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The Importance of the Quantity and the Distribution Assessment of Fat Tissue in a Diagnosis of Insulin Resistance

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ABSTRACT

Background: Accurate human body composition assessment is becoming very important in clinical practice due to the possibility of early diagnosis and preventive interventions of metabolic disorders. Fats are one of the most important elements in maintaining normal body structure and different methods are used to determine its total amount and distribution. The amount and distribution of abdominal white adipose tissue, and especially the visceral type, provides important parameters in the development assessment of central obesity, insulin resistance, diabetes and other chronic non-infectious diseases. **Objective:** The aim of the study was to determine the amount of visceral adipose tissue in adults who are overweight and then estimate the probability of developing insulin resistance (IR) in those with higher amounts of visceral adipose tissue. Based on a comparison of the amount of visceral adipose tissue and the frequency of IR, evaluate the clinical significance of a routine procedure for body structure assessment in relation to the amount of visceral adipose tissue. **Methods:** Subjects were adults of both sexes aged 20 to 77 years, who were patients in two family medicine clinics. Including criteria for the study were: increased body weight (BMI≥25) and normal blood glucose values (4.0 – 5.4 mmol/L). All subjects underwent anthropometric measurements (BMI, waist circumference, waist-hip ratio) and body structure assessment with bioelectrical impedance. According to the values for the amount of visceral adipose tissue (below and above 110 cm^2), the subjects were divided into two groups. All subjects underwent an IR test. We used the HOMA 1 value of 2 as a cut off for the risk of chronic non- infectious diseases in non-diabetic population. **Results:** The study included 80 patients. 14 patients did not complete the study, so the total number of subjects was 66 (39 women and 27 men). 36 subjects had elevated values of visceral adipose tissue (over 110 cm^2). In this group, the presence of IR was registered in 30 patients or 81%. In the control group with a normal amount of visceral adipose tissue, IR was registered in 10 subjects or 33%, which is a statistically significant difference. **Conclusion:** Increased amount of visceral adipose tissue in overweight patients significantly affects the occurrence of IR. For the patients with an increased amount of visceral adipose tissue, it is necessary to introduce intensive preventive measures to stop the development of diabetes and other complications as a result of IR presence.

Keywords: Visceral adipose tissue, Bioelectrical impedance, Insulin resistance, Obesity.

1. BACKGROUND

Accurate composition of the human body assessment is becoming very important in clinical practice, due to the possibility of early diagnosis and preventive interventions of some metabolic disorders. The human body consists of water, fats (lipids), proteins, carbohydrates, DNA and RNA, and minerals, which have important metabolic functions. Biochemical structure of the body assessment such as estimating the amount and distribution of water, fat, and muscle mass is useful in many clinical disciplines as an important procedure in early detection of metabolic disorders. Fats are one of the most important elements in maintaining the normal structure of the body and a number of different methods can be used to determine the total amount and distribution (1).Adipose tissue is a special type of connective tissue in which fat cells (adipocytes) predominate. These cells can be found in the connective tissue individually or in small groups, but they mostly join in large clusters that form adipose tissue, distributed throughout the body. There are two types of adipose tissue that differ in localization, structure, colour, and pathological characteristics. White adipose tissue (WAT) is made up of cells that contain one large droplet of yellow fat in their cytoplasm, and brown adipose tissue (BAT) is made up of cells that contain numerous drops of fat and many brown mitochondria, hence the name (2).

Distribution of fat tissue in adults depends on many innate (genetic) but also acquired life habits and especially diet. Most body fat is made up of white adipose tissue found in the abdomen, hips and thighs. It is a storehouse of energy that the body can use when starving and is located in the subcutaneous parts of the abdominal wall. WAT is found in almost all parts of the body. It is further divided into subcutaneous tissue and visceral adipose tissue (which envelops the omentum and abdominal organs). WAT, in addition to adipocytes, contains a matrix composed of collagen and reticular fibers, nerve fibers, stromovascular stroma, lymph nodes, immune cells in the form of macrophages, fibroblasts and preadipocytes that have the ability to secrete bioactive products (Figure 1). When the storage capacity in subcutaneous white adipose tissue is exceeded, either due to limited hyper-

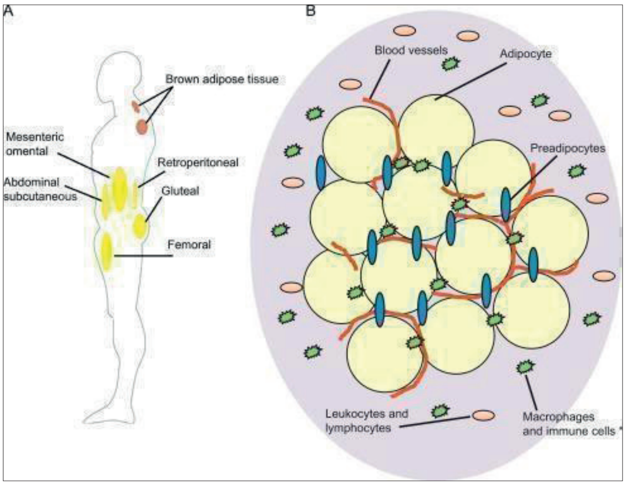

Figure 1. Histological structure and distribution of adipose tissue Retrieved from: https://www.sciencedirect.com/topics/immunology-and-microbiology/adipose-tissue99

plasia or limited hypertrophy, fats begin to accumulate ectopically in the abdominal organ area. When the body needs energy, certain hormones bind to receptors on adipocytes and lead to the hydrolysis of triacylglycerol to free fatty acids and glycerol (3).

The enzyme responsible for hydrolysis is lipase, and it activates adrenaline, noradrenaline, glucagon and adrenocorticotropin, which bind to the adipocyte membrane. Fat metabolism is also affected by: growth hormones, glucocorticoids, prolactin, corticotropin, insulin, and thyroid hormones (2). Adipocytes of visceral adipose tissue, in addition to receptors for certain hormones, also produces cytokines, growth factor and adipokines: TNF-α, leptin, adiponectin, resistin and ghrelin, which affect glucose homeostasis in the body, and directly affects insulin signaling. Insulin is the most powerful antilipolytic hormone in adipose tissue. It regulates the anabolic actions of fat cells, stimulates glucose uptake, free fatty acid uptake by the action of LPL on circulating triglycerides, inhibits lipolysis and re-esterifies

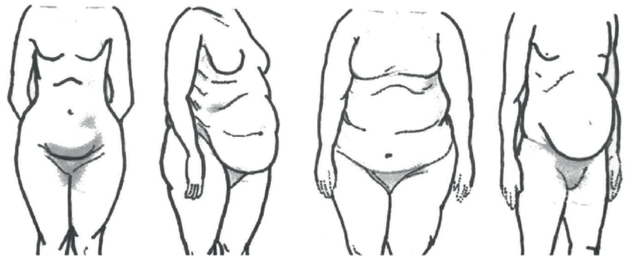

Figure 2. Adipose tissue distribution. Retrieved from: https://www.researchgate.net/publication/236934339

fatty acids into triglycerides. On average, adipose tissue makes up 15-20% in men and 20-25% in women.

Knowledge of different distributions of adipose tissue has clinical significance. Back in 1947, Jean Vague drew attention to two types of distribution of adipose tissue of this abdominal localization: android and gynoid type, i.e. central accumulation of fat and accumulation of adipose tissue in the lower body. So-called android fat. Central obesity is associated with an increased risk of diabetes and a number of chronic non-infectious diseases (4, 5).

White visceral adipose tissue is extremely important in the etiopathogenesis of insulin resistance (IR), and then pathological obesity, which is accompanied by the development of type 2 diabetes (T2DM) or complete metabolic syndrome (MetS) with cardiovascular and other complications. However it should be mentioned that visceral fat alone cannot directly cause IR because there are other factors that must be taken into account such as subcutaneous abdominal fat tissue and genetics (6, 7) Today, visceral adipose tissue is considered an endocrinological organ with a whole range of hormones that are the main mediators of IR development. The development of IR is directly related to the function of visceral adipose tissue, so the amount and distribution assessment of the adipose tissue is very important in monitoring these metabolic disorders. IR is primarily an acquired condition associated with excess body fat, although genetic causes have also been identified. It disrupts glucose deposition, which results in a compensatory increase in insulin production in the beta cells of the pancreas and this leads to hyperinsulinemia. The metabolic consequences of IR can result in hyperglycaemia, hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), but also other metabolic disorders (7).

According to the World Health Organization (WHO), overweight and obesity are defined as abnormal or excessive fat accumulation, which presents a health risk. Despite the widespread use of BMI in clinical practice, it has major limitations. It is a poor means of monitoring changes in body weight because there is no way to determine whether the changes come from fat or muscle weight, also, BMI does not distinguish visceral (central) fat from subcutaneous fat. Waist circumference, as a measure of central obesity, is another clinically feasible measurement that can be used independently or in conjunction with BMI to assess weight-related health risk. The WHO has identified gender-specific spectrum values indicating increased health risk (≥80 cm for women, ≥94 cm for men) and significantly increased health risk (≥88 cm for women, ≥102 cm for men). The ratio of waist and hip circumference is an even better indicator of central obesity, i.e. the presence of a larger amount of visceral adipose tissue (8) Adipose tissue can also be determined by measuring skin folds. Amount and distribution assessment of the adipose tissue can be performed by more sophisticated methods: DEXA scan, hydrostatic weighing, magnetic resonance imaging (MRI), computed tomography (CT) and bioelectrical impedance. These methods precisely specify the amount and type of adipose tissue, and are important for determining the impact of central obesity on the development of IR. Although CT and MRI are considered the gold standard in measuring the amount of intra-abdominal adipose tissue, these methods are expensive and impractical (9)

In the last few years, a positive correlation has been demonstrated between visceral adipose tissue measured by CT and visceral adipose tissue measured by bioelectrical impedance (10, 11). Unlike CT, bioelectrical impedance can be used in family medicine clinics. Visceral adipose tissue is seen as a highly active endocrine organ that synthesizes cytokines and hormones called adipokines or adipocytokines. They affect the function of surrounding and distant organs, as well as adipose tissue itself. These cytokines are: leptin, adiponectin, resistin, interleukin 6 (IL-6), plasminogen activator inhibitor (PAI-1), tumor necrosis factor (TNF-α) and many others (12) Growth hormone, glucocorticoids, prolactin, corticotropin, and thyroid hormones also play a role in different stages of adipose tissue metabolism. Some of the most important cytokines and hormones are produced exclusively in visceral adipose tissue.

Anatomically and functionally speaking, they belong to the portal vein system. The fatty acids created by lipolysis go directly to the liver and are associated with the development of hepatic steatosis, an important link in the etiopathogenesis of IR. The portal theory of the origin of IR is described, according to which the visceral adipose tissue of the omentum and mesentery plays the most important role in the development of IR (13). Visceral adipose tissue in the area of the mesentery and omentum has a specific histological structure and function. Increased WAT in the area of mesenterium with the omentum correlates with anthropometrically proven central obesity (14). Visceral adipose tissue provides the first metabolic responses to disorders that occur in the interaction between the CNS and the GIT and pathological changes in the small intestinal mucosa. Increased amount of visceral adipose tissue as a highly active endocrine organ can lead the onset of IR.

Evidence shows that even the smallest weight loss of 10% is considered a health success because it has been proven to bring health benefits. Persistence of medical staff and constant contact with people who are obese or/and have IR is the best way to prevent complications and relapse (7).

2. OBJECTIVE

The aim of this study were a) to determine the total amount of adipose tissue and the amount of visceral adipose tissue in selected adult patients with BMI≥25; b) to register clinical symptoms that could indicate insulin resistance; c) to perform insulin resistance tests in all patients; and d) to assess the correlation between the amount of visceral adipose tissue with laboratory-verified insulin resistance.

3. PATIENTS AND METHODS

Subjects were adults of both sexes ages from 20 to 77 years, who were patients in two family medicine clinics. Including criteria for entry into the study were: increased body weight, BMI ≥2, normal blood glucose values in several measurements. Subjects visited their family medicine doctor due to non-specific problems. Subjects were included in the study with voluntary consent. The study included 80 patients. 11 patients did not complete the study. All subjects underwent anthropometric measurements (BMI, Waist circumference, Waist-hip ratio) and body structure assessment using the bioelectrical impedance method. The amount of total adipose tissue was measured in kilograms, and the amount of adipose tissue in the size of surface areas (cm^2). According to the values of visceral adipose tissue, the subjects were divided into two groups: the experimental group that had pathological amount of visceral fat (VFA ≥ 110 cm^2 and the control group that had a normal amount of visceral fat (VFA < 100 cm^2). All patients underwent an oral glucose tolerance test (OGTT) and insulinemia . According to the results expressed using HOMA method, the presence of milder or more severe IR was determined. HOMA-1 values > 2 were used for the diagnosis of IR. The results obtained in both groups were statistically

Age	Total 20-77	20-29	30-39	40-49	50-59	60+
Female	39 (59.1%)	10 (83.3%)	7 (46.7%)	8 (44.4%)	7 (70.0%)	7 (63.6%)
Male	27 (40.9%)	2 (16.7%)	8 (53.3%)	10 (55.6%)	3 (30.0%)	4 (36.4%)
Total	66 (100.0%)	12 (18.2%)	15 (22.7%)	18 (27.3%)	10 (15.2%)	11 (16.7%)

Table 1. Demographic characteristics of the sample of all participants by gender and sex

Age	Total 20-75	20-29	30-39	40-49	50-59	60+
Female	17 (56.7%)	7 (100.0%)	3 (37.5%)	3 (33.3%)	2 (66.7%)	2 (66.7%)
Male	13 (43.3%)	0 (0.0%)	5 (62.5%)	6 (66.7%)	1 (33.3%)	1 (33.3%)
Total	30 (100.0%)	7 (23.3%)	8 (26.7%)	9 (30.0%)	3 (10.0%)	3 (10.0%)

Table 2. Demographic characteristics of the other paricipants in the study - control group

Age	Total 20-77	20-29	30-39	40-49	50-59	60+
Female	22 (61.1%)	3 (60.0%)	4 (57.1%)	5 (55.6%)	5 (71.4%)	5 (62.5%)
Male	14 (38.9%)	2 (40.0%)	3 (42.9%)	4 (44.4%)	2 (28.6%)	3 (37.5%)
Total	36 (100.0%)	5 (13.9%)	7 (19.4%)	9 (25.0%)	7 (19.4%)	8 (22.2%)

Table 3. The demographic characteristics of the experimental group

VISCERAL FAT AREA (cm^2) range	Total	M	F
VFA 110–149,9	10 (27.8%)	7 (50.0%)	3 (13.6%)
VFA 150–199,9	17(47.2%)	4 (28.6%)	13 (59.1%)
VFA 200–300	9 (25.0%)	3 (21.4%)	6 (27.3%)
Total	36 (100.0%)	14 (38.8%)	22 (61.1%)

Table 4. Visceral fat area in subjects of experimental group

	Experimental		Control	
HOMA-IR	N	%	N	%
HOMA–IR < 2	6	18.9	20	66.7
HOMA–IR > 2	30	81.1	10	33.3
Total	36	100.0	30	100.0

Table 5. Subjects of the experimental and group according to the results of IR-HOMA test

analyzed to determine whether the increased amount of adipose tissue had an impact on the occurrence of IR. For the amount and distribution of fat assessment, anthropometric measurements and a complete analysis of body structure will be performed using bioelectrical impedance.

Statistical analysis

Data is presented in a form of tables as the absolute numbers and percentages from total. Analysis of difference is performed by the nonparametric chi-square test at the level of significance of 95%. Analysis is performed using the statistical software for biomedical studies MedCalc v12.3 (Antwerp, Belgium).

4. RESULTS

Results of our study are presented in Tables 1-5.

Table 1 shows the demographic characteristics of all subjects. There were 39 women and 27 men with an average age of 50 years. All subjects underwent anthropometric measurements and body structure analysis. Statistical analysis of gender distribution between the age groups indicate that it is uniform without statistically significant difference between age groups ($\chi2=6.059$; $p=0.194$). Total amount of 36 patients had visceral fat values over 110 cm^2 and they represented the experimental group. 30 subjects had visceral fat values below 110 cm^2 and represented a control group. Both groups had subjects of both sexes and all age groups. The demographic characteristics of the control group are shown in Table 2, and demographic characteristics of experimental group in Table 3.

The tables indicate that subjects of both groups had similar demographic characteristics by age and gender. In that sense there were no statistically significant differences between the groups by gender ($\chi2=0.013$; $p=0.909$) nor age ($\chi2=3.758$; $p=0.232$). The amount of pathological value of visceral adipose tissue in the experimental group is shown in Table 4.

Statistical analysis of VFA between genders indicate that there is no statistically significant difference between males and females ($\chi2=5.877$; $p=0.053$).

Table 5 shows that in the experimental group 30 patients had IR, which is 81%, and in the control group 10 patients had a proven presence of IR, which is 33.3%. These statistically significant differences ($\chi2=15.104$; $p=0.0001$) show that the amount of visceral adipose tissue considerably affects the formation of IR.

5. DISCUSSION

According to the World Health Organization (WHO), overweight and obesity are defined as abnormal or excessive accumulation of fat that poses a health risk. In the general population, the measure of obesity is the body mass index (BMI), which is obtained by dividing a person's weight (in kilograms) by the square of his height (in meters). A BMI of 25 to 29.9 is defined as overweight, and a BMI greater than 30 corresponds to pathological obesity or obesity (8). Fats are one of the most important elements in maintaining the normal structure of the body and a number of different methods can be used to determine the total amount and distribution (1).

Adipose tissue is found within the human body in two forms: white adipose tissue (WAT) and brown adipose tissue (BAT). BAT is found in almost all parts of the body. It is further divided into subcutaneous tissue and visceral adipose tissue (which surrounds the omentum and abdominal organs). White adipocytes are a large reservoir of energy in the body. They play a role in energy consumption, energy storage in the form of individual drops of triacylglycerol and protection of other organs and tissues from ectopic fat accumulation, or lipotoxicity. When the storage capacity in subcutaneous white adipose tissue is exceeded, either due to limited hyperplasia or limited hypertrophy, fats begin to accumulate ectopically in the abdominal organ area. When the body needs energy, certain hormones bind to receptors on adipocytes and lead to the hydrolysis of triacylglycerol to free fatty acids and glycerol. This process is called lipolysis (2, 3).

Insulin is the strongest antilipolytic hormone in adipose tissue and its anabolic action stimulates the intake of glucose and free fatty acids by the action of LPL, on circulating triglycerides and by inhibiting lipolysis and re-esterification of fatty acids into triglycerides. The development of IR usually results in a compensatory increase in endogenous insulin production due to the impaired entry of glucose into the cells. Visceral adipose tissue also has its lymph nodes and there is a possibility of tissue infiltration with macrophages and high production of proinflammatory cytokines (low-grade chronic inflammatory condition). TNF-α and interleukins directly affect cell sensitivity to insulin with receptor blockade. Reduced production of hormones in fat cells, which prevent the metabolic effects of proinflammatory cytokines such as adiponectin and leptin, is the most important link in the pathophysiology of IR. Liver infiltration with fat leads to NAFLD, which can further affect the development of numerous CNDs (7).

Different anthropometric measurements are used to estimate the amount of adipose tissue and the degree of obesity. In practice, the waist and hip circumference and their ratio are most often used. According to WHO, BMI has not been shown to be an adequate parameter for assessing body structure and risk assessment for CVB (8). Other, more precise methods used are: hydrostatic weighing, DEXA scan, CT, MRI, ultrasound and BIA. Unlike anthropometric measurements, more sophisticated methods can accurately determine the amount of total body fat and compare it to the percentage of visceral adipose tissue, muscle and bone. CT and MRI are considered the gold standard. However, recent research suggests that BI could replace CT, as the gold standard, because of its affordability and cost (10, 11).

Unlike CT, bioelectrical impedance can be used in family medicine clinics. Visceral adipose tissue provides the first metabolic responses to disorders that occur in the interaction between the CNS and the GIT and pathological changes in the small intestinal mucosa. WAT, as a highly active endocrine organ with the possibility of an immune response, triggers metabolic disorders through hormonal imbalance and proinflammatory cytokines, so an increased amount of visceral adipose tissue with its endocrine and metabolic function is thought to precede the onset of IR (13, 14).

The results of this study showed that occurrence of insulin resistance more frequent in people with visceral adipose tissue compared to those with amount ≤ 110 $cm^{2.}$ Nowadays, in pandemic era of COVID-19, visceral fat tissue measurement is a very important diagnostic and prognostic factor. COVID-19 patients with higher amounts of visceral adipose tissue had more complications (15).

6. CONCLUSION

Abdominal fat tissue has two different location: subcutaneous area and visceral adipose tissue which is present in abdominal cavity. There is structural and functional differences between them. Visceral fat tissue is present mainly in the mesentery and omentum, and drains directly through the portal circulation on to the liver. It is highly active endocrine and immune organ.

Increased amount of visceral adipose tissue in overweight patients significantly affects the occurrence of IR. The results of this study showed that the occurrence of insulin resistance is significantly more frequent in people with quality of visceral fat tissue more than 110 cm^2 compared to those whose amount was less than 110 cm^2.

The measure of amount of visceral fat tissue should be routine procedure in family medicine practice.

In all patients with an increased amount of visceral adipose tissue, it is necessary to introduce intensive preventive measures to stop the development of diabetes and other complications as a result of IR presence.

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- **Conflict of interest**: None declared.
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