suffering from mental disorders]. Kazanskiy meditsinskiy zhurnal. 2012;3:532-4. Russian.

3. Mosolov SN. [Scales of psychometric assessment of the symptoms of schizophrenia and the concept of positive and negative disorders]. M, Novuy tsvet. 2001;238. Russian.

4. Revenok OA, Marunkevich YY. [Features of concomitant somatic pathology in patients with paranoid schizophrenia]. Arxiv psikhiatrii. 2014;4:75-79. Russian.

5. Semke AV, Mal`ceva YL. [Schizophrenia combined with somatic pathology: clinical, adaptive and rehabilitative aspects]. Sibirskiy vestnik psikhiatrii i narkologii. 2009;3:42-44. Russian.

6. Tyurkina TA. [Associated somatic diseases in patients with schizophrenia]. Sibirskiy vestnik psikhiatrii i narkologii. 2010;5:47-49. Russian.

7. Ringen PA, Engh JA, Birkenaes AB, et al. Increased Mortality in Schizophrenia Due to Cardiovascular Disease – A Non-Systematic Review of Epidemiology, Possible Causes, and Interventions. Front Psychiatry. 2014;5:137.

8. Meetoo D. Dangerous liaisons: The relationship between schizophrenia and diabetes. Journal of Diabetes Nursing. 2013;17:104-11.

9. Castle DJ, Buckley PF, Gaughran FP. Physical Health and Schizophrenia. Oxford University Press. 2017;136.

10. Tandon R. Medical comorbidities of schizophrenia. Digest of Psychiatry. 2013;3(42):55-51.

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THE IMPACT OF METABOLIC CHANGES IN TYPE 2 DIABETES ON BONE TURNOVER

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Ключевые слова: *сахарный диабет, инсулин, ремоделирование кости*

Abstract. The impact of metabolic changes in type 2 diabetes on bone turnover. Safarova Sain Sattar. *This article carried out analyzes which helps to identify risk factors associated with bone metabolism changes, and to determine indicators that are informative in terms of predicting the risk of low-traumatic fractures observed in patients with type 2 diabetes mellitus. This study revealed some correlation between serum insulin level, bone metabolism markers and bone mass density determined at the lumbar DXA in patients with type 2 diabetes mellitus. This suggests that the presence of type 2 diabetes in anamnesis aggravated violation of disturbances of bone remodeling, thus contributing to the development of osteoporosis. The purpose of this study was to identify complex relationships between the mineral, organic component of bone and the risk of fractures under the influence of metabolic changes associated with type 2 diabetes. This study suggests that obesity and hyperinsulinemia can not be bone-protective factors, this is confirmed by the growing body of evidence that points to the importance of measuring bone remodeling markers in combination with bone mineral density in assessing and predicting the risk of fractures. Clarification of the role of insulin in assessing bone health remains a matter of debate.*

Реферат. Вплив метаболічних змін при діабеті 2 типу на обмінні процеси в кістці. Сафарова С.С. *У статті проведено дослідження, що допомагає виявити фактори ризику, пов'язані зі зміною метаболізму кісткової тканини, і визначити показники, інформативні щодо прогнозування ризику нізькотравматичних переломів, що спостерігаються в пацієнтів з цукровим діабетом 2 типу. У ході цього дослідження виявлена певна кореляція між рівнем сироваткового інсуліну, маркерами кісткового метаболізму і щільністю кісткової маси, яка визначається при поперековій DXA у пацієнтів з цукровим діабетом 2 типу. Це дозволяє вважати, що наявність цукрового діабету 2 типу в анамнезі посилює порушення кісткового ремоделювання, тим самим сприяючи розвитку остеопорозу. Мета цього дослідження полягала у виявленні складних взаємозв'язків між мінеральним, органічним компонентом кістки і ризиком розвитку переломів під впливом метаболічних змін, пов'язаних з діабетом 2 типу. Це дослідження свідчить про те, що ожиріння і гіперінсулінемія не можуть бути факторами, що захищають кістку, і це доводить зростаюча кількість доказів, що вказують на важливість вимірювання маркерів кісткового ремоделювання в поєднанні з мінеральною щільністю кістки при оцінці і прогнозуванні ризику переломів. Уточнення ролі інсуліну в оцінці стану кістки, як і раніше, залишається предметом дискусій.*

Accumulated evidence confirms the connection between type 2 diabetes mellitus (DM2) and an increased risk of low-traumatic fractures against a background of high bone mineral density (BMD). Disturbance of metabolic processes in bone tissue in patients with diabetes mellitus can be caused by the direct effect of insulin deficiency and / or hyperglycemia on the bone, the accumulation of final glycation products in the bone matrix that breaks down the bone collagen synthesis, the production of inflammatory cytokines, the production of adipokines that induce a negative imbalance in bone remodeling and a violation of neuromuscular regulation [1].

Type 2 diabetes is associated with 1.5–2-fold increased odds of bone fracture risk than in a healthy population, which deterioration in the quality of bone tissue can be a major cause of bone fragility and does not depend on the decrease in bone mineral density. The data suggest that some indicators may be more informative in terms of predicting the risk of low-traumatic fractures observed in patients with diabetes and that in essence the BMD measurement does not reflect the real trend towards the development of bone remodeling disorders in patients with type 2 diabetes. This determines the need to develop improved methods for assessing bone properties to clarify stratification risk criteria.

The purpose of this study was to identify complex relationships between the mineral, organic component of bone and the risk of fractures under the influence of metabolic changes associated with type 2 diabetes.

MATERIALS AND METHODS

A transverse study was conducted, in which 137 patients with diabetes mellitus (85 female, 52 male) were included, who had not previously been diagnosed with bone metabolism and osteoporosis. The age of the examined patients is from 40 to 70 years old (58.4±0.9 years). The duration of diabetes was 8.1±0.7 years. All the subjects had diabetes in anamnesis, the body mass index (BMI) in kg/m^2 (30.0±0.3 kg/m^2) was calculated. The mean value of glycosylated hemoglobin (HbA1c) - 7.5±0.2% of blood was determined once. The control group consisted of 82 patients (48 women and 34 men, 55.9±0.9 years) without a history of diabetes.

Exclusion criteria: persons previously treated for osteoporosis or with a history of fracture, as well as diseases of the endocrine system, liver and kidneys of the non-diabetic nature, with a diabetic nephropathy of the 4-5 stage in anamnesis.

All patients underwent dual-energy X-ray Absorbtiometry (DXA) (Densitometer DXA, HOLOGIC, Discovery QDR 4500 A.USA model) of the lumbar spine (L1-L4) and the proximal and femoral neck areas. The IASC for WHO criteria applied to diagnosis was assessed as osteoporosis (T-score ≤ 2.5SD), osteopenia (T-score from -1 to -2.5 SD) and normal (T-score> -1).

Parameters of phosphorus-calcium metabolism were estimated by the concentration of ionized calcium (iCa) using the cresolphthalein and inorganic phosphorus (P) complex method by reducing phosphomolybdate in blood serum using a biochemical analyzer "COBAS INTEGRA 400/700/800" (Switzerland). The insulin, C-peptide, parathyroid hormone (PTH), calcitonin (CT) and vitamin D3 levels in the blood were evaluated by an enzyme-binding absorbent method (ELISA) using the Cis bio international test kit. The glomerular filtration rate (GFR) was calculated by the formula CKD-EPI. To assess the resistance to insulin, the HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index was calculated [6]. The state of bone tissue formation was judged by the activity of total alkaline phosphatase (ALP) and the content of the amino-terminal propeptide of procollagen type I (PINP) in serum. The significance of the C-terminal telopeptide of type I collagen (beta-CTx) as a serum bone resorption marker using an automatic electro- chemiluminescence analyzer COBAS e41 (Switzerland),

using the "Roch Diagnostics" reagents (Germany) was estimated.

Statistical analysis was carried out using "BioStat Pro 6.2.2.0" program. Statistical analysis was done using unpaired parametric data analyzed by Mann—Whitney U test. Spearman's rank correlation was calculated to assess the power of connection between the parameters. $P< 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Characteristics of subjects and clinical characteristics for the study groups are shown in Table.

Characteristics of subjects, Mean ± mean error (M ± m) and (95% CI)

Characteristics	T2DM, n = 137	Non-DM Controls, n=82
Sex (M:F)	52/85	39/43
Age (years)	58,4±0,56 (57,3-59,6)	55,9±0,87 (54,2-57,7)
Duration of DM (years)	8,1±0,42 (7,2-8,9)	-
BMI (kg/m ^{2})	30,02±0,31 (29,4-30,6)	28,7±0,37 (27,9-29,5)
HbA1c, %	7,5±0,16 (7,2-7,8)	4,9±0,06 (4,7-5,0)
tCa, mg/dL	9,4±0,05 (9,3-9,5)	9,5±0,05 (9,4-9,6)
iCa, mmol/L	1,07±0,01 (1,04-1,08)	1,13±0,01 (1,11-1,15)
Inorganic P, mmol/L	5,0±0,08 (4,8-5,2)	5,1±0,09 (4,9-5,2)
eGFR (mL/min/1,73 m ^{2})	88,5±1,52 (85,4-91,5)	95,2±1,71 (91,8-98,6)
PTH, pg/mL	51,7±1,44 (48,8-54,6)	45,1±2,33 (40,2-49,8)
Vitamin D3, ng/mL	25,1±1,08 (22,9-27,2)	30,41±1,72 (26,95-33,86)
C-peptide, ng/ dL	4,3±0,26 (3,7-4,8)	3,5±0,15 (3,1-3,8)
HOMA-IR	8,6±0,52 (7,5-9,6)	2,8±0,18 (2,4-3,1)
ALP, IU/L	122,2±3,01 (116,2-128,1)	123,5±4,88 (113,8-133,2)
PINP, ng/mL	42,08±1,15 (39,8-44,3)	47,09±2,14 (42,82-51,35)
b-CTx, ng/mL	0,495±0,02 (0,456-0,533)	0,424±0,02 (0,383-0,466)
Spine T-score (L1-L4)	-1,08±0,12 (-1,3; -0,8)	-0,73±0,19 (-1,1; -0,3)
Spine Z- score (L1-L4)	-0,03±0,14 (-0,3; 0,2)	0,27±0,18 (-0,08; 0,6)
Femoral neck T– score	-1,12±0,12 (-1,3; -0,8)	-0,64±0,18 (-1,0; -0,2)
Femoral neck Z – score	0,02±0,12 (-0,2; 0,3)	0,22±0,17 (-0,1; 0,5)

According to the analysis of the study results, the dynamics of insulinemia in patients with diabetes was characterized by an increase in insulin response (HOMA IR - 8.6±0.52). The mean values of serum Hb1Ac were within the norm: for the whole group of examined patients - 7.5±0.16% (7.2-7.8). In patients with type 2 diabetes, the serum PTH level was also associated with the insulin resistance index, the HOMA-IR index, as indicated by the rank correlation coefficient r= -0.273, p=0.01. PTH can affect the release of insulin by the pancreas, acting on the metabolism of insulin and glucose. Thus, with an increase in the concentration of PTH, an increase in the level of glucose in the plasma is observed [3].

In type 2 diabetes, the P1NP value was statistically significantly different from the control group (p>0.05). However, we found a trend towards a statistically significant increase in P1NP in men with a duration of DM2 type of less than 10 years compared with women in this group (p<0.05), consistent

with the data of a number of authors (Sathyapalan T., 2017) and is presumably associated with insulin resistance [4]. Thus, the resistance to insulin, including osteoblast-specific receptors for insulin which develops against hyperinsulinemia leads to a disruption in the differentiation of osteoblasts and a decrease in the formation of the trabecular bone. Another factor that negatively affects bone remodeling is a decrease of blood flow to the bone tissue [5].

Conducted correlation analysis in the study groups revealed a higher BMI in individuals with a low serum b-CTx, which was described earlier and in a number of other studies [6]. In patients with type 2 diabetes, significant correlations were observed between b-CTx and BMI (r= -0.163, p=0.04), insulin concentration (r= -0.210, p=0.02), C-peptide (r= -0.402, p=0.001) and the HOMA-IR index (r= -0.191, p=0.04). Also, in patients with DM2 with a duration of disease up to 10 years, the P1NP level was weak, but statistically significantly associated with the HOMA-IR index, with a rank correlation coefficient r=0.217, p=0.05. Biochemical markers of bone remodeling in obesity are lower than in individuals with normal weight [7], but the difference in the values of resorption markers is somewhat greater than the difference in the values of the formation markers. This results in a higher risk of bone fracture associated with obesity due to the fact that pro-inflammatory cytokines from visceral fat, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), increase bone resorption, negative impact on the IPC [8].

Our results showed that the level of HbA1c in patients with diabetes has a negative correlation with the marker of bone formation P1NP: (r= -0.254, p=0.01). The negative association of P1NP with HbA1c [9] indicates that the formation of bone tissue is disturbed by high blood glucose levels; accordingly, people with diabetes with unsatisfactory glycemic control have a greater risk of low-traumatic fractures. Studies have shown that P1NP values are associated with glucose tolerance and insulin secretion [8], although mechanisms are not fully understood.

In patients with DM2, a correlation was found between the change in the T-score measured in the lumbar spine and C-peptide: r=0.346, p=0.02. In addition, a positive relationship between the body mass index and bone mineral density, particularly pronounced with the duration of the underlying disease of less than 10 years, has been revealed. Thus, with DM2, a significant dependence was found between the change in the T-score measured in the femoral neck and BMI: r=0.310, p=0.02; as well as, with the HOMA-IR index: r=0.293, p=0.04. In men with DM2, a significant relationship was also found between the T-score measured in the L1-L4 and BMI regions: r=0.314, p=0.04. The existence of a positive connection between BMI and bone mineral density is confirmed by the data of other authors [10]. This confirms the evidence that the BMD determined by DXA is higher in obese people, and in part, this is due to the fact that higher BMI and soft tissue thickness cause an error in DXA measurements [7]. However, with DM2, there was no correlation between the BMI score and the T-score of the BMD measured in the neck region of the femur, which indicates different sensitivity of different sites to metabolic changes, as the cortical and spongy bone may react differently to insulin, glucose, BMI and parathyroid hormone [6]. In addition, overweight is associated with a delayed loss of bone mass in menopause [9], consistent with a trend toward a positive bone balance in women with obesity.

The smaller values of the BMD measured in the L1-L4 region and the decrease in bone metabolism from the analysis of bone markers manifested by inhibition of bone formation processes - P1NP, may be caused by insulin resistance in the early stages of DM2 (r=0.255, p=0.02) and insulinopenia at long course of DM2, as well as hyperglycaemia [10]. However, it is obvious that due to the fact that the state of the glycemic profile is a very dynamic index, the correlation between the level of HbA1c and the decrease in the T-score of the MIC was not found, which agrees with the results of a number of other authors [7]. When comparing the data of the T-score of the lumbar spine with the level of b-CTX in patients with diabetes, a significant relationship was found between these indices (r=-0.231, p=0.02). In the study, a link between the Z-criterion of the lumbar spine and the level of b-CTX in patients with diabetes mellitus was found to show a significant relationship between these indices (r= -0.227, p=0.02). In women with DM2 in premenopause, there was no significant dependence on these parameters. However, in a subgroup of postmenomausal women with DM2, a reliable relationship was found for these parameters (r= -0.302, p=0.04), which indicates that the physiological decrease in bone mineral density after 45 years should also be taken into account. Also, in a subgroup of women, a correlation was found between these values according to the Z-criterion (r= -0.365, p=0.01), which emphasizes the relationship between these indicators, and hence the association with osteoporosis in the study group.

This study is an attempt to indicate the importance of serum insulin as a possible marker of bone remodeling in patients with diabetes. Also

significant is the fact that bone remodeling markers were considered as the most informative markers for assessing the complex effect of insulin on bone metabolism in modern clinical practice, regardless of the type of disturbance of its secretion (meaning the stage of hyperinsulinemia / insulin resistance or relative secretory insufficiency with DM2) [9]. In patients with type 2 diabetes mellitus, changes in bone mineral density were detected only in 16% of cases corresponded to osteoporosis and osteopenia was noted more often than osteoporosis. Another aspect of the problem is related to the fact that in diabetes mellitus a higher level of bone resorption markers than among people who are not diabetic, but the mechanism underlying this process remains not completely clear [10].

CONCLUSIONS

In this study, it was found that increased insulin resistance and / or hyperinsulinemia can affect the anabolic response of bone tissue, adversely affecting bone strength. This study suggests that obesity and hyperinsulinemia can not be bone-protective factors, which is confirmed the growing body of evidence that points to the importance of measuring bone remodeling markers in combination with bone mineral density in assessing and predicting the risk of fractures. Further studies are needed to determine the pathophysiological mechanisms by which insulin resistance can adversely affect bone metabolism.

The author states that there is no conflict of interest.

REFERENCES

1. Farr JN, Khosla S. Determinants of bone strength and quality in diabetes mellitus in humans. Bone. 2016;82:28-34.
2. Kahn SE. The relative contributions of insulin resistance and β–cell dysfunction to the patophysiology of type 2 diabetes. Diabetologia. 2005;48:3-19.
3. Premaor MO, Comim FV, Compston JE. Obesity and fractures. Arq Bras Endocrinol Metabol. 2014;58:470-7.
4. Hewston P, Deshpande N. Falls and balance impairments in older adults with type 2 diabetes: thinking beyond diabetic peripheral neuropathy. Can. J.Diabetes. 2016;40:6-9.
5. Riddle RC, Clemens TL. Insulin, osteoblasts, and energy metabolism: why bone counts calories. J Clin Invest. 2014;124:1465-7.
6. Manavalan JS, et al. Circulating osteogenic precursor cells in type 2 diabetes mellitus. J. Clin. Endocrinol. Metab. 2012;97:3240-50.
7. Pramojanee SN, Phimphilai M, Chattipakorn N, Chattipakorn SC. Possible roles of insulin signaling in osteoblasts. Endocrine Research. 2014;39(4):144-51.
8. Bredella MA, Gill CM, Gerweck AV, Landa MG, Kumar V, Daley SM, et al. Ectopic and serum lipid levels are positively associated with bone marrow fat in obesity. Radiology. 2013;269:534-41.
9. Russell M, Mendes N, Miller KK, Rosen CJ, Lee H, Klibanski A, et al. Visceral fat is a negative predictor of bone density measures in obese adolescent girls. J Clin Endocrinol Metab. 2010;95:1247-55.
10. Starup-Linde J, Vestergaard P. Biochemical bone turnover markers in diabetes mellitus – a systematic review. Bone. 2016;82:69-78.

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