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Взаимосвязь композитного состава тела с минеральной плотностью костной ткани у женщин с сахарным диабетом 2 типа в постменопаузе

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Цель. *Определить взаимосвязь между минеральной плотностью костей (МПК) и композитным составом тела (КСТ) у женщин с сахарным диабетом 2 типа (СД2), находящихся в постменопаузе.*
Материалы и методы. *Обследованы 78 женщин, от 50 до 70 лет (медиана 63 года). Нормальный индекс массы тела (ИМТ) имели 20 женщин, избыточную массу тела – 29, ожирение – 29. Исследование МПК и КСТ проводилось с помощью двухэнергетической рентгеновской абсорбциометрии.*
Результаты. *У больных с нормальной МПК зафиксированы более высокие показатели ИМТ, массы жировой ткани, большая масса туловищного жира, а также более высокая «тощая» масса в сравнении с пациентами с остеопорозом и остеопенией (все $p<0,05$). Женщины с остеопорозом имели меньшую массу жира на бедрах по сравнению с женщинами с нормальной МПК. Масса жировой ткани, масса жировой ткани на туловище, а также «тощая» масса положительно коррелировали с МПК в поясничном отделе позвоночника, проксимальном отделе бедра, шейке бедра, предплечье. В многофакторном регрессионном анализе масса жировой ткани была независимым предиктором общей МПК, после учета возраста, ИМТ, длительности постменопаузы, уровня HbA_{1c}, скорости клубочковой фильтрации и других параметров КСТ.*
Заключение. *У женщин с СД2, находящихся в постменопаузе, ИМТ и масса жировой ткани положительно ассоциированы с МПК.*
Ключевые слова: *сахарный диабет 2 типа; минеральная плотность костей; композитный состав тела; ожирение; остеопороз; менопауза; жировая ткань*

The relationship of total body composition with bone mineral density in postmenopausal women with type 2 diabetes

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Aim. *To determine the relationship between bone mineral density (BMD) and total body composition in postmenopausal women with type 2 diabetes.*
Materials and Methods. *The study included 78 women, from 50 to 70 years of age (median 63 years). Twenty women had normal body mass index (BMI), 29 ones were overweight and 29 had obesity. The body composition and BMD was studied by dual-energy X-ray absorptiometry.*
Results. *Women with normal BMD had higher BMI, total and truncal fat mass, as well lean mass as compared to women with osteoporosis and osteopenia (all $p<0.05$). Patients with osteoporosis had a lower fat mass at the hips, compared with those with normal BMD. Total and truncal fat mass, as well as lean mass were positively correlated with BMD in the lumbar spine and proximal femur, femoral neck and radius. In multivariate regression analysis fat mass was an independent predictor for total BMD, after adjusting for age, BMI, duration of menopause, HbA_{1c}, glomerular filtration rate and other total body composition parameters.*
Conclusions. *In postmenopausal type 2 diabetic women BMI and fat mass is associated positively with BMD.*
Keywords: *type 2 diabetes; bone mineral density; total body composition; obesity; osteoporosis; menopause; adipose tissue*

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The role of Type 2 diabetes (T2D) as a possible risk factor for osteoporosis and low-energy fractures remains controversial. A meta-analysis of 15 observational studies has revealed that patients with T2D have higher bone mass density (BMD) in comparison with general population [1]. In Rotterdam study BMD in the lumbar spine and femur was higher in patients with T2D as compared to those without. However, the fracture risk in patients with T2D was

greater then that in general population [2]. The mechanisms underlying this paradox are currently under investigation.

It is known that obesity has a modifying effect on BMD in patients with T2D. The results of several studies and meta-analysis [3-5] indicated direct correlation between BMD and body mass index (BMI). It has been suggested that the link between BMD and BMI is determined by the complex interactions between fat, muscle and bone tissue [6, 7]. The pathogenic role of the mass ratio of these tissues, known as the total body composition (TBC), in energy metabolism and endocrine regulation disorders is in the focus of special interest.

Aim

The aim of our study was to assess the relationship between BMD and TBC in post-menopausal women with T2D.

Materials and methods

Our study included 78 women with T2D, aged between 50 and 70 years (median 63 years). Twenty women had normal weight, 29 were overweight and 29 ones had obesity, BMI ranged from 24 to 42.5 kg/m^2 (median 32.2 kg/m^2). All women were postmenopausal, with the duration of menopause ranging from 1 to 27 years (median 12 years).

The course of T2D from the time of diagnosis ranged from 2 to 41 years (median 16 years). Most patients were receiving insulin therapy (n = 71). In addition to insulin, 36 subjects were taking metformin, 4 ones received sulfonylurea and 9 patients were taking a combination of metformin and sulfonylurea. Among insulin-naive subjects one received metformin alone and six were taking a combination of metformin and sulfonylurea. The glycated haemoglobin (HbA_{1c}) levels ranged from 5.7% to 14.8% (median 9.2%).

Co-morbidities included arterial hypertension (n = 77), coronary artery disease (n = 28) and well-controlled hypothyroidism (n = 18). Chronic kidney disease (CKD) stage 3a was diagnosed in 11 patients, stage 3b – in 19 ones and stage 4 was revealed in 2 patients.

The exclusion criteria included: age >70 years; history of endocrine disease (hypercortisolism, hyperthyroidism, hypopituitarism, polyglandular syndromes); rheumatic diseases (rheumatoid arthritis, ankylosing spondylitis, diffuse connective tissue disease); diseases of the digestive system (malabsorption syndrome, gastrectomy, gastric bypass or other bypass surgery in the gastrointestinal tract, liver failure); non-diabetic kidney disease; any blood disease; alcoholism and/or drug addiction; history of the treatment with glucocorticoids, immunosuppressive drugs, thiazolidinediones, bisphosphonates, calcitonin or strontium, as well as post-menopausal hormone replacement therapy.

The assessments of BMD were conducted using dual energy X-ray absorptiometry with a GE Lunar Prodigy bone densitometer (USA). Assessment variables were BMD and T-criteria at the lumbar spine (L1–L4), proximal femur, femoral neck and forearm of a non-dominant arm. For TBC determination, the TBC program was used according to the densitometer manufacturer's instructions. Bone mass, total and trunk fat mass, as well as lean mass was determined. Fat distribution patterns were differentiated based on the ratio of fat tissue in the abdomen and hip areas. The android fat was measured in the area from the top of the iliac crest to 20% of the distance from the iliac crest to the neck. Upper boundary of gynoid region was below the pelvis line by the distance of 1.5 times of the android region area. The altitude of the gynoid area is normally two times larger than that of android one.

Fracture Risk Assessment Tool (WHO FRAX, web version 3.8, adjusted for Russia) was used to determine the risk of major osteoporotic fractures.

The study protocol was approved by a local ethics committee. All patients signed informed consent forms to participate in this study.

Statistical analyses were conducted using STATISTICA 10 (StatSoft Inc., 2011, USA). Because of non-normal distributions of most of the studied variables, non-parametric tests were used for statistical comparisons. Group comparisons were obtained using the Mann–Whitney or Kruskal–Wallis ANOVA tests, as appropriate. The correlation between variables was assessed using Spearman rank correlation and multivariate stepwise regression analyses. The non-normal distributed data were log-transformed before inclusion into a multivariable analysis. The critical level of significance for testing statistical hypotheses was 0.05. Results are provided as medians (25th, 75th percentiles).

Results

Based on the smallest T-criterion value, most patients had osteopenia (n = 36), followed by normal BMD (n = 29) and osteoporosis (n =13). Patients with osteoporosis were slightly older and had lower BMI as compared to those with normal BMD (Table 1). Patients with osteopenia had lower BMI than those with normal BMD also. The diabetes duration, HbA_{1c} level and glomerular filtration rate (GFR) demonstrated no significant differences between the groups. Based on FRAX assessments, the 10-year risk of major low-energy fractures and the hip fractures was expectedly higher in patients with osteoporosis and osteopenia as compared to subjects with normal BMD ($p < 0.0001$).

Patients with normal BMD had higher total and trunk fat mass, as well as lean mass, as compared to those with osteoporosis and osteopenia (Table 2). Women with osteoporosis had lower fat mass in the hip area than those with normal BMD. However, there were no differences in the ratios of fat mass in the central abdominal and hip areas between patients with different BMD.

Spearman rank correlation analysis revealed a weak direct relation between BMI and BMD in the proximal femur and femoral neck (both $r = 0.25$, $p = 0.03$). Waist circumferences and BMD in different parts of the skeleton were not correlated. However, total BMD was related to BMI and waist circumference (both $r = 0.3$, $p = 0.0008$).

There were weak positive correlation between BMD in all tested areas, total and truncal fat masses (Table 4). Android and gynoid adipose tissue masses positively correlated with BMD in the proximal femur and femoral neck. Moreover, gy-

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Table 1

Characteristics of T2D-patients with different BMD

Variable	Groups		
	Normal BMD (n = 29)	Osteopenia (n = 36)	Osteoporosis (n = 13)
Age, years	60 (56; 65)	62.5 (59; 67)	64 (64; 67)*
Post-menopausal duration, years	13 (6.5; 17)	12 (8; 19)	16.5 (9; 17.5)
BMI, kg/m^2	35.3 (31.2; 38.2)	32.1 (29.3; 35.4)*	31 (29.4; 32.4)*
Waist circumference, cm	109 (104; 115)	102 (95; 106)	108 (96; 112)
T2D duration, years	14 (14; 20)	16 (11; 20)	18 (15; 25)
HbA_{1c}, %	9.7 (8.1; 10.5)	9.2 (7.4; 9.7)	8.4 (7; 10.1)
GFR, ml/min/1.73 m^2	64 (49; 70)	65 (58; 82)	64 (48; 78)
Ten-year risk of fracture based on FRAX, %	6.3 (6; 6,8)	8.3 (7.6; 9.3)*	8.7 (8; 9.8)*
Ten-year risk of hip fracture based on FRAX, %	0.2 (0.1; 0.2)	0.75 (0.5; 1)*	0.8 (0.6; 1)*

*Statistically significant ($p < 0.05$) difference compared with patients with normal BMD.

Table 2

The parameters of TBC in T2D-patients with different BMD

Variable	Groups		
	Normal BMD (n = 29)	Osteopenia (n = 36)	Osteoporosis (n = 13)
Total fat mass, kg	36.6 (31.9; 43.2)	31,3 (27,4; 37,7)*	26.7 (23.1; 32.4)*
Total fat mass, %	44.2 (41.7; 46.5)	42 (39.7; 46.5)	39.9 (37; 46.4)
Truncal fat mass, kg	22.5 (20; 25.1)	18.9 (16.8; 21.6)*	17.3 (16.1; 23.4)*
Android fat mass, kg	4.3 (3.5; 4.9)	3,3 (2.9; 4.3)*	3.3 (2.9; 4.5)
Gynoid fat mass, kg	5.7 (4.6; 6.6)	4.8 (3.6; 6.7)	4.1 (3.4; 5.6)*
Android/gynoid ratio	0.73 (0.66; 0.82)	0,7 (0.58; 0.95)	0.86 (0.72; 0.93)
Lean mass, kg	46.7 (43.5; 51.8)	44.1 (39.8; 47.4)*	42 (40.4; 45.3)*
Lean mass, %	53.6 (52.2; 57.6)	55.5 (51.2; 59.5)*	58.9 (55.4; 60.2)*

Statistically significant differences ($p < 0.05$): *compared with those with normal BMD.

Table 3

Correlations between anthropometric parameters and BMD in women with T2D

Variable	BMD			
	Lumbar spine	Proximal femur	Femoral neck	Forearm
BMI	0.18	0.25*	0.25*	0.18
Waist ciucumference	0.21	0.15	0.15	0.1

Table 4

Correlations between TBC variables and BMD in women with T2D

Variable	BMD			
	Lumbar spine	Proximal femur	Femoral neck	Forearm
Total fat mass	0.26*	0.27*	0.33*	0.33*
The proportion of fat mass (%)	0.06	0.13	0.13	0.28
Truncal fat mass	0.26*	0.38*	0.39*	0.35*
Android fat mass	0.1	0.27*	0.26*	0.26*
Gynoid fat mass	0.13	0.16	0.23*	0.32*
Android/gynoid ratio	-0.05	-0.02	-0.08	-0.27
Lean mass	0.24*	0.27*	0.28*	0.37*

Note: Spearman rank correlation coefficients are demonstrated.
*Statistically significant correlation ($p < 0.05$)

noid fat mass had a weak positive correlation with BMD only in the femur neck area. Android/gynoid ratios of adipose tissue masses were not correlated with BMD. All studied BMD variable were positively correlated with lean tissue masses.

BMD was not correlated with post-menopausal period or diabetes durations, HbA_{1c} levels and GFR ($r < 0.12$; $p > 0.05$ for all variables).

In the model of multivariate stepwise regression analysis, included the age, BMI, post-menopausal period duration, diabetes duration, HbA_{1c} level, GFR and TBC parameters as independent variables, the fat mass was the most significant predictor for total BMD ($\beta = 0.83$; $R2 = 0.19$; $p = 0.005$). In stepwise discriminant analysis the age and fat mass was the most significant factors associated with osteoporosis ($p = 0.03$

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and p = 0.0003, respectively; model parameters: p < 0.0005; F = 6.73; recognition accuracy, 84.6%).

Discussion

The obtained results demonstrate there is a positive relationship between fat mass and BMD at the sites of lumbar spine, proximal femur, femoral neck and forearm in post-menopausal women with T2D. The mass of adipose tissue in patients with osteoporosis was, on average, 9.9 kg lower than that in subjects with normal BMD. Previously a correlation between fat mass, total BMD and BMD in the femoral neck was demonstrated in middle-aged women with T2D who did not receive insulin [8].

A growing body of evidence indicates that adipose tissue can influence on BMD by several ways. A mechanical theory attributes the increase in BMD in obesity to the incremented load on the musculoskeletal system. An endocrine theory suggests that the increase of BMD in obesity is due to hormonal disturbances including hyperinsulinaemia, increased free sex hormone levels and enhanced conversion of oestrogen to androgens. The effects of leptin, adiponectin and other adipokines on bone remodelling are studied intensively [9].

We did not find any relation between fat distribution and BMD. The femoral neck and forearm BMD correlated with both android and gynoid fat mass.

In our study BMD correlated positively not only with fat mass but also with lean mass, wherein a substantial proportion of the muscle tissue. A positive correlation between lean mass and total BMD, as well as between lean mass and BMD in the femoral neck, has been previously shown for middle-aged men and women with T2D [8]. A correlation between fat mass, lean mass and lumbar BMD can be found in women as early as 20–25 years of age [10]. A large epidemiological study demonstrated a nearly linear relation between lean mass and femoral BMD for men and women older than 50 years [11].

Some data indicate that adipose tissue and muscles produce diverse effects on the bone quality, geometry and microarchitecture. A study conducted in Canada revealed that lean mass had greater effect than adipose tissue on mechanical strength of bones in men and women [11]. In patients with metabolic syndrome a positive correlation was found between muscle (lean) mass, BMD and parameters of bone quality, as determined by quantitative high-resolution computed tomography [12]. It has been shown that greater muscle mass is associated with a lower risk of fractures in post-menopausal women [13]. Muscle strength also demonstrated independent correlation with osteoporosis in this group [14]. The risk of falls and fractures may be enhanced by lower muscle mass and reduced muscle strength, which is distinguishes T2D-patients from those without [15].

Despite the positive correlation with BMD, obesity can hardly be regarded as a protective factor against fractures. In the Global Longitudinal Study of Osteoporosis in Women (GLOW), collected information on bone fractures within two years for 60,393 post-menopausal women, obesity was associated with an increased rate of femoral and ankle fractures but with a reduced incidence of fractures of forearm [16]. A recent prospective study conducted in Japan (6.7 years, n = 1,614) demonstrated that the risk of vertebral fractures was 39% lower for post-menopausal women with normal body weights than that for overweight or obese women [17]. An increased risk of fractures in obese patients is believed to be associated with more pronounced vitamin D deficiency, excess production of pro-inflammatory cytokines (IL-6, TNF-α), lower physical activity and the effect of co-morbid conditions, including T2D [9]. The Rotterdam study demonstrated that in patients with T2D with poor glycaemic control (HbA_{1c} ≥ 7.5%) the risk of fracture is increased by 47%–62%, together with increase in BMD by 1.5%–5.6%, as compared to those with HbA_{1c} <7.5% and subjects without diabetes [2]. The defects in bone microarchitecture which can result in reduced mechanical strength were revealed in women with T2D [18]. It could be speculated that overlapping effects of obesity and hyperglycaemia on the bone microarchitecture determine the increased risk of fractures in T2D-patients.

Conclusion

Obesity has a modifying effect on BMD at different sites of the skeleton in post-menopausal women with T2D. The positive correlation between BMD and BMI in these patients is mediated by the increases in both fat and lean masses. The fat mass is the most important predictor for total BMD, the effect remains significant after adjusting for age, BMI, duration of post-menopausal period, HbA_{1c} levels, GRF and other body composition parameters. The value of fat mass to lean mass ratio as a possible predictor of fractures in patients with T2D should be elucidated in the future studies.

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Список литературы

1. Ma L, Oei L, Jiang L, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. Eur J Epidemiol 2012;27(5):319–332. doi: 10.1007/s10654-012-9674-x
2. Oei L, Zillikens MC et al. High Bone Mineral Density and Fracture Risk in Type 2 Diabetes as Skeletal Complications of Inadequate Glucose Control: The Rotterdam Study. Diabetes Care 2013;36(6):1619–1628. doi: 10.2337/dc12-1188
3. Shan P, Wu X, Zhang H et al. Bone mineral density and its relationship with body mass index in postmenopausal women with type 2 diabetes mellitus in mainland China. J Bone Miner Metab 2009;27(2):190–197. doi: 10.1007/s00774-008-0023-9
4. Zhou Y, Li Y, Zhang D, Wang J, Yang H. Prevalence and predictors of osteopenia and osteoporosis in postmenopausal Chinese women with type 2 diabetes. Diabetes Research and Clinical Practice 2010;90(3):261–269. doi: 10.1016/j.diabres.2010.09.013
5. Leidig-Bruckner G, Grobholz S, Bruckner T, Scheidt-Nave C, Nawroth P, Schneider JG. Prevalence and determinants of osteoporosis in patients with type 1 and type 2 diabetes mellitus. BMC Endocr Disord 2014;14(1):33–1186. doi: 10.1186/1472-6823-14-33
6. Datta NS. Muscle-bone and fat-bone interactions in regulating bone mass: do PTH and PTHrP play any role? Endocrine 2014;47(2):389–400. doi: 10.1007/s12020-014-0273-3
7. Kaji H. Interaction between Muscle and Bone. J Bone Metab 2014;21(1):29–40. doi: 10.11005/jbm.2014.21.1.29
8. Moseley KF, Dobrosielski DA, Stewart KJ, De Beur SMJ, Sellmeyer DE. Lean mass and fat mass predict bone mineral density in middle-aged individuals with noninsulin-requiring type 2 diabetes mellitus. Clinical Endocrinology 2010;74(5):565–571. doi: 10.1111/j.1365-2265.2010.03965.x
9. Gonnelli S, Caffarelli C, Nuti R. Obesity and fracture risk. Clin Cases Miner Bone Metab 2014;11(1):9–14.
10. Wang MC, Bachrach LK, Van-Loan M, et al. The relative contributions of lean tissue mass and fat mass to bone density in young women. Bone 2005;37(4):474–481. doi: 10.1016/j.bone.2005.04.038
11. Leslie WD, Orwoll ES, Nielson CM et al. Estimated Lean Mass and Fat Mass Differentially Affect Femoral Bone Density and Strength Index But Are Not FRAX Independent Risk Factors for Fracture. J Bone Miner Res 2014;29(11):2511–2519. doi: 10.1002/jbmr.2280
12. Madeira E, Mafort TT, Madeira M et al. Lean mass as a predictor of bone density and microarchitecture in adult obese individuals with metabolic syndrome. Bone 2014;59:89–92. doi: 10.1016/j.bone.2013.11.004
13. Capozza RF, Cure-Cure C, Cointry GR et al. Association between low lean body mass and osteoporotic fractures after menopause. Menopause 2008;15(5):905–913. doi: 10.1097/gme.0b013e318164ee85
14. Rikkonen T, Sirola J, Salovaara K et al. Muscle Strength and Body Composition Are Clinical Indicators of Osteoporosis. Calcif Tissue Int 2012;91(2):131–138. doi: 10.1007/s00223-012-9618-1
15. Akeroyd JM, Suarez EA, Bartali B et al. Differences in skeletal and non-skeletal factors in a diverse sample of men with and without type 2 diabetes mellitus. J Diabetes Complications 2014;28(5):679–683. doi: 10.1016/j.jdiacomp.2014.05.007
16. Compston JE, Watts NB, Chapurlat R et al. Obesity Is Not Protective against Fracture in Postmenopausal Women: GLOW. The American Journal of Medicine 2011;124(11):1043–1050. doi: 10.1016/j.amjmed.2011.06.013
17. Tanaka S, Kuroda T, Saito M, Shiraki M. Overweight/obesity and underweight are both risk factors for osteoporotic fractures at different sites in Japanese postmenopausal women. Osteoporos Int 2012;24(1):69–76. doi: 10.1007/s00198-012-2209-1
18. Burghardt AJ, Issever AS, Schwartz AV et al. High-Resolution Peripheral Quantitative Computed Tomographic Imaging of Cortical and Trabecular Bone Microarchitecture in Patients with Type 2 Diabetes Mellitus. The Journal of Clinical Endocrinology & Metabolism 2010;95(11):5045-5055. doi: 10.1210/jc.2010-0226

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