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PECULIARITIES OF BONE REMODELLING AND BONE TISSUE STATUS IN POSTMENOPAUSAL WOMEN WITH TYPE 2 DIABETES MELLITUS

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FEATURES OF BONE REMODELLING AND BONE METABOLISM IN POSTMENOPAUSAL WOMEN WITH TYPE 2 DIABETES MELLITUS
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Postmenopausal women with type 2 diabetes mellitus (T2DM) have increased bone fragility and fracture risk, despite higher bone mineral density as measured by dual-energy X-ray densitometry (DEXA). Therefore, although DEXA is a standard method for detecting decreased bone mass and osteoporosis, and given that bone fracture may be the first symptom of osteoporosis, DEXA does not reflect changes in bone metabolism.

The aim of the article is to study the features of bone metabolism according to clinical and laboratory data in postmenopausal women with T2DM to identify additional markers of BMD and osteoporosis decline.

Materials and methods. The study included 160 postmenopausal patients divided into two groups, group 1 – 80 women diagnosed with T2DM, group 2 – 80 women without T2DM. All patients underwent a general clinical examination, densitometry, functional assessment, and biochemical markers: glycosylated blood hemoglobin, estradiol, ionised calcium (iCa2+), 25-hydroxyvitamin D (vitamin D), total alkaline phosphatase, osteocalcin (OC), Beta-CrossLaps (bCTx), parathyroid hormone (PTH), tartrate-resistant acid phosphatase (TRAP5b) in the blood serum.

Results. Postmenopausal women with type 2 diabetes mellitus have a higher risk of falls, decreased muscle strength while maintaining muscle mass, decreased bone metabolism, which is manifested by decreased bone formation parameters such as iCa2+, vitamin D and OC and decreased resorption parameters such as TRAP5b and bCTx. A negative correlation was found between glycemia levels and bone formation markers vitamin D and OC, and a negative correlation with bCTx.

Key words: diagnosis, type 2 diabetes mellitus, postmenopause, bone metabolism, vitamin D.

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ОСОБЛИВОСТІ КІСТКОВОГО РЕМОДЕЛЮВАННЯ ТА СТАНУ КІСТКОВОЇ ТКАНИНИ У ЖІНОК У ПОСТМЕНОПАУЗІ, ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ
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Метою дослідження було вивчення особливостей кісткового метаболізму за клінічними та лабораторними даними у жінок у постменопаузі, хворих на цукровий діабет 2 типу (ЦД2), для визначення додаткових маркерів зниження кісткової маси та остеопорозу. В обстеження було включено 160 пацієнток у постменопаузі, котрі розділені на дві групи: групу 1–80 жінок зі встановленим діагнозом ЦД2, групу 2–80 жінок без ЦД2. Всім пацієнткам проводилось загальноклінічне дослідження, денситометрія, функціональна оцінка, визначення глікозильованого гемоглобіну крові, рівню естрадіолу, маркерів формування та резорбції кісток.

Жінки в постменопаузі з ЦД2 мають вищий ризик падіння, зниження сили м'язів за збереження м'язової маси, зниження активності кісткового метаболізму.

Ключові слова: діагностика, цукровий діабет 2 типу, постменопауза, кістковий метаболізм, вітамін D.

Introduction. Type 2 diabetes mellitus (T2DM) is a chronic disease that leads to a number of complications, including bone mass loss and increased risk of fracture [1]. Menopause is also a risk factor for osteoporosis and increased fracture risk [2].

A number of studies have shown that patients with T2DM may have normal or even higher bone density as measured by dual-energy X-ray densitometry (DEXA) [3; 4]. A higher body mass index (BMI) in diabetics may initially protect against bone loss, but this effect diminishes with longer duration of diabetes mellitus [5]. Postmenopausal women with T2DM are known to have increased bone fragility and fracture risk, despite having higher bone mineral density (BMD) compared to postmenopausal women without T2DM [6]. This condition is partly related to poor bone quality and increased bone metabolism [7]. The risk of fractures in this population is also associated with an increased tendency to fall [8].

Changes in serum markers of bone metabolism differed from study to study, so it is currently unknown whether bone metabolism markers can be used as predictors of future fractures in patients with T2DM.

In our opinion, although DEXA is a standard method for detecting decreased bone mass and osteoporosis, and given that a bone fracture may be the first symptom of osteoporosis, DEXA does not reflect changes in bone metabolism and only states that osteoporosis has developed.

So, in patients with T2DM, DEXA does not always meet the clinical needs for the diagnosis of decreased body mass and osteoporosis, and it would be advisable to focus on other indicators (clinical, laboratory). Therefore, the study of the features of bone remodelling and bone tissue status in postmenopausal women with T2DM according to clinical and laboratory data is an urgent problem and requires research.

The aim of the article is to study the features of bone metabolism according to clinical and laboratory data in postmenopausal women with T2DM to determine additional markers of body mass and osteoporosis reduction. To determine the possibility of early clinical and laboratory diagnosis and possibilities of correction of bone metabolism disorders in postmenopausal women in order to prevent fractures and improve the quality of life.

Material and methods. The study was conducted at the Multidisciplinary Medical Centre of Odesa National Medical University (ONMedU) from June 2022 to September 2023 following the protocol approved by the ONMedU Bioethics Commission (Protocol No. 4 of 06.06.2022), after filling out the written consent of the participants in accordance with the principles of bioethics set out in the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects and the Universal Declaration of Bioethics and Human Rights (UNESCO).

The study included 160 patients. The patients were divided into 2 groups. The observation group (group 1) included 80 patients diagnosed with T2DM according to the criteria of the American Diabetes Association (ADA), 2011 (80 women). The age of the examined patients in group 1 was from 50 to 65 years (60.4±3.1) years, and patients with T2DM duration of more than 5 years and glycated hemoglobin level over 7.5% were included in the study. The duration of diabetes mellitus was (9.1±1.2) years. The control group (group 2) consisted of 80 women aged 50 to 65 years, the mean age (58.43±2.8) years without T2DM. All patients with T2DM took oral hypoglycaemic drugs according to ADA 2022 guidelines.

Exclusion criteria: Previously diagnosed osteoporosis/ low body mass, ovariectomy, history of bone fractures in adulthood; documented oncological pathology, patients with acute conditions (infections, acute myocardial infarction, trauma, surgery) at the period less than 2 months before the start of the study, type 1 diabetes mellitus, family history of hip or spine fractures, rheumatoid arthritis, thyrotoxicosis, smoking, alcohol abuse, chronic use of glucocorticosteroids, estrogen replacement therapy, refusal to be monitored by a physician or to participate in the study program, 2–3 stage obesity.

All patients underwent a general clinical examination: personal and anamnestic data (age, date of birth, comorbidities), collection of complaints, anamnesis, physical examination of patients, as well as BMI, DEXA, and questionnaire assessment of quality of life using the SF-36 questionnaire.

Body weight, height, physical activity, grip strength, muscle performance, and osteosacropenia were examined to determine the risk of falling. Body weight (kg) was measured using a mechanical scale (with a 0.1 kg increment), while height (cm) was measured using a stadiometer, as we considered the average of the two subsequent measurements (with a 0.1 cm increment). BMI was calculated using the accepted formula (BMI=weight/ height^2, kg/m^2), and overweight and obesity were assessed according to WHO guidelines. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ).

Handgrip strength (HGS) was measured using digital dynamometry. We considered the best of three measurements (kg) on the dominant hand (approximately 0.1 kg).

A short set of general condition tests (SPPB) was also used to assess muscle performance. During the DEXA together with BMD determined body composition with an assessment of upper and lower limb muscle mass (ALM) and adipose tissue.

Osteosarcopenia was defined as low BMD (T-score<-1), low muscle mass (ALM<15 kg) and muscle weakness (HGS<16 kg) and/or low muscle performance (SPPB<8).

Determination of biochemical markers: control of carbohydrate metabolism: glycosylated blood hemoglobin. Determination of female sex hormones: estradiol level. Markers of bone metabolism were determined. Markers of bone formation: ionised calcium (iCa2+), 25-hydroxyvitamin D (25-(OH)D), total alkaline phosphatase (ALP), osteocalcin (OC); bone resorption: Beta-CrossLaps (bCTx), parathyroid hormone (PTH), tartrate-resistant acid phosphatase (TRAP5b) in the blood serum.

The statistical analysis of the data was performed using the variational and mathematical methods of Statistica 12.6. The data are presented as the arithmetic mean (M) and 95% confidence interval for the mean (95% CI) and Student's t-test with a normal distribution of values. The values were considered statistically significant at $p<0.05$. Spearman correlation analysis (r) was used to study the dependencies between the parameters.

Results and their discussion. We analyzed the subjective complaints of patients, among which we identified complaints that affect the risk of falling, such as periodic dizziness, unsteadiness of gait, muscle weakness, visual impairment, nocturia, and assessment of overall quality of life. The data obtained are presented in Table 1.

Table 1 shows that patients with T2DM have a higher risk of falls, as symptoms that directly affect this risk were more common in group 1. Thus, periodic dizziness is significantly ($p<0.05$) more common in group 1 – 32.5% vs. 8.75% in group 2, unsteadiness of gait, respectively 15% and 3.75% ($p<0.05$), muscle weakness 45% and 18.75% ($p<0.05$), visual impairment 23.75% and 7.5%, nocturia 53.75% and 11.25% ($p<0.05$). A subjective decrease in quality of life was noted in 36.25% of patients in group 1 and 12.5% in group 2 ($p<0.05$).

According to the literature, when assessing quality of life using the SF-36 questionnaire, women with T2DM more often reported lower scores in the following domains: physical functioning, role functioning due to physical condition, body pain, and vital activity [9]. These domains are significantly influenced by factors such as age, obesity, duration of diabetes mellitus, and comorbidities [9; 10].

Table 1

Subjective symptoms in postmenopausal women associated with the risk of falling (n, %, p)

Subjective symptoms	Group 1 (observation) (n=80)	Group 2 (control) (n=80)	p
Periodic dizziness	26 (32.5%)	7 (8.75%)	<0.05
Unsteady gait	12 (15%)	3 (3.75%)	<0.05
Muscle weakness	36 (45%)	15 (18.75%)	<0.05
Impaired vision	19 (23.75%)	6 (7.5%)	<0.05
Nocturia	43 (53.75%)	9 (11.25%)	<0.05
Decreased quality of life	29 (36.25%)	10 (12.5%)	<0.05

Notes.

1. Quantitative data are presented in the form (M±m) – mean ± mathematical error of the mean.
2. Comparison of percentages between groups was performed by χ^2 criterion.
3. The difference was considered significant at p<0.05.

Table 2 shows the data on the overall assessment of quality of life and the factors that determine it according to the SF-36 questionnaire.

The data presented in Table 2 indicate that in general, the assessment of quality of life in group 1 is lower, with a significant decrease in physical functioning 50.19±5.37 and 63.89±5.74 (p<0.05), role functioning due to physical condition 30.64±3.29 and 37.95±4.62 (p<0.05), general health 31.63±3.96 and 43.20±3.29 (p<0.05), mental health 50.38±5.98 and 59.04±4.66 (p<0.05), which ultimately leads to a significant decrease in the physical component of health 37.31±3.35 and 53.34±6.19 (p<0.05) and overall quality of life 50.74±5.66 and 59.21±5.30 (p<0.05). Although some indicators of mental health were reduced, the overall component of psychological health was not significantly reduced 62.01±6.77 and 65.32±7.60 (p>0.05).

We assessed BMD by DEXA (T-score of the lumbar spine (L1-L4) and femoral neck) and body composition. As well as BMI, physical activity, muscle mass and function. The data are presented in Table 3.

Table 2

Assessment of quality of life in postmenopausal women according to the SF-36 questionnaire

Total	Group 1 (observation) (n=80) M±S.D.	Group 2 (control) (n=80) M±S.D.	p
Physical functioning	50.19±5.37	63.89±5.74	<0.05
Role functioning due to physical condition	30.64±3.29	37.95±4.62	<0.05
Intensity of pain	72.76±10.23	75.17±5.90	0.28
General state of health	31.63±3.96	43.20±3.29	<0.05
Role functioning due to emotional state	54.20±5.55	58.22±6.56	<0.05
Life activity	65.95±6.88	65.61±5.09	0.691
Mental health	50.38±5.98	59.04±4.66	<0.05
Social functioning	64.32±5.46	69.29±6.91	0.24
Physical component of health	37.31±3.35	53.34±6.19	<0.05
Psychological component of health	62.01±6.77	65.32±7.60	0.13
Overall quality of life	50.74±5.66	59.21±5.30	<0.05

Notes:

1. Quantitative data are presented in the form (M±m) – mean ± mathematical error of the mean.
2. The difference was considered significant at p<0.05.

Table 3

DEXA, BMI, physical activity, muscle mass and function scores

Results	Group 1 (observation) (n=80)	Group 2 (control) (n=80)	p
T-index of the lumbar spine (L1-L4)	T=0.83±0.47	T=-0.43±0.10	<0.05
T-index of the femoral neck	T=0.53±0.37	T=0.43±0.17	>0.05
BMI, kg/m²	31.5±2.3	27.5±1.7	>0.05
ALM, kg	12.34±2.20	14.26±2.43	>0.05
Handgrip strength, kg	10.09±4.02	18.40±6.83	<0.05
SPPB<8	8(10%)	2(2.5%)	<0.05
Decline over the past year	0	0	–
Osteosacropenia	0	0	–

Notes:

1. Quantitative data are presented in the form (M±m) – mean ± mathematical error of the mean.
2. The difference was considered significant at p<0.05.

The presented data indicate that BMI was higher in the control group than in the observation group, but not statistically significant (p>0.05) (31.5±2.3) kg/m² and (27.3±1.7) kg/m², respectively. Hip BMD in both groups was within normal limits, but there was a greater range of fluctuations in the values in group I. This may be explained by the higher weight of patients, which is a factor of higher BMD on the one hand, and the negative impact of diabetes mellitus on bone metabolism. Despite the absence of a difference in ALM (p>0.05), patients in group 1 showed lower handgrip strength by 58.34% ((10.09±3.02) kg vs. (18.40±6.83) kg, p<0.05) and lower SPPB<8 10% vs. 2.5%, (p<0.05), which demonstrates a decrease in physical strength, which is positively correlated with the physical component of health (r=0.646, p<0.05).

A study by Paul D. Loprinzi shows that handgrip strength was associated with HGA1c in women with type 2 diabetes mellitus [11].

We evaluated laboratory parameters of bone metabolism and their relationship.

Table 4 shows that all postmenopausal patients, with an average duration of (8.5±0.7) years in group 1 and (6.8±0.5) years in group 2, had their estradiol levels determined. The level of estradiol did not differ statistically in the groups (p>0.05), it was (9.2±0.8) pg/ml in group 1 and (11.6±0.7) pg/ml in group 2, the norm in postmenopausal women is 0-30 pg/ml.

The correlation between laboratory markers of diabetes mellitus and changes in bone metabolism was determined by correlation analysis. In group 1 and group 2, iCa2+ levels did not differ statistically (p>0.05). Group 1 – iCa2+ level was (1.15±0.14) mmol/l, in group 2 – (1.23±0.20) mmol/l.

In both groups, the level of 25-(OH) D (normal 25-(OH) D>30ng/ml) is not statistically different (p>0.05), in group 1, 25-(OH) D insufficiency (25-(OH)D=10-29 ng/ml) was found in 55%, deficiency (25-(OH)D<10 ng/ml – in 27.5%, the average level was (18.4±1.4) ng/ml compared to the control group of 25-(OH)D (21.7±1.5) ng/ml. A correlation was found between iCa and 25-(OH)D levels in patients with T2DM (r=0.246. p< 0.05), which in some studies is associated with insulin resistance [12]. This is also due to the fact that insulin secretion in response to elevated plasma glucose concentrations is a Ca2+-dependent process [13]. The level of 25-(OH)D and iCa2+ does not correlate with the duration of T2DM (r=0.046, p>0.05, r=-0.016, p<0.05) and the level of glycated hemoglobin (r=0.078, p<0.05).

There was no significant difference (p=0.14) in ALP levels between patients with T2DM (120.4±2.7) U/L and control (114.0±3.4) U/L, with a weak positive correlation between ALP levels and T2DM duration (r=0.118, p<0.05). The study indicates that the role of ALP in bone metabolism remains controversial, with no significant difference in BMI in T2DM [14].

The level of OC in group 1 (Fig. 1) was statistically significantly lower (2.5±0.74) ng/ml compared to group 2 (5.4±0.92) ng/ml (p<0.05). The level of OC in group 1 was negatively correlated with HbA1c (r=-0.219, p<0.05) and weakly negatively correlated with the duration of diabetes mellitus (r=-0.143, p<0.05), and weakly positively correlated with 25-(OH)D level (r=0.178, p<0.05).

According to clinical studies, lower levels of OC were associated with a higher risk of diabetes mellitus in a cohort of Japanese postmenopausal women [15]. And a decrease in OC levels in women with diabetes mellitus is associated with a decrease in BMD, indicating a dual role of OC in both bone and glucose metabolism [16].

In our study, the level of OC was within the normal range in both groups, but significantly lower in group 1. In group 1, compared to group 2, handgrip strength was positively correlated with OC (r=0.251, p<0.05) and negatively correlated with HbA1c (r=-0.294, p<0.05). A study by Pei-Yun Chen showed that in postmenopausal women with T2DM, higher OC levels (OC≥11.4 ng/ml) were dose-dependently associated with an increased risk of deterioration in handgrip strength and physical performance [17]. Other studies have shown that the ratio of carboxylated OC (GluOC) to total OC (tOC) (GluOC/tOC)

Table 4

Clinical and laboratory indices of bone metabolism in patients with type 2 diabetes mellitus and control group, M (95% CI)

Results.	Group 1 (observation) (n=80)	Group 2 (control) (n=80)	p
Age, years	60.4±3.1	58.43±0.8	>0.05
Duration of postmenopause, years	8.5±0.7	6.8±0.5	>0.05
Estradiol, pg/ml	9.2±0.8	11.6±0.7	>0.05
Duration of diabetes mellitus, years	9.1±0.9	–	–
HbA1c, %.	8.9±0.6	4.8±0.3	<0.05
iCa2+, mmol/l	1.15±0.14	1.23±0.20	>0.05
25-(OH)D, ng/ml	18.4±1.4	21.7±1.5	>0,05
ALP, U/l	120.4±2.7	114.0±3.4	>0.05
OC, ng/ml	2.5±0.54	5.4±0.82	<0.05
PTH, pg/ml	55.22±5.91	47.22±5.17	>0.05
bCTx, ng/ml	0.291±0.084	0.537±0.09	<0.05
TRAP5b, ng/ml	1.4±0.4	1.5±0.4	>0.05

Notes.

1. Quantitative data are presented in the form (M±m) – mean ± mathematical error of the mean.

2. The difference was considered significant at p<0.05.

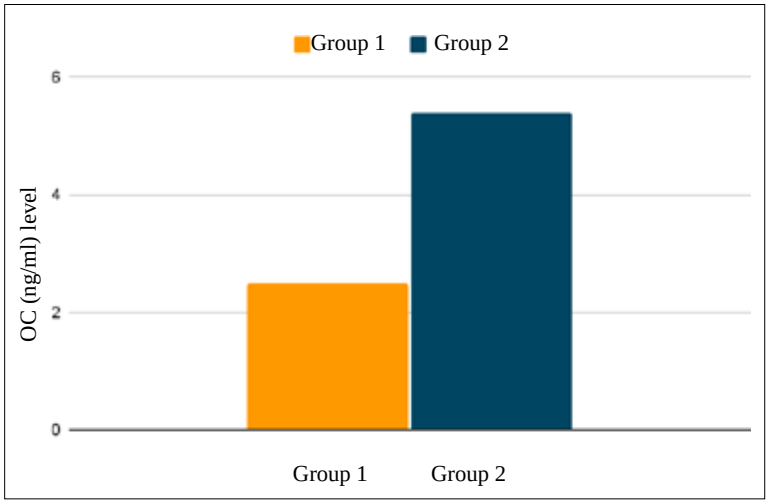

Fig. 1. OC levels (ng/ml) in groups 1 and 2

in women over 70 years of age is positively associated with hip flexor, hip extensor, and quadriceps muscle strength, as well as cognitive function [18; 19].

We analyzed markers of bone resorption. It is known that bCTx is a product of the breakdown of mature type I collagen by osteoclasts, making it a key marker of bone resorption.

The level of bCTx was significantly reduced ($p<0.05$) in group 1 (0.291±0.084) ng/ml vs (0.537±0.09) ng/ml in group 2. There was a negative correlation between bCTx and HbA1c ($r=-0.257$, $p<0.05$) and bCTx and duration of T2DM ($r=-0.213$, $p<0.05$), a positive correlation between bCTx and 25-(OH)D ($r=0.204$, $p<0.05$). This indicates a decrease in bone metabolism. There are studies in which the duration of T2DM is associated with an increase in bone resorption, as evidenced by higher levels of bCTx and a corresponding decrease in BMD [3,15].

TRAP5b levels did not differ statistically between groups ($p>0.05$). No significant correlations were found between TRAP5b, 25-(OH)D, HbA1c levels. J. Yang's meta-analysis showed that TRAP5b levels did not have a statistically significant difference in levels between the T2DM group and the control group [20].

Serum PTH levels were within the reference values, in group 1 they were higher than in group 2, but not statistically significant ($p=0.20$) (55.22±5.91) pg/ml vs (47.22±5.17) pg/ml. PTH levels did not correlate with the duration of T2DM ($r=-0.043$, $p=0.35$) and HbA1c ($r=-0.143$, $p=0.12$). PTH levels showed a significant negative correlation with 25-(OH)D ($r=-0.391$, $p<0.05$).

The literature on this issue is contradictory. There are studies that have shown that postmenopausal women with T2DM have lower PTH levels compared to nondiabetic controls [21], and some have shown significantly higher PTH levels compared to controls [22], especially in patients under 50 years of age [23]. It is believed that 25-(OH)D deficiency is common among postmenopausal women with T2DM and is associated with increased PTH levels as a compensatory response to maintain calcium homeostasis [21].

The mean HbA1 level was significantly higher ($p<0.05$) in group 1 (8.2±0.6)% than in group 2 (4.8±0.3)%. The level of HbA1c in patients with T2DM was negatively related to the markers of bone formation 25-(OH)D ($r=-0.221$, $p<0.05$) and OC ($r=-0.281$, $p<0.05$), which indicates a violation of bone formation at high blood glucose levels.

HbA1c level has a negative correlation with bCTx ($r=-0.257$, $p<0.05$), no correlation with TRAP5b ($r=0.10$, $p<0.05$) and PTH, which indicates a decrease in bone metabolism activity at high blood glucose levels.

The role of PTH in the assessment of bone metabolism in postmenopausal women with T2DM requires more research [24], and some studies have shown that elevated PTH levels are associated with a higher risk of developing T2DM.

Conclusions

1. Postmenopausal women with T2DM with hyperglycaemia and normal BMD, according to DEXA, have a higher risk of falling, a 58.34% decrease in handgrip strength, while maintaining muscle mass (ALM (12.34±2.20) kg) and an increased body mass index (31.5±2.3 kg/m²) compared to those without T2DM.

2. Postmenopausal women with T2DM with hyperglycemia and normal BMD, according to DEXA, compared to those without T2DM, have a decrease in bone metabolism, which is manifested by reduced bone formation, such as ionised calcium (1.15±0.14) mmol/l, 25-hydroxyvitamin D (18.4±1.4) ng/ml, osteocalcin (2.5±0.54) ng/ml and reduced resorption indices such as beta-CrossLaps (0.291±0.084) ng/ml and increased parathyroid hormone levels (55.22±5.91) pg/ml.

3. For early diagnosis of bone metabolism disorders in postmenopausal women with T2DM with hyperglycaemia and normal BMD, DEXA data should be used to determine the level of 25-hydroxyvitamin D, ionised calcium, osteocalcin and parathyroid hormone, especially in patients with insufficient glycaemic control.

4. Normalisation of ionised calcium, 25-hydroxyvitamin D and glycaemic levels may improve bone metabolism in postmenopausal women with T2DM with hyperglycaemia and normal BMD, according to DEXA.

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