Trabecular bone score in obese patients with and without diabetes

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ABSTRACT

The link between obesity, diabetes and bone metabolism is quite complex and not entirely clear. Although many clinical and epidemiological studies demonstrate that obesity enhances bone mineral density, its effect on bone microarchitecture is uncertain. The objective of this study was to examine the bone microarchitecture in obese patients with and without diabetes. The study included 119 individuals with ages from 30 to 50. Participants were divided into three groups: obese patients, obese diabetic patients, and a healthy control group. Results showed that obesity has a positive effect on trabecular bone score (TBS). Diabetes and obesity have a significant interactive impact on bone microarchitecture (TBS). Furthermore, HbA1c influences TBS in both obese diabetic patients and obese non-diabetic subjects. In contrast to the majority of studies, we found that obesity positively influenced TBS. TBS was inversely related to HbA1c levels in obese type 2 diabetics. Diabetes and obesity have a significant interactive impact on bone structure, in particular on bone microarchitecture.

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Introduction

Osteoporosis is a condition characterized by low bone mass, degeneration of bone tissue, and disturbance of bone microarchitecture, which can result in decreased bone strength and an increased risk of fracture.[1] Only one-third of fractures are diagnosed, with the remainder going undiagnosed. Fractures most commonly affect the spine, hip, and wrist, but they can also affect other bones, upper arms, or ribs. The diagnosis of osteoporosis is made utilizing dual-absorption osteodensitometry (DXA), laboratory bone biomarkers of bone resorption (amino- and carboxy-terminal cross-linked telopeptide type 1 collagen), and markers of bone formation (osteocalcin, alkaline phosphatase, and aminoterminal polypeptide type 1 collagen). Osteodensitometry (DXA) measures bone mineral density (BMD). A T-score of -2.5 standard deviations or more (compared to the average values in young adult females) indicates osteoporosis. Typically, osteoporosis is diagnosed only after the first fracture.[2] Based on the evidence, national and international guidelines have been developed to address the issue of osteoporosis screening.[3-5]

Obesity has expanded throughout the world in recent decades and has become a serious public health concern.[6] It may affect as much as more than half of the population by 2030, necessitating an assessment of the risk of obesity-related fractures.[7] The mechanism of association between obesity, obesity comorbidities, and bone metabolic activity remains undetermined. Clinical studies in recent years have shown that abdominal obesity may be associated with lower bone density, while other studies have shown this association to be dependent on the location and character of the fractures. Obesity is frequently associated with elevated or preserved BMD, as well as impaired bone myoarchitecture (*i.e.*, trabecular bone damage), which leads to frequent fractures despite normal BMD.[8-10]

In general, adipose tissue and bone have a twofold relationship: mechanical and metabolic. Obese people had lower

levels of biochemical indicators of bone turnover than lean people. This distinction appears to be more significant for bone resorption indicators than bone production markers.[11] During maturity, these effects contribute to bone mass maintenance. During menopause, increased body weight appears to slow bone loss. If physical stress was the primary cause of the increased BMD, bone size should rise due to bone apposition. However, the results do not always support this hypothesis: bone size at the radius and tibia, as measured by high-resolution peripheral quantitative computed tomography (CT), is not different between obese and normal-weight controls.[12] These data imply that, while the loading factor represents a component of the bone-fat connection, it is insufficient to fully explain the relationship.

Adipose tissue is one of the major sources of aromatase, which synthesizes estrogens from androgen precursors. Estrogens have a key role in the maintenance of skeletal homeostasis, promoting bone formation and reducing bone resorption; therefore, protecting the bone. Obese postmenopausal women have been shown to have higher serum concentrations of estrogens compared with non-obese controls. These findings may partly explain the positive association between BMD and body mass index (BMI). However, it has become apparent that estrogens are not the only regulator of bone mass.[13]

Additionally, obese people often have an elevated parathyroid hormone (PTH) level and lower circulating vitamin D levels.[12-14] BMI is an important factor in fracture risk assessment (FRAX), with higher BMD resulting in lower fracture risk.[15] The FRAX model is used to predict fracture risk by combining clinical risk factors with the osteodensitometry results.[5] Peripheral quantitative CT can assess trabecular and cortical bone, *i.e.*, volumetric BMD, bone geometry, and BMC.

Unregulated diabetes may also have an impact on bone density. Poor metabolic control leads to the accumulation of products of non-enzymatic glycosylation of proteins in collagen, which affects the bone microarchitecture, decreasing strength and increasing fragility. Glycosuria promotes hypercalciuria, causing hypocalcemia and the onset of osteoporosis. Diabetes causes an increase in proinflammatory cytokines which leads to accelerated bone resorption and bone loss.[11,14] Diabetes increases PTH levels, and this effect is linked to metabolic control quality, illness duration, diabetic complications, and hereditary risks.

Materials and Methods

The case-control study was conducted at the Polyclinic ST Medicina in Novi Sad, as well as the Aqva - Lab laboratories in Novi Sad and Belgrade. For each subject, a detailed history, clinical examination, BMI, HbA1c, 25(OH)D3, osteocalcin, beta crosslaps (Beta-CrossLaps serum assay measures C-terminal telopeptide of type I collagen and represents a reliable serum marker for bone resorption), and DXA dual-absorption osteodensitometry with lateral scan (DXA), TBS T-score determination and lateral vertebral assessment (or vertebral fracture assessment morphometry) were performed. Each patient signed an informed consent form for the participation in the study.

The Roche Cobasintegre 400 plus ECLIA411E spectrophotometer was used to quantify bone biomarkers, HbA1c, and vitamin D. DXA osteodensitometry was performed using the GE Lunar Prodigy Primo device.

The study included 119 patients, 56 of whom were women (47.1%) and 63 men (52.9%). The subjects' age ranged from 30 to 50. The research included obese diabetics who were treated with oral hypoglycemic medications rather than insulin. The patients utilized oral hypoglycemic agents *e.g.*, metformin, GLP-1 receptor agonists, and dipeptyl peptidase-4 inhibitors. None of the diabetic individuals reported thiozolidine or sulfonylureas therapy. Thyroid gland abnormalities and the occurrence of autoimmune thyroid disease, parathyroid gland dysfunction and the presence of menopause were ruled out in female subjects. Participants were divided into three groups. The first group of 40 subjects included obese patients with diabetes, and the second group of 39 included obese patients without diabetes. The third group of 40 subjects was a healthy control, with a normal BMI (*e.g.*, 18.5-24.9 kg/m^2, no glucose tolerance disorders, no thyroid function disorders, and no parathyroid gland function disorders.

Statistical methodology: SPSS 25.0 software package was used for data analysis. The study data is presented graphically, tabularly, and textually. descriptive statistics procedures included frequencies and percentages for categorical variables, minimum, maximum, mean value and standard deviation for numerical variables. Two-factor analysis of variance was used in statistical inference procedures to determine the existence of differences in TBS values between men and women, obese patients with diabetes, obese subjects without diabetes, and the control group and the interaction between gender and diagnosis. Pearson correlation was used to determine the relationship between metabolic indicators and bone strength indicators. All tests were carried out at the 5% level of significance.

Results

The study included 119 patients, 56 of whom were women and 63 men, aged 30 to 50, distributed into three groups: obese patients with diabetes (40 patients *e.g.*, 33.6%), obese subjects without diabetes (39 patients, 32.8%) and healthy control (40 patients, 33.6%).

Table 1 shows the descriptive characteristics of the metabolic indicators studied: BMI, vitamin D [reference range (RR): 75-200nmol/L], glycosylated hemoglobin (RR: 4.8-5.9%), bone markers osteocalcin (RR: women 11.0-43.0 ng/mL, men 14-42 ng/mL) and betacrosslaps (RR: women 0.0-573.0 pg/mL, men 0.0-584.0 pg/mL), and TBS, indicator of bone strength, *i.e.*, the degree of bone microarchitecture disruption (TBS).

Table 2 displays the mean values and standard deviations of the TBS for each of the observed subgroups. TBS values did not differ noticeably between men and women, as well as depending on the diagnosis.

The main individual effects of gender and osteoporosis on TBS values (determined by two-way ANOVA) are shown in Table 3, as well as the interaction effect. It is important to note that the main effect of osteoporosis on TBS value is statistically significant, while the effect of gender is not. The results also demonstrate that the diagnosis and gender have a significant interactive effect on TBS values.

The extent of the impact (partial eta squared) shown in

Table 3 is based on the correlation between osteoporosis and gender and TBS values; the correlation level between osteoporosis and TBS is moderate, while the correlation between osteoporosis and TBS is strong.

We used the supplementary Tuckey test (Table 4) in addition to the previous ANOVA results to determine the statistical differences between the groups. This test shows that the mean TBS value of obese people without diabetes differs significantly from obese people with diabetes and the control group. Obese diabetics' TBS values are not markedly different from those of healthy controls.

The Pearson correlation (Table 5) was used to examine the relationship between metabolic indicators and TBS bone strength indicators. The results show that there is a statistically significant association between TBS values and BMI. This correlation is positive, which means that as the value of BMI rises, so does the value of TBS. There were no significant correlations between TBS and the other indicators.

When only obese patients with diabetes are analyzed (Table 6), the results show a statistically significant, moderate-level correlation between TBS and HbA1c values, as well as TBS and 25(OH)D. The correlation between TBS

Table 1. Metabolic indicators and trabecular bone score values in three examined groups.

Metabolic parameters	Obese patients with diabetes	Obese patients without diabetes	Control group
BMI (kg/m^2)	33.65±7.22	35.84±4.85	23.13±1.98
HbA1c (%)	7.84±1.67	5.16±0.46	4.85±0.33
25(OH)D (nmol/L)	51.39±17.89	54.93±20.85	48.64±19.08
Osteocalcin (ng/mL)	13.05±5.54	11.47±4.37	14.89±4.35
Beta Crosslaps (pg/mL)	229.77±93.46	203.00±86.83	235.09±136.54
TBS			
L1 - L4	1.533±0.122	1.474±0.153	1.419±0.068
L1 - L3	1.531±0.124	1.467±0.153	1.406±0.075
L1 - L2	1.517±0.124	1.450±0.153	1.377±0.085
L2 - L3	1.554±0.124	1.484±0.156	1.437±0.068
L2 - L4	1.548±0.122	1.488±0.155	1.444±0.065
L3 - L4	1.549±0.124	1.498±0.158	1.459±0.071
Mean TBS	1.539±0.122	1.477±0.154	1.426±0.068

TBS, trabecular bone score.

Table 2. Mean trabecular bone score levels in the examined groups.

	Mean TBS
Obese diabetic patients	1.48±0.13
Obese non-diabetic patients	1.54±0.12
Controls	1.43±0.07

TBS, trabecular bone score.

Table 3. Interaction between trabecular bone score, gender, and respective pathology.

Source	Type III sum of squares	Mean square	F	P	Partial eta squared
Corrected model	0.414	0.083	6.209	0.0001	0.217
Intercept	187.810	187.8	14079922	0.0001	0.992
Osteoporosis	0.300	0.150	11.235	0.0001	0.167
Gender	0.027	0.027	2.047	0.155	0.018

Table 4. Tukey's honestly significant difference test.

		Mean difference (I-J)	P
Obese patients with diabetes	*vs.* Obese people without diabetes	-0.06±0.02	0.03
	vs. Control group	0.05±0.02	0.129
Obese patients without diabetes	*vs.* Obese patients with diabetes	0.06±0.02	0.04
	vs. Control group	0.11±0.02	0.0001
Healthy controls	*vs.* Obese patients with diabetes	-0.05±0.02	0.129
	vs. Obese patients without diabetes	-0.11±0.02	0.0001

and Hba1c values is negative, implying that as the Hba1c value rises, so does the TBS value, and *vice versa*. The correlation between the TBS value and the 25(OH)D value, on the other hand, is positive, implying that as the 25(OH)D value rises, so does the average TBS value, and conversely. The results obtained in the obese patients with diabetes were not identical to the obese patients without diabetes samples. Specifically, there is no significant correlation between any metabolic indicator and TBS in obese patients without diabetes. The results of the evaluation of the correlations in the control group match the results obtained on the entire sample; there was a significant positive correlation of moderate strength between BMI and TBS values.

Discussion

Bone tissue is made up of an organic matrix (proteins, primarily collagen), minerals (calcium and phosphorus), and bone cells (osteoblasts, osteocytes, and osteoclasts).[2] In human serum and plasma, B cross-laps, a degradation product of type 1 collagen, is a marker of bone resorption.

Advanced age, comorbidities, medications, disorders in the secretion, release, and action of hormones, and mutations in the collagen type 1 gene may all affect mineral bone density. Secondary osteoporosis is caused by hormonal dysfunction (hypogonadism, hyperprolactinemia, hyperthyroidism, and hyperparathyroidism).[8]

Our study examined the effects of obesity, as well as obesity associated with diabetes, on bone microarchitecture in a control group of healthy subjects. Obesity has a significant impact on bone microarchitecture, which is consistent with the findings in other studies.[8] Two-way ANOVA findings show differences in TBS between the groups of obese patients with diabetes, obese individuals without diabetes, and the control group.

Romagnolli *et al*., in their research, found an adverse impact of obesity on TBS, despite constant BMD levels. Changes in the homeostasis of glucose and sex hormone levels appear to impact this association, whereas calciotropic hormones play no function. The effect of waist circumference on TBS is greater than that of BMI.[16]

The mean value of TBS in obese subjects without diabetes differs from obese patients with diabetes and the control group, indicating that they have significantly higher TBS values than other participants. TBS values in obese subjects with diabetes, however, did not differ significantly from those in the control group. As expected, another factor influencing TBS values was gender. The results also show that the interaction between diabetes, obesity and gender has a statistically significant influence on TBS values.

In a study by Turcotte *et al.*,[7] who examined obesity and fracture risk in a systematic review that included more than five million subjects, the results showed that obese women and men had a significantly lower risk of fracture when compared to non-obese subjects. Obese postmenopausal women had a 25% lower risk of hip fracture, a 15% lower risk of wrist fracture, and a 1.6-fold increased risk of ankle fracture compared to non-obese women. Obese men had a 41% lower risk of hip fracture than non-obese men, indicating that fracture risk is related to anatomical site of the skeleton and gender.[9] In contrast to these findings, another meta-analysis found that abdominal obesity was associated with an increased risk of hip fracture in men and women over the age of 40.

In our research, Pearson's correlation including all of the surveyed patients demonstrated a significant relationship between bone microarchitecture and BMI. The results concerning the diabetic group only show a medium-strength inverse correlation between TBS and HbA1c values, as well as a positive correlation between TBS and 25(OH)D.

The relationship between obesity and bone composition is complex.[17] The increase in body weight causes an increase in BMD, both for a mechanical effect and for the greater amount of estrogens present in the adipose tissue. Nevertheless, despite an apparent strengthening of the bone witnessed by the increased BMD, the risk of fracture is higher.

Table 5. The relationship between trabecular bone score and metabolic markers.

TBS	BMI	Hba1c	25(OH)D	Osteokalcin	Beta Crosslaps
Correlation Coefficient	0.244	-0.139	0.082	-0.049	-0.022
P	0.008	0.134	0.376	0.596	0.811

BMI, body mass index; TBS, trabecular bone score.

Table 6. Correlation between trabecular bone score values and metabolic indicators in a subsample of obese patients with diabetes, obese patients without diabetes, and in control group.

TBS	BMI	Hba1c	25(OH)D	Osteokalcin	Beta Crosslaps
Obese patients with diabetes					
Correlation coefficient	-0.137	-0.425	0.334	0.053	0.030
P	0.401	0.006	0.035	0.745	0.855
Obese non-diabetic patients					
Correlation coefficient	-0.008	0.235	-0.260	-0.055	-0.170
P	0.964	0.149	0.110	0.739	0.300
Control group					
Correlation coefficient	0.404	-0.036	-0.087	-0.016	0.075
P	0.011	0.826	0.599	0.924	0.648

TBS, trabecular bone score.

Obesity was positively associated with BMD, compared to subjects with normal body weight, in a 2020 meta-analysis study by Qiao *et al.*;[18] the correlation was positive concerning BMD of the lumbar spine and femoral neck, while the link between obesity and osteoporosis was inverse; these results are consistent with the findings of our study. According to a study published in 2020 by Gkastaris *et al.*, the mechanical effect of obesity is positively correlated with BMD findings, but the systemic effect of obesity, visceral adipose tissue, low degree of inflammation, and adipogenesis is responsible for impaired bone microarchitectonics.[8]

The various results obtained in different studies can be explained by focusing on general obesity and osteoporosis rather than isolated abdominal obesity and its association with low-grade inflammation, insulin resistance, oxidative stress, and altered hormonal status affecting bone metabolism. In a study published in 2022 by Shuangling *et al.*[19] that followed the relationship between HbA1c levels and osteoporosis, a negative relationship between HbA1c levels and osteoporosis was proven in elderly men with type 2 diabetes, while such a relationship was not established in women. In the Chinese study,[20] systolic blood pressure, waist circumference, and serum levels of triglyceride and glucose exhibited a negative association with TBS.

In type 2 diabetes, tissue hypoxia might be explained by secondary anemia,[21] hypoxia mediates the development of osteoporosis by increasing the formation of osteoclasts threefold and stimulating the formation of resorption pits multiple times. The increased risk of osteoporosis in men with type 2 diabetes associated with low HbA1c levels should prompt clinicians to investigate the etiology of anemia and prevent osteoporosis complications.

Conclusions

In contrast to the majority of studies, we found that obesity positively influenced TBS. TBS was inversely related to HbA1c levels in obese type 2 diabetics. Diabetes and obesity have a significant interactive impact on bone structure, in particular on bone microarchitecture.

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