Age median of our volunteers was 10 years lower than for group tested by Miazgowski et al. [22], and despite comparable BMIs and fat-free mass (so-called lean mass), fat mass in our group is lower. This can be also a result of the equipment used in this study and its accuracy in comparison with reference method [15].

It seems interesting that trunk fat mass is correlated negatively with fasting concentration of glucose ($r = -0.417$; $p = 0.014$). In volunteers participating in the study, normal fasting glucose concentrations were found, but those were high values (median 5.1 mmol/l). However, there was no dependence found for fasting insulin nor any other insulin resistance indices in relation to trunk fat mass while correlation of C-peptide with the total body fat mass was found to be significantly positive ($r = 0.532$; $p = 0.005$). C-peptide is synthesised by pancreas beta cells in equimolar quantities in relation to insulin, but due to the longer half-life, C-peptide concentrations in fasting conditions were five times higher than for insulin. C-peptide determination allows evaluation of current functional conditions of pancreas beta cells and is very useful parameter prior to development of overt insulin resistance [32]. Therefore, in potentially healthy people, from a diagnostic perspective, C-peptide seems a more adequate parameter than insulin for determination of function of pancreas beta cells. Moreover, Min et al. has found that C-peptide is a better predictor of risks of complications of cardiovascular and coronary artery disease than the glycated hemoglobin, or concentration of glucose in fasting conditions [12].

Our research, although conducted on a relatively small group of subjects, provides results justify its continuation on extended young people population, especially regarding the diagnostic importance of C-peptide as one of parameters of tissue insulin resistance development.

Conclusions

In young, non-obese women there is a significant correlation between total and trunk body fat and fasting C-peptide concentration. There was no such correlation for insulin and FM or TFM, in any of the three timepoints of the OGTT. Therefore, during the assessment of insulin resistance risk in young people, next to routinely performed glycemia assays, it seems justified to perform additional determination of C-peptide concentration and regular examination of total fat mass, with special emphasis on trunk fat mass. As it turns out, calculation of BMI may be definitely insufficient for determination of cardiometabolic risks in young women, as every fifth subject with normal BMI had abnormal waist circumference. And as the study shows, it is the trunk fat mass that is significantly correlated with C-peptide. At the time of diabetes epidemic, early diagnosis of disturbances in carbohydrate metabolism and determination of risk of development of insulin resistance in young, potentially healthy persons is a crucial action for preventing development of civilisation diseases.

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