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DIFFERENCES IN METABOLIC PARAMETERS IN PATIENTS WITH DIFFERENT DEGREES OF OBESITY

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Abstract. Background: *The current obesity epidemic inevitably affects the health of patients and leads to a deterioration in their quality of life. According to scientific literature, obesity per se leads to multiple metabolic abnormalities. However, it is still not clarified what the precise interrelations between the degree of obesity and the presence of various metabolic and hormonal disturbances are, especially in women.* ***Objective:*** *The present study aimed to compare the differences in metabolic parameters between premenopausal women with overweight and obesity, thus evaluating the role of obesity in the occurrence of metabolic imbalance.* ***Materials and methods:*** *We conducted a retrospective study of a total of 352 overweight and obese patients (18-50 years) with a body mass index (BMI)≥25 kg/m^2. The obesity classification of the selected cohort of patients was based on the WHO criteria for BMI. Clinical, anthropometric, and metabolic parameters were extracted from the medical records and analyzed.* ***Results:*** *In the investigated women, BMI increase correlated significantly with higher levels of uric acid ($p = 0.019$) and alanine aminotransferase ($p = 0.015$), as well as with elevated fasting insulin levels and insulin resistance index ($p<0.001$). Conversely, lipid profile parameters, prevalence of carbohydrate abnormalities, and hypertension did not differ between patients with slight, moderate, and severe obesity ($p>0.05$). Patients with severe obesity had slightly higher TSH levels (2.8 vs. 2.5 mIU/L, $p = 0.041$), and significantly increased fatty liver index ($p<0.001$) compared to leaner women.* ***Conclusions:*** *The increase of fat mass deposition in premenopausal women is associated mainly with enhanced insulin resistance, hepatic disturbances, and uric acid elevation, which could be the earliest markers of metabolic dysfunction. Screening and monitoring of metabolic parameters in obese premenopausal women is essential for the prevention of further health complications.*

Key words: *metabolic abnormalities, fatty liver, obesity, overweight, hypertension, diabetes*

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INTRODUCTION

Adipose tissue is the major energy storage site in the human body [1]. The combination of caloric intake and low physical activity leads to weight gain, which can subsequently promote overweight and obesity [2]. When energy intake chronically exceeds energy expenditure, adipose tissue undergoes transformation through the hypertrophy and hyperplasia of adipocytes. This leads to the accumulation of fat mass and is associated with increased tissue remodeling, activation of inflammation, and the

development of metabolic abnormalities, such as insulin resistance [3, 4].

According to recent data, obesity has reached pandemic proportions, presenting a significant social and health problem [5]. In 2024, Gaskin CJ et al. reported that over 660 million adults and over 100 million children suffer from obesity [6].

Obesity is a chronic disease that can lead to an increased risk of type 2 diabetes and cardiovascular diseases, as well as joint and reproductive health disturbances, thus significantly affecting the quality of life [7]. Recently, Romeo et al. introduced the concept of systemic metabolic disorder (SMD) and distinguished different stages of obesity-related metabolic abnormalities, which affect morbidity and mortality. The development of a new clinical system for evaluation and staging of obesity, considering different metabolic complications, is a key prerequisite for improving public health, endorsed by multiple international societies [8, 9, 10, 11]. Overweight and obesity are usually diagnosed by using the body mass index (BMI), which correlates directly with many cardiometabolic outcomes [12]. Nevertheless, BMI is a surrogate marker of obesity, and additional measurements, such as waist circumference, improve the diagnosis of the condition [10]. However, imaging studies, such as magnetic resonance and computed tomography, remain the gold standard for determining body composition [13].

Obesity is strongly associated with metabolic disturbances, but individuals with similar BMI might be in different SMD stages [11]. Some normal-weight individuals present with pronounced insulin resistance and elevated triglyceride levels, predisposing them to a higher cardiovascular risk. Conversely, some overweight or obese patients might be metabolically healthy (MHO), although over time, the majority of them develop metabolic disturbances [14-17].

Despite the presence of MHO, obesity is still associated with more than 200 metabolic and non-metabolic chronic diseases [18]. Therefore, obesity prevention is the key factor in reducing the incidence of socially significant chronic conditions, deteriorating the health of the population [11]. Moreover, it is important to explore if and how the degree of obesity influences complications. Therefore, our study aims to explore the associations between different obesity categories and metabolic disturbances by focusing on the specific group of premenopausal women, who represent a rarely investigated group of patients because of the well-known protective estrogen effects on metabolism.

MATERIALS AND METHODS

Participants and procedures

This retrospective study includes patients referred to a tertiary endocrine center for overweight, obesity and/or metabolic disorders for the period 2019-2022. Inclusion criteria were Caucasian origin, female sex, reproductive age (18-50 years), and body mass index (BMI) ≥ 25 kg/m^2. The study was approved by the Local Ethics Committee, and patients gave informed consent for anonymous use of their data. A total of 352 female patients between 18 and 50 years of age were selected. Their anthropometric, biochemical, and hormonal parameters were extracted from the hospital's electronic database. The pseudonymized data, considering different anthropometric and clinical characteristics (height, weight, waist circumference, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP) values, and concomitant therapy), have been collected and used for analyses.

Collected laboratory data included blood count, fasting glucose, oral glucose tolerance test (OGTT) in patients without diabetes mellitus type 2 (DMT2), total cholesterol, low-density cholesterol (LDL-ch), high-density cholesterol (HDL-ch), triglycerides (TG), uric acid (UA), creatinine, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma-glutamyl transferase (GGT), fasting insulin, and thyroid-stimulating hormone (TSH). Biochemical parameters were measured enzymatically with an automatic analyzer (Cobas Mira Plus; Hoffmann-La Roche). TSH and insulin were measured with commercially available IRMA kits.

Measurements and definitions

The BMI and waist circumference (WC) cut-off values were estimated based on the recommendations of the World Health Organization [5] and the International Diabetes Federation [19]. According to the WHO, obesity is defined by BMI according to the formula: weight (kg)/height (m^2), with overweight patients being those with a BMI of 25-29.99 kg/m^2, and obese patients being those with a BMI above 30 kg/m^2. Obesity degree group I has been defined as BMI 30-34.99 kg/m^2, group II as BMI 35-39.99 kg/m^2, and group III as BMI ≥ 40 kg/m^2. Prediabetes (impaired fasting glycemia and/or impaired glucose tolerance) and DMT2 were diagnosed according to generally accepted international criteria [20].

HOMA-IR (fasting insulin level (μU/L) × fasting plasma glucose level (mmol/L)/22.5) was used as a tool to estimate insulin resistance.

The fatty liver index (FLI) was calculated using the formula: FLI = (e 0.953*loge (triglycerides) + 0.139*BMI + 0.718*loge (ggt) + 0.053*waist circumference - 15.745)/(1 + e 0.953*loge (triglycerides) + 0.139*BMI + 0.718*loge (ggt) + 0.053*waist circumference - 15.745) * 100 [21].

Statistical analysis

All indicators are presented as mean ± SD [median]. For the analysis of dichotomous variables, χ^2 and Fisher's exact test were used. The Kruskal-Wallis test and the Mann-Whitney test were used for intergroup analysis because of the non-parametric data distribution. Statistical significance was set at the "p" level < 0.05. Statistical analysis was performed with MedCalc Statistical Software version 23.3.7 (MedCalc Software Ltd, Ostend, Belgium).

RESULTS

The metabolic parameters of the patients with different degrees of obesity are presented in Table 1. There were no significant differences in the age distribution of women across the four groups (overweight, obesity groups I, II and III) (p = 0.2646). As expected, parameters such as BMI and waist circumference showed significant differences among the studied groups. Metformin was the most common drug used in the cohort. The percentage of patients treated with metformin was similar across the groups with different degrees of obesity, as well as between patients with obesity group III compared to the leaner individuals (34.03% vs. 40.35%, p = 0.249).

When comparing the metabolic parameters, no statistically significant difference was found in lipid parameters (HDL-ch, LDL-ch, TG, total cholesterol), while uric acid levels increased significantly with a higher degree of obesity (p = 0.019). Regarding liver enzymes (ASAT, ALAT, GGT), ALAT levels increased gradually in parallel with increased fat mass deposition, while the levels of ASAT and GGT did not differ significantly among obesity groups.

When comparing fasting glucose levels, patients among the four groups did not show significant differences (p = 0.152), while fasting insulin levels and HOMA-IR were significantly higher in women with a greater degree of obesity (p < 0.001).

When comparing groups with BMI below and above 40, women with BMI ≥ 40 had notably higher uric acid levels (p = 0.010) and higher insulin levels (p < 0.001). When analyzing the data of obese patients (BMI ≥ 30) only, similar results were obtained. Fasting insulin and uric acid levels were increased in patients with more severe obesity (Table 1).

The occurrence of arterial hypertension was similar between individuals with BMI≥40 and those with lower BMI (47.4% vs. 44.1%, p = 0.567). The prevalence of impaired glucose tolerance (2% vs. 5%), impaired fasting glucose (4% vs. 5%), and DMT2 (11.8% vs. 16. 6%) was also similar in the two groups (p>0.05 for all).

Additionally, patients with severe obesity (BMI ≥ 40) showed increased TSH levels compared to leaner women (2.8 vs. 2.5 mIU/L, p = 0.041).

The fatty liver index was used to indirectly assess liver dysfunction, and significant differences were observed between the groups (Figure 1).

In non-diabetic patients, the values of glucose and insulin were monitored during the oral glucose tolerance test at 120 minutes post-glucose load. Insulin and glucose levels at the second hour after glucose load did not show statistically significant differences between the patients in different obesity categories (p > 0.05).

DISCUSSION

Our results showed the differences in metabolic parameters between overweight individuals and obese patients with different degrees of obesity. The percentage of hypertension, carbohydrate, and lipid abnormalities did not differ significantly among the monitored groups. However, levels of insulin and uric acid increased in parallel with increasing fat mass. Obesity is a well-established risk factor for hypertension, dyslipidemia, and hyperuricemia, and plays an important role in the development of metabolic syndrome [22]. Several large epidemiological studies in recent decades have shown that the prevalence of metabolic syndrome is positively associated with serum uric acid levels, which in turn are related to waist circumference and BMI [23-27]. In women, several studies have investigated the associations between increased uric acid and obesity complications. Li Y. found that the risk of metabolic syndrome was higher in premenopausal women than in postmenopausal women in the highest quartile of uric acid [28]. Feng et al. demonstrated that hyperuricemia correlated with higher BMI (p < 0.0001), systolic blood pressure, diastolic blood pressure, fasting blood glucose, triglycerides (p = 0.0006), total cholesterol, LDL-cholesterol, and lower HDL-cholesterol levels [29]. Additionally, a large study involving 3,808 women from the Jinchang cohort examined the relationship between serum uric acid levels and metabolic syndrome in premenopausal and postmenopausal women. Premenopausal and postmenopausal women with hyperuricemia were 2.81 (95% CI: 1.72–4.61) and 2.10

Table 1. Anthropometric, biochemical, and hormonal indicators in women with varying degrees of obesity according to BMI

	Oveweight n = 24	Obesity group I n = 111	Obesity group II n = 103	Obesity group III n = 114	p_1	p_2
Age (years)	38.21 ± 8.47 [39.5]	37.29 ± 8.91 [39.0]	35.15 ± 10.19 [36.0]	35.67 ± 8.63 [36.0]	0.265	0.244
BMI (kg/m^2)	28.325 ± 1.17 [28.26]	32.976 ± 1.26 [33.25]	37.02 ± 1.45 [37.02]	46.04 ± 5.65 [44.44]	< 0.001	< 0.001
Waist (cm)	98.58 ± 8.78 [99.0]	98.58 ± 7.13 [104.0]	111.43 ± 8.04 [111.0]	127.00 ± 15.69 126.0]	< 0.001	< 0.001
Height/waist	0.59 ± 0.05 [0.59]	0.34 ± 0.04 [0.63]	0.68 ± 0.05 [0.67]	0.76 ± 0.1 [0.77]	< 0.001	< 0.001
Systolic BP (mmHg)	121.96 ± 9.88 [120.0]	122.92 ± 20.58 [120.0]	124.90 ± 17.66 [124.5]	127.35 ± 17.32 [120.0]	0.133	0.129
Diastolic BP (mmHg)	79.96 ± 8.73 [80.0]	79.01 ± 12.68 [80.0]	80.29 ± 9.71 [80.0]	80.35 ± 10.14 [80.0]	0.449	0.273
HOMA-IR	2.74 ± 1.74 [2.18]	3.95 ± 2.62 [3.42]	4.97 ± 2.68 [4.25]	7.89 ± 13.56 [4.78]	< 0.001	0.001
Fasting glucose (mmol/l)	6.08 ± 1.14 [5.65]	5.90 ± 1.11 [5.65]	6.11 ± 1.57 [5.71]	6.29 ± 1.56 [5.86]	0.153	0.074
Glucose 120' after glucose load (mmol/l)	5.99 ± 2.07 [5.25]	5.82 ± 2.07 [5.25]	5.86 ± 2.12 [5.40]	5.82 ± 2.08 [5.45]	0.941	0.974
Total Cholesterol (mmol/l)	5.17 ± 0.97 [5.11]	5.18 ± 0.98 [5.26]	4.96 ± 1.12 [4.96]	4.96 ± 0.93 [4.91]	0.173	0.112
HDL-cholesterol (mmol/l)	1.35 ± 0.35 [1.26]	1,25 ± 0.35 [1.19]	1.21 ± 0.31 [1.15]	1.18 ± 0.28 [1.10]	0.084	0.209
LDL-cholesterol (mmol/l)	3.02 ± 0.76 [3.07]	3.17 ± 0.87 [3.12]	3.039 ± 1.02 [2.95]	3.09 ± 0.78 [2.99]	0.662	0.464
Triglycerides (mmol/l)	2.49 ± 3.69 [1.61]	1.75 ± 1.05 [1.52]	1.57 ± 0.84 [1.37]	1.53 ± 0.68 [1.41]	0.501	0.380
ALAT (IU/l)	20.90 ± 11.91 [19.00]	27.54 ± 19.73 [21.0]	29.65 ± 17.553 [25.50]	31.44 ± 22.21 [27.0]	0.015	0.095
ASAT (IU/l)	19.06 ± 10.91 [15.0]	22.48 ± 21.53 [17.0]	21.03 ± 12.95 [17.0]	22.57 ± 16.32 [19.0]	0.135	0.281
GGT (IU/l)	46.00 ± 67.34 [21.00]	42.58 ± 89.88 [24.50]	39.60 ± 53.66 [26.0]	36.87 ± 33.72 [27.0]	0.180	0.524
Uric Acid (µmol/l)	320.44 ± 110.98 [305.0]	331.56 ± 85.23 [327.0]	344.82 ± 69.63 [338.0]	358.09 ± 87.18 [363.0]	0.019	0.025
TSH (mIU/L)	3.67 ± 3.45 [2.70]	2.87 ± 2.19 [2.60]	3.35 ± 5.85 [2.40]	3.51 ± 3.10 [2.80]	0.165	0.084

p_1 – differences between the four groups of women with overweight and obesity; p_2 – differences between the obesity groups – group I, II and III

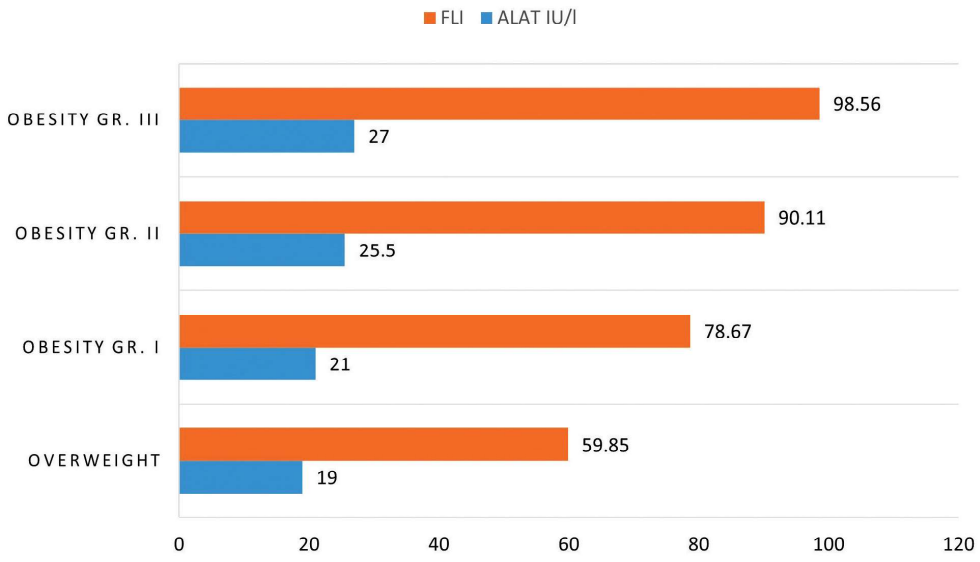

Fig. 1. The levels of ALAT and fatty liver index (FLI) among individuals with different obesity categories

(95% CI: 1.44–3.08) times more likely to have metabolic syndrome than women without hyperuricemia. The study found a significant correlation between uric acid levels and metabolic syndrome, with the relationship being stronger in premenopausal than in postmenopausal women [30]. Thus, uric acid might be an important early marker for health deterioration in premenopausal women associated with the degree of obesity.

The interrelations between hyperinsulinemia, insulin resistance, and arterial hypertension are also important for clinical practice. According to some studies, more than 50% of patients with arterial hypertension have insulin resistance [31]. Decreased insulin effects and compensatory hyperinsulinemia might aggravate the inflammatory response, increase the activity of the sympathoadrenal system, stimulate the renin-angiotensin-aldosterone system, leading to elevated circulating blood volume, cardiac output, and total peripheral vascular resistance [32]. There is evidence that insulin resistance is an independent risk factor and predictor of the development of arterial hypertension [33].

Moreover, hyperuricemia, insulin resistance, increased HbA1c, and obesity might potentiate each other and synergically facilitate the progression of metabolic complications. Just as obesity alters the balance between pro- and anti-inflammatory factors and causes insulin resistance, so the hyperuricemic state induces oxidative stress and inflammatory response [34], thus amplifying insulin resistance [35, 36]. Therefore, individuals with hyperuricemia, high HbA1c levels, insulin resistance, and obesity should be considered high-risk and prioritized for early detection, prevention, and treatment in order to slow the progression of metabolic complications [32, 36].

Our study showed significant differences in fatty liver index (FLI) in different obesity categories despite similar lipid and glucose levels. Regarding the FLI and its relationship with other metabolic abnormalities, Hirata A. et al. studied 1,498 men and 2,941 women in the general Japanese population for a period of 3 years, analyzing the role of FLI for the development of diabetes. When comparing the groups with high and low FLI without impaired fasting glycemia, the high FLI was significantly associated with the development of diabetes in both men (HR 1.90; 95% CI, 1.08–3.36) and women (HR 1.72; 95% CI 1.18–2.51). The authors concluded that FLI is associated with the development of diabetes, irrespective of gender and carbohydrate intake, and may be a useful predictor of future diabetes risk even in people without increased fasting glucose [37]. Another Asian retrospective longitudinal study showed that with increasing FLI levels, the risk of major cardiovascular events rose, especially in the presence of MetS. The risk of liver-related mortality is also increased with a higher FLI score [38].

According to our results, TSH levels are similar in most obese patients. However, they increased slightly in patients with excessive grade-III obesity. Thyroid hormones play a crucial role in regulating glucose and lipid metabolism, blood pressure, and energy expenditure. Recent studies have found that patients with hypothyroidism have an increased risk of metabolic syndrome [39]. In a cross-sectional study in a Chinese population, Song B. examined the association of elevated body mass index (BMI) and metabolic disorders with thyroid diseases, demonstrating that metabolically unhealthy individuals have a higher risk of developing thyroid disorders than metabolically healthy individuals, regardless of BMI [40]. Leptin has been reported to be directly related to thyroid disorders by increasing the expression and synthesis of thyrotropin-releasing hormone (TRH), which, in turn, affects serum TSH levels [41].

Considering the metabolic complications of obesity, it should be noted that almost half of the patients classified as MHO at baseline developed at least one metabolic abnormality by follow-up [42]. Individuals with MHO can be detected at any age, but the prevalence of MHO progressively decreases with age [43]. In women, the prevalence of MHO is significantly lower in postmenopausal compared to premenopausal female individuals, and one-third of MHO women become metabolically unhealthy during menopause [44]. Different risk profile of women before and after menopause suggests the need for specific investigations in both groups in order to reveal the proper associations between obesity degree and metabolic complications. For instance, in a group of high-risk elderly men and women attending an emergency clinic, the obesity grade increase was associated with a higher prevalence of hypertension, as well as a gradual increase in glucose levels [45].

On the other hand, our study in younger premenopausal women did not find similar associations. The most important parameters influenced by the increase in our cohort were insulin resistance, markers of hepatic impairment, and uric acid levels. Further studies are needed to reveal the significance of these parameters for postmenopausal women.

CONCLUSIONS

In conclusion, our study emphasizes the differences in metabolic parameters in premenopausal women with different degrees of obesity. The increase of fat

mass deposition has been associated mainly with enhanced insulin resistance, hepatic disturbances, and uric acid elevation, while lipid profile, hypertension, and carbohydrate disturbances have not been related to the BMI category. The main limitation of our study is its retrospective design. Thus, further studies are needed to establish the influence of the degree on menopausal metabolic changes. Nevertheless, early diagnosis and treatment of metabolic abnormalities associated with obesity in premenopausal women might be an important tool for the prevention of late health complications in the postmenopausal period.

Conflict of interest: *The authors declare that they have no conflict of interest.*

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Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki. The study was approved by the Local Ethics Committee, and patients gave informed consent for anonymous use of their data.*

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