Ann. Acad. Med. Siles. (online) 2016; 70: 133–142
eISSN 1734-025X
DOI:10.18794/aams/62402

PRACA ORYGINALNA
ORIGINAL PAPER

Evaluation of bone metabolism in obese men and women with metabolic syndrome

Wpływ zespołu metabolicznego na metabolizm kości otyłych mężczyzn i kobiet

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ABSTRACT

BACKGROUND: It was suggested that metabolic syndrome (MS) is an additional risk factor that increases the risk of osteoporotic fractures. The aim of this study was to evaluate the impact of metabolic syndrome on bone metabolism and the risk of osteoporotic fracture in obese men and women.
MATERIALS AND METHODS: The study involved 40 obese men and 40 obese women, divided into 2 subgroups: patients **without MS** (20 men and 20 women); and patients with MS (20 men and 20 women). The serum levels of PTH, 25-OH-D_3, CTX1, osteocalcin, FGF23, total Ca and P were determined. The total absolute fracture risk was estimated using the Fracture Risk Assessment Tool. The control group consisted of 15 normal body mass, healthy men and women similar in age.
RESULTS: Obese women with MS have a higher risk of osteoporotic fractures (3.0 vs. 1.6%; $p < 0.001$) and serum levels of phosphorus (1.8 vs. 1.12 mmol/l; $p < 0.001$) but lower 25(OH)D_3 (7.3 vs. 34.6 ng/ml; $p < 0.01$) than obese women without MS.
There were no differences in the risk of osteoporotic fracture or other study parameters between obese men with and without MS.
Women with MS had lower serum CTX_1 levels (0.27 ng/ml vs. 0.41 ng/ml; $p < 0.05$) than men.
CONCLUSIONS: Metabolic syndrome does not influence the **selected parameters of bone metabolism** in either men or women. However, women with metabolic syndrome have lower serum 25-OH-D_3 levels.
Women, but not men with metabolic syndrome have a higher 10-year absolute fracture risk than **obese women without metabolic syndrome**.

KEY WORDS
metabolic syndrome, obesity, bone metabolism, fracture risk

Received: 13.02.2016 **Revised:** 27.03.2016 **Accepted:** 30.03.2016 **Published online:** 21.07.2016

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STRESZCZENIE

WSTĘP: Wydaje się, że zespół metaboliczny (MS) jest dodatkowym czynnikiem zwiększającym ryzyko złamań osteoporotycznych. Celem tego badania była ocena wpływu zespołu metabolicznego na metabolizm kości i ryzyko złamań osteoporotycznych u otyłych mężczyzn i kobiet.
MATERIAŁ I METODY: W badaniu wzięło udział 40 otyłych mężczyzn i 40 otyłych kobiet. Badanych podzielono na 2 grupy: pacjentów z otyłością bez MS (20 mężczyzn i 20 kobiet) i pacjentów z MS (20 mężczyzn i 20 kobiet). W grupach badanych oznaczono w surowicy stężenie parathormonu (PTH), 25-OH-D_3, C-końcowego usieciowanego peptydu kolagenu typu 1 (CTX1), osteokalcyny, FGF23, wapnia (Ca) i fosforu (P). Ryzyko złamania osteoporotycznego oszacowano, stosując skalę FRAX (Fracture Risk Assessmen Tool). Grupę kontrolną stanowiło 15 zdrowych mężczyzn i kobiet w podobnym wieku.
WYNIKI: Otyłe kobiety z MS charakteryzowały się większym ryzykiem złamań osteoporotycznych (3,0 vs 1,6%; $p < 0,001$), stężeniem w surowicy fosforu (1,8 vs 1,12 mmol/l; $p < 0,001$) oraz mniejszym stężeniem 25-OH-D_3 (7,3 vs 34,6 ng/ml; $p < 0,01$) w porównaniu z kobietami bez MS. Nie stwierdzono istotnych różnic w ryzyku złamań osteoporotycznych i stężeniach ocenianych parametrów między mężczyznami z otyłością bez MS i z MS. Kobiety z MS miały niższe stężenie CTX-1 (0,27 ng/ml vs. 0,41 ng/ml; p) w porównaniu z mężczyznami.
WNIOSKI: Zespół metaboliczny nie wpływa na wskaźniki metabolizmu kostnego u mężczyzn i kobiet. Kobiety z zespołem metabolicznym charakteryzują się jednak mniejszym stężeniem 25-OH-D_3. Kobiety, ale nie mężczyźni, z zespołem metabolicznym, wykazują większe 10-letnie ryzyko złamania osteoporotycznego niż kobiety z otyłością bez zespołu metabolicznego.

SŁOWA KLUCZOWE
zespół metaboliczny, otyłość, metabolizm kości, ryzyko złamań

INTRODUCTION

The last decade has led to new insight into the role of fat tissue in the body's homeostasis. Adipose tissue, which in addition to adipocytes contains connective tissue cells, nervous, circulatory and immune system cells [1], is now regarded as not only as a deposit of energy, but also as an endocrine organ, which is the source of numerous hormones and cytokines such as leptin, TNFα, IL6, adiponectin, resistin, RAAS components (renin-angiotensin-aldosterone system) and others [1,2]. The results of studies on visceral fat have shown that its accumulation in the abdominal cavity is the starting point for adverse changes leading to metabolic syndrome (MS). Researchers do not fully agree on the existence of a link between MS and bone metabolism. Drawing conclusions is hampered by the fact that patients with MS are a very heterogeneous group (not every patient has all the components of MS). Von Muhlen et al. [3] demonstrated that MS can be an additional risk factor for osteoporotic fractures. The authors found that bone mineral density (BMD) in MS patients was lower than in those without this syndrome. Moreover, the incidence of osteoporotic non-vertebral fractures was higher in participants with MS. Szulc et al. [4] reported the existence of an inverse correlation between BMD and visceral fat, however, no correlation with the other MS components was noticed. Additionally, MS patients, despite a higher number of falls observed, had a lower number of fractures.

Observations of bone metabolism in obese men are rare. It is not known whether the rate of both bone turnover and bone loss in obese men are comparable with this rate in obese women. The available literature also lacks data on the impact of MS on bone metabolism in both women and men. Therefore, the aim of this study was to evaluate the impact of MS on bone metabolism and the risk of osteoporotic fracture in obese men and women.

MATERIALS AND METHODS

The study included 40 obese women: BMI > 30 kg/m^2, age 59 (55–67,4) years, and 40 obese men: BMI > 30 kg/m^2, age 59.5 (56–63) years, **treated in the Outpatient Weight Management Clinic.** The study group was divided into 2 subgroups:

– A – obese patients without MS and
– B – patients with MS.

The inclusion criteria in the subgroup of obese patients without MS were: stable body weight within 3 months prior to the study, normal lipid profile and glucose, blood pressure of less than 140/90 mmHg, no history of chronic inflammatory diseases, the lack of medication affecting bone metabolism (including contraceptives and hormone replacement therapy), **menopausal status, no history of prior osteoporotic fractures.**

The group of obese patients consisted of 20 women: age 55 (54–61,5) years, and 20 men: age 58.5 (56––62,5) years.

The inclusion criteria in the subgroup of obese patients with MS were: waist circumference in women ≥ 80 cm and in men ≥ 94 cm; coexistence 2 of 4 of the following abnormalities: serum triglycerides level > 150 mg/dL, serum HDL cholesterol level < 40 mg/dL in men and < 50 mg/dL in women, systolic blood pressure ≥ 130 mmHg and diastolic blood pressure ≥ 85 mmHg, fasting glucose serum level ≥ 100 mg/dl orconcomitant drug due to lipid disorders, hypertension or type 2 diabetes.

The group of obese patients with MS included 20 women: age 64 (58–71), and 20 men: age 60 (58–63) years.

The patients' characteristics are shown in Table I.

None of the patients smoked tobacco. The study was approved by the Bioethics Committee of the Medical University of Silesia (NN-013-64/03). Each participant was informed about the study design and signed a consent form.

Venous blood samples (20 ml) were drawn into plastic test tubes (Vacutiner system). Serum samples obtained after centrifugation (1000 G for 10 min) were stored at -70°C until assessment of the parathyroid hormone (PTH), 25-OH-D3, C-terminal telopeptide of type I collagen (CTX1), osteocalcin (OC), and fibroblast growth factor 23 (FGF23). Serum calcium, inorganic phosphate, and creatinine levels were measured as part of the routine work-up. The estimated glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula [5].

Table I. Characteristics of patients with metabolic syndrome
Tabela I. Charakterystyka chorych z zespołem metabolicznym

	Women with MS [n = 20]	Men with MS [n = 20]
Visceral obesity	20 (100%)	20 (100%)
Diabetes type 2	7 (35%)	12 (60%)
Oral agents	7 (35%)	11 (55%)
Insulin therapy	0 (0%)	4 (20%)
IFG	1 (5%)	0 (0%)
Hypertension	12 (60%)	20 (100%)
ACE-Is	10 (50%)	16 (80%)
Calcium blockers	0 (0%)	6 (30%)
Beta-blockers	0 (0%)	5 (25%)
Dyslipidemia	15 (75%)	20 (100%)
Statins	9 (45%)	6 (30%)
Fibrates	6 (30%)	10 (50%)

IFG – impaired fasting glucose, ACE-I – angiotensin – converting enzyme inhibitors

The control group consisted of 15 healthy non-obese women (BMI 23.5 (22.6–24.5) kg/m^2) and 15 healthy non-obese men (BMI 24.4 (23,3–25,5) kg/m^2) in the same age as the obese patients with and without MS. The same laboratory and anthropometric measurements as in the study group were performed. **The total, absolute fracture risk** was estimated by WHO recommendations based on FRAX – the WHO Fracture Risk Assessment Tool (http://www.shef.ac.uk/FRAX/tool.jsp).

Measurements

Weight and height were measured in the fasting state by a medical electronic scale (RADWAG). The body mass index (BMI) was calculated using the following formula: BMI = body weight (kg)/height (m^2). Waist circumference was measured midway between the lower costal margin and the superior iliac crest. Body composition was analyzed using a bioimpedance method (Bodystat 1500, Bodystat Ltd., United Kingdom). Blood pressure measurements were made using a standard mercury sphygmomanometer cuff (12 x 23 cm) on the left forearm, after 10 minutes in the sitting position.

Laboratory tests

Laboratory measurements were conducted at the Department of Pathophysiology, Medical University of Silesia in Katowice.

- serum concentrations of the parathyroid hormone (PTH), osteocalcin and C-terminal telopeptide of type I collagen (CTX1) were determined by an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics GmbH, Germany);
- serum concentration of 25-(OH)-D_3 was determined by the radioimmunoassay technique (RIA) (Bio Source-EUROPE SA, Nivelles, Belgium);
- serum concentrations of the total calcium, inorganic phosphate, glucose, and lipids were determined by spectrophotometry (Point Scientific Inc., Michigan, USA);
- serum concentration of iFGF-23 was performed by ELISA (Immutopics, San Clemente, USA).

Statistical analysis

The obtained values are presented as means with standard deviations. All the statistical analyses were performed using STATISTICA 8.0 PL software. The distribution was analyzed using the Kolmogorov-Smirnoff test. Because of the size of the control group and the subgroups and the nonparametric distribution of some of the parameters, the U Mann-Whitney test was used to compare the study groups. Correlation

coefficients were calculated according to Spearman. **Multivariate regression analyses (backward regression models) were performed for variables describing bone turnover and calcium-phosphate homeostasis including potential explanatory variables: age, sex, MS, the percentage of fat, and eGFR.** $p < 0.05$ was considered statistically significant.

RESULTS

The characteristics of the study group and the controls are presented in Tables II–IV.

Women with MS vs obese women without MS

The women with MS were older than the obese women without MS. These patients were characterized by a higher absolute risk of osteoporotic fracture assessed by FRAX, higher concentrations of phosphorus and lower levels of 25-OH-D_3. No other differences in bone metabolism were noticed. The women with MS were also characterized by lower serum levels of HDL-cholesterol, which probably was associated with the lipid-lowering therapy conducted in this group.

Men with MS vs obese men without MS

The men with MS had higher glucose levels than the obese men without MS. There were no differences in either bone or calcium-phosphate metabolism.

Women with MS vs men with MS

Similar indexes of obesity were observed in both subgroups. The women with MS were characterized by a greater absolute risk of osteoporotic fracture and a tendency to lower concentrations of C-terminal telopeptide of type I collagen. The men with MS were characterized by higher serum creatinine.

Obese women without MS vs men without MS

The obese women without MS were characterized by lower levels of phosphorus, FGF23, a tendency of higher levels of 25-OH-D_3 and PTH.

MS vs control group

Women

The women with MS had a higher body weight, body fat percentage, and greater BMI, waist, hips and WHR than the controls. They demonstrated higher phosphorus serum levels and lower serum vitamin D levels. The control group had higher levels of total cholesterol and HDL-cholesterol. The women with MS had a higher serum concentration of triglycerides.

Men

The men with MS were characterized by a higher body weight, greater BMI, waist and hip circumference and greater body fat percentage than the controls. The men with MS had higher serum concentrations of phosphorus, glucose and creatinine. The controls were characterized by significantly higher serum concentrations of osteocalcin.

Obese vs controls

Women

The obese women had a higher body weight, higher BMI, larger waist and hip circumference and greater body fat percentage than the controls.

Men

The obese men without MS had a greater weight and BMI, larger waist and hip circumference and greater percentage of body fat than the controls. The obese men without MS had higher serum concentrations of phosphorus, glucose, creatinine and a lower serum concentration of osteocalcin than in the controls.

Multivariate regression

The prevalence of MS was related to reduced serum calcium and vitamin D levels and increased serum phosphorus levels. The variability of calcium levels in the study group was also affected by the respondent's age (Tab. V).

Table II. Characteristics of study and control groups (median and interquartile distribution)
Tabela II. Charakterystyka grupy badanej i kontrolnej (mediana i przedziały międzykwartylowe)

Parameters	Women				Men			
	non-MS [n = 20]	MS [n = 20]	Control [n = 15]	?	non-MS [n = 20]	MS [n = 20]	Control [n = 15]	
Age*	55.5 (54–61.5)	64 (58–71)	60 (56–64)	MS vs O p < 0.01	58.5 (56–62.5)	60 (58–63)	57.5 (55–61)	Ns
Body mass	94.9 (87.9–101.9)	96,5 (91.9–101.1)	64.7 (60.4–69.0)	MS vs C p < 0.001 O vs C p < 0.001	100.3 (93.1–107.4)	99.7 (94.8–104.7)	76.9^ (71.7–82.0)	MS vs C p < 0.001 O vs C p < 0.001
BMI	36.6 (33.8–39.5)	35.4 (33.7–37.2)	23.5 (22.6–24.5)	MS vs C p < 0.001 O vs C p < 0.001	32.8^ (31.0–34.7)	33.6 (31.9–35.3)	24.4 (23.3–25.5)	MS vs C p < 0.001 O vs C p < 0.001
Waist	103 (98–108)	109 (102–116)	82 (78–85)	MS vs C p < 0.001 O vs C p < 0.001	114 (108–121)	114 (108–121)	91 (83–99)	MS vs C p < 0.001 O vs C p < 0.001
HIP	119 (115–123)	114 (109–120)	99 (95–103)	MS vs C p < 0.001 O vs C p < 0.001	116 (108–124)	110 (105–115)	93 (85–101)	MS vs C p < 0.001 O vs C p < 0.001
WHR	0.87 (0.84–0.90)	0.95 (0.89–1.02)	0.83 (0.79–0.86)	MS vs C p < 0.01	1.00^^ (0.93–1.06)	1,05 (0.99–1.10)	0.98^^ (0.92–1.03)	Ns
Fat percentage	48.8 (45.6–52.0)	48.7 (45.7–51.8)	37.4 (32.6–42.1)	MS vs C p < 0.001 O vs C p < 0.001	53.7 (51.2–56.2)	49.7 (47.5–52.0)	28.1^^ (26.4–29.8)	MS vs C p < 0.001 O vs C p < 0.001

* schedule nonparametric – median and interquartile range (in other cases mean and 95% CI ^ p < 0.05 ^^ p < 0.001; ^^^ p < 0.001 with respect to corresponding subgroup; **non-MS** – without metabolic syndrome

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Table III. Bone metabolism indicators of study and control groups (median and interquartile distribution)
Tabela III. Wskaźniki metabolizmu kości u chorych z grupy badanej i kontrolnej (mediana i przedziały międzykwartylowe)

Parameters	Women				Men			
	non-MS [n = 20]	MS [n = 20]	Control [n = 15]		non-MS [n = 20]	MS [n = 20]	Control [n = 15]	
FRAX*	1.65 (1.5–2.4)	3.0 (2.3–4.6)	2.9 (2.0–3.5)	MS vs O p < 0.001	1.7 (1.5–1.75)	1.6^^^ (1.5–1.8)	2.0 (1.9–2.1)	Ns
Calcium*	2.22 (2.20–2.29)	2.11 (2.08–2.47)	2.26 (2.15–2.40)	Ns	2.27 (2.22–2.39)	2.28 (2.03–2.44)	2.27 (2.23–2.34)	Ns
Phosphorus*	1.12 (1.03–1.18)	1.81 (1.58–2.01)	1.14 (1.05–1.31)	MS vs C p < 0.001 O vs MS p < 0.001	1.37^^ (1.04–2.02)	1.92 (1.31–2.24)	1.07 (0.75–1.22)	MS vs C p < 0.001 O vs C p < 0.05
25-OH-D3*	34.6 (19.5–42.0)	7.3 (4.5–12.6)	29.5 (24.0–37.2)	MS vs C p < 0.01 O vs MS p < 0.01	22.2 (16.9–42.1)	19.5 (8.8–35.1)	35.5 (26.2–48.0)	Ns
iPTH*	42 (33–60)	37 (28–54)	35 (24–50)	Ns	32 (24–46)	37 (30–49)	29 (23–34)	Ns
FGF-23*	7.7 (6.5–8.9)	10.7 (3.9–15.5)	6.5 (5.3–8.2)	Ns	17.9^ (3.7–43.2)	14.7 (6.1–48.2)	21.0 (1.8–30.0)	Ns
Osteocalcin*	4.1 (3.4–5.0)	3.6 (2.1–8.1)	5.0 (3.6–7.8)	Ns	3.3 (2.1–6.3)	4.2 (2.9–7.1)	10.2^^^ (5.5–13.6)	MS vs C p < 0.001 O vs C p < 0.001
CTX*	0.25 (0.19–0.35)	0.27^ (0.19–0.35)	0.27 (0.21–0.46)	Ns	0.39 (0.29–0.48)	0.41 (0.22–0.53)	0.33 (0.26–0.53)	Ns

* schedule nonparametric – median and interquartile range (in other cases mean and 95% CI ^ p < 0.05 ^^ p < 0.001; ^^^ p < 0.001 with respect to corresponding subgroup; **non-MS** – without metabolic syndrome

Table IV. Plasma lipid profile, blood glucose and creatinine in study and control groups (median and interquartile distribution)
Tabela IV. Profil lipidowy, stężenie glukozy i kreatyniny u chorych z grupy badanej i kontrolnej (mediana i przedziały międzykwartylowe)

Parameters	Women				Men			
	non-MS [n = 20]	MS [n = 20]	Control [n = 15]		non-MS [n = 20]	MS [n = 20]	Control [n = 15]	
Total cholesterol	209 (195–224)	178 (152–205)	225 (203–248)	MS vs C p < 0.05	203 (181–225)	207 (185–228)	169^ (140–197)	Ns
LDL	123 (109–137)	112 (89–135)	117 (140–162)	Ns	112 (129–147)	113 (131–149)	88 (108–129)	Ns
HDL	57 (48–71)	48 (39–54)	62 (58–76)	MS vs C p < 0.001 O vs MS p < 0.05	41^^ (37–45)	46 (41–50)	41^^^ (23–53)	Ns
Triglycerides*	109 (87–120)	147 (89–178)	90 (65–107)	MS vs C p < 0.05	144 (117–162)	142 (115–170)	116 (93–121)	Ns
Glucose*	99 (95–104)	101 (98–111)	89 (80–97)	Ns	101 (88–104)	112 (99–144)	89 (84–92)	MS vs C p < 0.001 MS vs O p < 0.05
Creatinine	0.94 (0.87–1.04)	0.89 ()0.80–0.97)	0.87 (0.77–1.00)	Ns	0,96 (0.87–1.03)	1,07^ (0.94–1.16)	0,90 (075–1.04)	MS vs C p < 0.001
eGFR-MDRD	64 (57–70)	68 (61–76)	70 (58–78)	Ns	85^^ (79–95)	74 (67–87)	92^^ (79–114)	MS vs C p < 0.001

* schedule nonparametric – median and interquartile range (in other cases mean and 95% CI ^ p < 0.05 ^^ p < 0.001; ^^^ p < 0.001 with respect to corresponding subgroup; **non-MS** – without metabolic syndrome

Table V. Backward models of multiple regression analyses in obese men and women. Models include potential explanatory factors: age, sex, metabolic syndrome, percentage of fat, eGFR

Tabela V. Modele retrospektywne analizy regresji wielokrotnej u otyłych mężczyzn i kobiet. Modele obejmują potencjalne czynniki wyjaśniające, takie jak: wiek, płeć, zespół metaboliczny, procent tłuszczu, eGFR

Dependent variable	Factors	beta ± SD	p
Calcium [mmol/l]	age [years]	0.456 ± 0.110	< 0.001
	metabolic syndrome	-0.206 ± 0.110	0.06
Phosphorus [mmol/l]	metabolic syndrome	0.355 ± 0.105	0.001
25-OH-D_3 [ng/ml]	metabolic syndrome	-0.322 ± 0.107	0.004

DISCUSSION

The present study is one of the few comparing bone metabolism between obese men and women with and without MS. As previously mentioned, disorders that make up metabolic syndrome, including in particular visceral obesity, affect many organs and systems, including bones. It is also known that the skeleton, in addition to its primary function of maintaining and protecting organs, is involved in maintaining the balance of calcium and phosphate and it is the source of numerous substances with pleiotropic functions. Despite the obvious differences between adipose tissue and bone, it appears that they have some elements in common. Adipocyte and osteoblasts are derived from common progenitor cells. The fatty tissue and bone are subject to the regulatory mechanisms of the central and peripheral nervous system, and the development of diseases of both tissues is affected by genetic and environmental factors [6,7]. It also appears that substances secreted by both bone tissue and visceral fat, interact. The degree of complexity is the reason for the mixed results of research published so far on the subject.

Indicators of bone turnover in obese patients with and without metabolic syndrome

In the obese men the serum osteocalcin concentration was lower than in the controls. This relationship was significant, both when taking into account the study group as a whole and after splitting them into subgroups (obese without MS, and MS). Other researchers also made similar observations [8,9,10]. Perhaps this is associated with a lower rate of bone formation in obese patients. This hypothesis is supported by the positive correlation between serum osteocalcin with FRAX (found only in men) which could explain the influence of lower bone turnover in patients with a higher body weight on the fracture risk.

Men have a higher concentration of CTX compared to women, both in the subgroup of obese without and with MS. The results are not surprising, as the previously published studies showed diminished bone formation in both peri- and postmenopausal women [11,12].

In obese postmenopausal women, not only a reduction in the levels of osteocalcin and CTX1, but also a decrease in the amplitude of their circadian rhythms were observed [13]. The effect of bone formation inhibition in women can be seen in the fracture risk assessment. The women in the study group were characterized by a higher risk of osteoporotic fracture assessed by the FRAX calculator. Therefore, a greater concentration of bone turnover indicators in men, regardless of the fact that it is a classic indicator of bone resorption, supports the active bone metabolism in this group.

Impact of obesity and metabolic syndrome on vitamin D serum concentration

The women with MS were characterized by lower serum vitamin D levels than the obese women without MS and women with normal body weight. Obese women without MS were characterized by higher serum vitamin D levels compared with obese men. Body weight and BMI correlated negatively with serum vitamin D concentration. A low level of vitamin D in patients with MS was also observed by other researchers [14,15,16,17]. Ford et al. [14] in a large study of the U.S. population observed a negative correlation between serum vitamin D levels and the incidence of MS. Similar results were presented by Lu et al. in the Chinese population [15]. McGill et al. [18] observed an inverse relationship between serum vitamin D concentration and waist circumference, being indicative of visceral obesity, but did not confirm the influence of body fat or MS on serum vitamin D concentration.

As mentioned above, obesity, which is a part of MS, is associated with reduced serum vitamin D levels. There are several potential reasons for that phenomenon. There is lower skin synthesis of vitamin D, its sequestration in adipose tissue and increased conversion of the active form of vitamin D to its inactive metabolites, such as calcitroic acid in obese patients. In turn, vitamin D deficiency may increase insulin resistance [14,15,19], which is a dominant disorder in MS, leading to the mechanism of the 'vicious circle'. Vitamin D receptors are present, *inter alia*, on muscle and adipose cells [20], and those tissues just decide on peripheral insulin sensitivity. In addition, vitamin D deficiency, by increasing PTH serum levels, leads to an increase in intracellular calcium con-

centration in insulin target cells. This results in diminished insulin-stimulated glucose transport [21,22].
In the present study, no significant differences were observed between the serum vitamin D levels either in the examined men or controls, probably due to the small sample size. There was only a tendency of lower concentrations of vitamin D in both the obese patients with and without MS as compared to the controls.

PTH and calcium concentrations in obese subjects with and without metabolic syndrome

In obese women without MS, both higher serum levels of vitamin D and PTH than in obese men without MS were observed. The PTH levels were positively correlated with age. Interestingly, serum calcium was increased in obese patients without MS, which does not correspond to a similar trend with respect to PTH (higher concentration of calcium inhibits the secretion of PTH). In contrast, in patients with MS, there was no association between an increase in calcium concentration and age. In our study we did not evaluate data on the patients' diet, therefore it is difficult to clearly assess if the lower serum calcium concentration in patients with MS results from eating habits. However, it was observed that the calcium content in the diet had an effect on both the metabolism of fatty tissue and body weight. Zemel et al. [23] found that a diet rich in calcium with a concomitant reduction in calorie intake was associated with a significantly greater reduction in body weight and body fat when compared with the controls using only a restriction of calorie intake. The authors also observed that increasing dietary calcium inhibited lipogenesis and stimulated lipolysis [23]. The result is a decrease in fat mass. In contrast, reduced dietary calcium intake increases the formation of the active form of vitamin D which increases adipocyte intracellular Ca2+, stimulates lipogenesis and inhibits lipolysis, and in turn results in increased accumulation of triglycerides in adipocytes [24].
People who consume more dairy products are characterized by higher levels of calcium and a lower incidence of MS [25,26]. In another study by Zemel et al. [27], it was shown that an increase in calcium intake (from 400 mg to 1200 mg) during weight loss therapy was associated with a significant reduction in both body weight and body fat (about 26% and 38%) compared to the controls. In the same study, the authors observed a greater reduction in visceral adipose tissue in patients on a diet rich in calcium when compared with a standard one (36% vs. 19%, respectively).
In another study, Reis et al. [17] demonstrated that serum PTH levels positively correlated with MS in men > 50 yrs, which was neither seen in women nor in younger males. It seemed that PTH may have a significant effect on fatty tissue. According to McCarthy et al. [28], PTH excess may promote weight gain by impeding catecholamine-induced lipolysis. Obesity may therefore be a factor stimulating the secretion of PTH, which, in turn, enhances the growth of adipose tissue. This hypothesis was supported by Andersen et al. [29] who described a dependence of serum PTH concentration on the degree of obesity.

Effect of obesity and metabolic syndrome on concentrations of phosphorus and FGF23

In both men with and without MS, the concentration of phosphorus was higher than in the controls. Obese men were characterized by higher serum levels of phosphorus than women, and women with MS had a higher concentration of phosphorus than obese women without MS. This observation may be due to the differences in dietary habits in the various subgroups of our patients. Products containing a large amount of phosphorus, such as meat, dairy products and processed foods, often contain a large amount of fat and are of high in calories . In this study, the phosphorus levels were positively correlated with body weight, BMI, waist circumference and percentage of body fat. A higher serum phosphorus level, even within the normal range, is now considered to be a cardiovascular risk indicator [30,31].
Therefore, the increased concentration of phosphorus may be potentially responsible for the increased risk of cardiac events in patients with MS. However, it should be noted that there are numerous mechanisms regulating the phosphorus serum concentration (kidney, gastrointestinal tract, bone, parathyroid), so dietary phosphorus has only a limited effect on its serum concentrations [32,33]. The men in the study group were characterized by higher levels of FGF23 as compared to the women. A similar relationship was observed in relation to phosphorus, however, these results are not surprising, as the phosphaturic effect of FGF23 was previously well described. It is also known that dietary phosphorus influences the serum concentration of FGF23 [33], although such a relationship has not been confirmed by all investigators [34].

The effect of obesity and metabolic syndrome on 10-year absolute fracture risk

The positive influence of body weight on bone mineral density has been well documented [35,36,37,38,39]. Nevertheless, it is not known whether it results in lowering fracture risk. De Laet et al. [40], in their meta-analysis undermine the protective effect of obesity on bone. This meta-analysis indicated that BMI, as a risk factor for fracture risk, varies according to the BMI level. Low body weight is associated with an increased risk of osteoporotic fracture, but with an increase in weight and BMI > 26 kg/m^2, the beneficial effects are definitely weaker. Some other authors

suggest that obesity has a negative impact on fracture risk independent of BMD [41].

In all the examined groups, women were characterized by a higher absolute fracture risk than men. The fact that women are more susceptible to low-energy fractures, and that they occur at a younger age as compared to men, is well known and documented [42,43]. Nonetheless, the similar FRAX score in both obese men and women without MS may suggest that in women aged > 54 years, contrary to men, fat tissue plays a protective role. This may be due to the conversion of adrenal androgens into estrogens in adipose tissue. On the other hand, in men we found a negative correlation between fracture risk and BMI, waist circumference, and body fat, while in women only a weak negative correlation between fracture risk and BMI was observed. Thus, the effect of body weight on the fracture risk remains ambiguous. We cannot either, rule out the significant impact of the small number of study participants on the obtained results.

In women with MS we observed a higher fracture risk than in obese women without MS. The negative impact of MS on bone has also been observed by other investigators, however, a decrease in bone mineral density was not associated with an increased risk of fracture in every case [3,4,44]. There are also some opposite results. Ahmed et al. [45] found that MS was associated with a reduced risk of non-vertebral fracture, wherein in females this beneficial effect was dependent mostly on BMI, while in males it was with the coexistence of hypertension.

The observed differences in fracture risk between obese women with and without MS may result from several causes. The first is the age of the study group, which negatively correlated with risk for osteoporotic fracture (both in women and men, while in women to a greater extent). The other is the potential influence of proinflammatory cytokines released by fat tissue, such as TNFα, Il-1, IL-6, which stimulate the differentiation and activation of osteoclasts [46].

This article has some limitations. The first is the limited number of patients, which is mainly due to difficulties in the recruitment of 'healthy' obese people over 54 years of age. Another, is the lack of densitometry measurements (DXA) for a more accurate assessment of bone mineralization. It should be noted, though, that 55–75% of fractures occur in individuals who do not meet the densitometric criteria for osteoporosis (with a T-score around -1.5, so with bone mass on the borderline between the norm and osteopoenia). Thus, reduced bone mineral density increases fracture risk, but normal values do not exclude it. The diagnosis of osteoporosis on the basis of age and only one parameter (which is BMD) limits the ability to assess the fracture risk. There are some additional factors (besides BMD and age), which adversely affect bone mass, such as alcohol abuse, smoking, low body weight and physical inactivity. The current WHO guidelines recommend calculating a 10-year absolute fracture risk, where the outcome of densitometry is just one of the elements taken into account. Moreover, exclusion it, does not mind in estimating fracture risk. In clinical practice, one should use the10-year absolute fracture risk calculator (FRAX), which has been used in this study.

CONCLUSIONS

1. Metabolic syndrome does not influence the **selected parameters of bone metabolism** in either men or women. However, women with metabolic syndrome have lower serum 25-OH-D_3 levels.
2. Women, but not men with metabolic syndrome have a higher 10-year absolute fracture risk than **obese women without metabolic syndrome**.

The research was covered by a grant from Medical University of Silesia (**KNW-1-133/N/4/0)**

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