BIOCHEMICAL BASIS OF OSTEOPOROSIS IN WOMEN

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Annotatsiya: Osteoporoz – bu suyak tizimining uzoq davom etadigan metabolik kasalligi bo‘lib, aholi orasida, ayniqsa, yoshi katta guruhlar orasida keng tarqalgan. Suyak to‘qimasida doimiy ravishda suyak hosil bo‘lishi va suyak yemirilishi jarayonlari kechadi; ular vaqt va joy jihatidan o‘zaro chambarchas bog‘liq bo‘lib, “suyak remodellanishi birligi” tushunchasini tashkil etadi. Suyak massasining kamayishi esa rezorbsiyaning (suyak yemirilishi) va suyak hosil bo‘lish jarayonining nomutanosibligi natijasida yuzaga keladi.

Kalit so‘zlar: D vitamini, postmenopauza, menopauza, somatik kasalliklar, kollagen, suyak remodellanishi, suyak plastinkalari, osteogenez markerlari, osteoporoz, osteotsitlar

Аннотация: Остеопороз – это длительно протекающее метаболическое заболевание костной системы, которое широко распространено среди населения, особенно в старших возрастных группах. В костной ткани постоянно происходят процессы костеобразования и костной резорбции; они тесно взаимосвязаны по времени и месту, формируя понятие «единица ремоделирования кости». Уменьшение костной массы является результатом дисбаланса между процессами резорбции (разрушения кости) и формирования костной ткани.

Ключевые слова: витамин D, постменопауза, менопауза, соматические заболевания, коллаген, костное ремоделирование, костные пластинки, маркеры остеогенеза, остеопороз, остеоциты.

Annotation: Osteoporosis is a long-lasting metabolic disease of the skeletal system and is widespread among the population, especially in older age groups. Bone tissue continuously undergoes processes of bone formation and bone resorption; these processes are closely interconnected in time and location, forming the concept of the “bone remodeling unit.” The decrease in bone mass is the result of an imbalance between bone resorption (bone degradation) and the process of bone formation.

Keywords: vitamin D, postmenopause, menopause, somatic diseases, collagen, bone remodeling, bone lamellae, osteogenesis markers, osteoporosis, osteocytes.

Introduction.

Our goal was to look into the connection between serum vitamin D levels and menopausal symptoms. We used the Menopause Rating Scale (MRS)

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questionnaire to assess menopause symptoms in 90 postmenopausal women between the ages of 45 and 60. Based on their serum 25-OH vitamin D levels, patients were split into three groups: sufficient (>20 ng/mL), insufficient (12-20 ng/mL), and deficient (<12 ng/mL). These groups were then compared. The cut-off level of serum vitamin D for menopausal symptoms was established. The connections between vitamin D levels and symptoms were computed. Of the individuals, 42.2% (38/90) had vitamin D insufficiency. The vitamin D insufficiency group had a considerably higher total MRS score than the others (p<0,002), at 20,87±2,61. Somatic, psychological, and urogenital subscale scores were greater in the deficient group than in the other groups (p<0,002, p=0,006, and p=0.035, respectively). The current investigation showed a connection between menopause-related symptoms in the postmenopausal population and serum vitamin D levels. Menopausal symptoms may worsen if vitamin D levels are low during this time.

Aim**.** To look into the connection between serum vitamin D levels and menopausal symptoms. To develop preventive measures for osteoporosis in menopausal women considering their Vitamin D levels and to study their health and quality of life.

LITERATURE REVIEW. This disease is characterized by a progressive decrease in bone mass per unit volume compared to normal values for individuals of the same sex and age, as well as by disruption of the microarchitecture of bone tissue, leading to increased bone fragility and a higher risk of fractures resulting from minimal trauma or even without it [1]. Bone tissue is constantly undergoing processes of bone formation and bone resorption, which are closely interconnected in both time and location, forming what is known as the bone remodeling unit. The reduction in bone mass is the result of an imbalance between the processes of bone resorption and bone formation, which under normal conditions should be well balanced.

Vitamin D and its active metabolites are components of the hormonal system that regulates phosphorus–calcium metabolism. On one hand, they participate in the mineralization of bone tissue, and on the other hand, in maintaining calcium homeostasis. The biological effect of active vitamin D metabolites consists primarily in stimulating intestinal absorption of calcium and phosphorus, activating metabolism, and increasing calcium excretion in urine.

Glucocorticoids. Osteoblasts contain cytoplasmic glucocorticoid receptors that mediate the direct action of glucocorticoids on bone.

Thyroxine exerts a direct effect on cartilage formation through its interaction with IGF-1.

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Estrogens play an important role in skeletal formation and the prevention of bone mass loss. They prevent bone resorption by suppressing osteoclast activity.

Androgens play a significant role in bone metabolism in both women and men. The mechanism of androgen action on bone tissue is not fully understood. However, it is known that their effects on other target tissues are mediated by growth factors.

Growth hormone (somatotropin). The action of GH is associated with the production of local factors in bone tissue, such as IGF-1, transforming growth factor, bone morphogenetic proteins, and others. GH has a stimulatory effect on the proliferation of chondrocytes within the growth plate.

Treatment with calcifediol (20 mg/day = 0.800 IU/day of vitamin D3) improved walking speed more than treatment with cholecalciferol (20 mg/day) in healthy postmenopausal women with low serum 25(OH)D levels [9]. The cessation of menstruation for a year in women with no apparent underlying causes is known as natural menopause. In the menopausal phase, low estrogen and high follicle stimulating hormone (FSH) concentrations are detected due to the decline or absence of ovarian follicles [10]. Numerous medical and psychological issues, including vasomotor symptoms, genito-urinary symptoms, mood swings, and sleep disturbances, might be brought on by this hormonal instability during the menopausal phase [11]. A fat-soluble vitamin, vitamin D has crucial roles in the musculoskeletal system and calcium metabolism. Vitamin D may control a wide range of other cellular processes in addition to its function in maintaining calcium and bone homeostasis. Accordingly, a lack of vitamin D can lead to a number of autoimmune, cardiovascular, and infectious illnesses [12]. Additionally, it was demonstrated that vitamin D protects women from cardiovascular risks [13]. Furthermore, a number of studies points to a possible link between vitamin D insufficiency and genitourinary symptoms, heat flashes, and irritability

In their randomized control experiment, researchers found that severe vitamin D deficiency was associated with anxiety, depression, and reduced functioning in both men and women (9). One year without menstruation is known as menopause, which occurs between the ages of 45 and 60 and is characterized as the end of the menstrual cycle due to decreased secretions of estrogen and progesterone [14]. Estrogen upregulates the VDR and enhances the activity of 1-α-hydroxylase, which is expressed in the kidneys and is responsible for activating vitamin D. The amount of estrogen generated by the ovaries gradually decreases during the menopausal periods [15], which contributes to vitamin D insufficiency. A reduction in the amount of VDR is linked to the ensuing vitamin D deficiency.

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In addition to preserving calcium homeostasis, vitamin D is crucial for a number of non-calcemic illnesses, including cancer, autoimmune disorders, neurological disorders, and infections. Because postmenopausal women lose estrogen, they are more likely to suffer from a number of chronic illnesses. Because of changes in blood lipids and body composition (increased belly fat), a decrease in estrogen raises the risk of both breast cancer and cardiovascular disease (CVD). The body requires calcium, a necessary mineral, to form healthy bones and teeth and to participate in other biochemical processes. Osteoporosis is a severe health issue that results from its loss during menopause.After the ovaries stop producing estrogen, menopausal osteoporosis develops.

MATERIAL AND METHODS. 90 postmenopausal women who applied for a standard gynecological checkup at a tertiary center gynecology clinic participated in this cross-sectional study. Each patient's signed informed consent and local ethical approval were obtained before demographics, medical histories, physical and gynecological examination results, including body mass index (BMI), and the participants' time since menopause were documented. Not experiencing menstrual bleeding for more than a year was considered menopause. Measurements were made of the patients' serum levels of 25-OH vitamin D, calcium (Ca), estradiol (E2), and follicule stimulating hormone (FSH). The Meopause Rating Scale (MRS), a questionnaire designed for Uzbek-speaking individuals, was used to assess menopausal symptoms in all patients (10).

A score of 0–4 is assigned to each of the 11 items in the MRS, which indicate how severe the symptom is (0, nonexistent; 1, mild; 2, moderate; 3, severe; 4, very severe) (Table 1). Three domains make up this questionnaire: the psychological subscale, which includes depressed mood, irritability, anxiety, and physical and mental exhaustion (items 4–7); the urogenital subscale, which includes sexual problems, bladder problems, and vaginal dryness (items 8–10); and the somatic subscale, which includes hot flashes, heart discomfort, sleep issues, and muscle and joint discomfort (items 1-3,11). The sum of the scores on each subscale is the overall MRS score. Severe scores were characterized as somatic scores greater than 8, psychological scores greater than 6, urogenital scores greater than 3, and total MRS scores greater than 16.

Table 1.

Menopause Rating Scale (MRS)

№	Symptoms	Score					
		0	1	2	3	4	Total score

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1.	Hot flashes, sweating						
2.	Heart discomfort						
3.	Sleep problems						
4.	Depressive mood						
5.	Irritability						
6.	Anxiety						
7.	Physical and mental exhaustion						
8.	Sexual problems						
9.	Bladder problems						
10.	Dryness of vagina						
11.	Joint and muscular discomfort						

Results and discussions. The patients' ages ranged from 45 to 60 years old, with a mean age of 53.8 years. The patients' mean time since menopause was 6.1 years, with a range of 1 to 20 years. Of the individuals, 42.2% (38/90) had vitamin D insufficiency. 25-OH serum Thirty women had adequate levels of vitamin D (≥20 ng/mL). The remaining 38 patients had inadequate vitamin D levels, ranging from 12 to 19 ng/mL. Age, BMI, duration since menopause, and laboratory characteristics did not differ across groups (Table 2). The vitamin D insufficiency group's total MRS score was 22,97±2,71, which was substantially greater than the others' (p=0,002) (Table 2). Additionally, the deficient group's urogenital, psychological, and physical subscale scores were higher (Table 2; p=0,012, p=0,007, and p=0,036, respectively) than the other groups. In line with posthoc analysis, the deficient group's psychological ratings (8,02±2,87 and 9,42±5,15) differed significantly from the other groups. Similar to the insufficiency group (n=38), the deficiency group's urogenital subcale and total scores were considerably greater than those of the sufficiency group (Table 2). Patients' assessments for anxiety, emotional and physical exhaustion, sexual difficulties, and

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vaginal dryness were comparable between groups. In addition, the remaining MRS questionnaire values showed significant differences across groups (Table 3). The remaining 38 patients had inadequate vitamin D levels, ranging from 12 to 19 ng/mL. Age, BMI, duration since menopause, and laboratory characteristics did not differ across groups (Table 2). The vitamin D insufficiency group's total MRS score was 22,97±2,71, which was substantially greater than the others' (p=0,002) (Table 2).

Table 2.

Demographic, laboratory characteristics and rating scores of the subjects among groups. 25-OH vitamin D Levels

Vitamin D levels And number of women	≥20 ng/mL n=26	12-19 ng/mL n=30	<12 ng/mL n=34	P
Age (y)	51,20±4,68	52,50±4,33	51,71±3,87	NS
BMI (kg/m2)	30,45±4,60	31,04±4,37	30,34±4,77	NS
Time since menopause (y)	5,40±4,03	6,48±5,68	6,38±4,09	NS
Serum FSH (mIU/mL)	65,10±22,78	64,29±21,82	63,08±20,64	NS
Serum E2 (pg/mL)	17,41±14,89	19,09±11,18	16,56±10,90	NS
Serum Ca (mg/dL)	10,76±0,35	9,63±0,42	9,66±0,40	NS
Somatic subscale score	4,00±2,42	6,39±2,94	8,02±2,87	<0,002
Psychological subscale score	6,46±3,10	7,16±3,73	9,42±5,15*	0,007
Urogenital subscale score	3,90±2,02	5,23±3,09	5,52±2,71**	0,036

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Total MRS score	13,73±5,93	17,71±7,55	21,97±2,71**	<0,002

y: years, BMI: body mass index, kg: kilogram, m:meter, FSH: Follicule stimulating hormone, E2: estradiol, Ca: calcium, MRS: Menopause reting scale, NS: non-significant.

*Statistical difference arises from group 1 and 2.

** Statistical difference arises from group 1.

p <0.051 was considered significant.

Table 3.

Results of Menopause Rating Scale parameters among serum 25-OH Vitamin D levels.

Parameters	25-OH Vitamin D levels			p
	≥20 ng/Ml n=26	12-19 ng/mL n=30	<12 ng/mL n=34	
Hot flushes	1,31±1,01	1,73±0,99	2,30±1,02	<0,001
Heart discomfort	0,39±0,56	1,00±0,95	1,50±1,01	<0,001
Sleep problems	1,190±1,09	1,34±1,23	1,83±1,11	0,043
Depressive mood	1,49±1,04	1,56±1,13	2,30±1,07	0,003
Irritability	1,53±1,07	1,76±1,19	2,38±1,16	0,006
Anxiety	1,35±1,03	1,81±1,14	2,79±4,78	NS
Physical and mental exhaustion	2,03±1,21	1,77±1,26	1,91±1,07	NS
Sexual problems	1,56±0,93	1,97±1,28	1,73±1,28	NS
Joint and muscular discomfort	1,20±1,09	1,58±1,28	2,09±1,22	0,041
Bladder problems	1,10±1,11	1,59±1,28	2,09±1,22	NS

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Dryness of vagina	1,30±1,04	1,56±1,32	1,71±1,17	0,041

Additionally, the somatic, psychological, and urogenital subscale ratings in the deficient group were greater than those in the other groups (p=0,012, p=0,007, and p=0,036, respectively) (Table 2). Posthoc analysis revealed that the deficient group's psychological scores (8,02±2,87 and 9,42±5,15) differed significantly from the other groups. Similar to the insufficiency group (n=30), the deficiency group's urogenital subcale and total scores were considerably greater than those of the sufficiency group (Table 2). Patients' assessments for anxiety, emotional and physical exhaustion, sexual difficulties, and vaginal dryness were comparable between groups. In addition, the remaining MRS questionnaire values showed significant differences across groups (Table 2).

Menopausal symptoms were chosen for their study, and participants were asked to rate the severity of each symptom. The total number of symptoms, regardless of severity, was used to calculate the total score. Therefore, in contrast to ours, the study did not use any validated questionnaires. In addition, the mean period after menopause in the aforementioned study was roughly 10 years longer than ours, and their individuals were older (60 years). The significant percentage of women who experienced menopause for more than ten years may be the reason they did not report any correlation between vitamin D levels and menopausal symptoms. Vitamin D must be converted by enzymes into active metabolites because it is physiologically inert when consumed through food or produced by the skin. It has been demonstrated that estrogen contributes to the rise in the vitamin D activating enzyme [17].

Thus, it is possible that the decline in estrogen levels during the postmenopausal phase could exacerbate neuropsychiatric problems and other subclinical vitamin D insufficiency symptoms. Data assessing vitamin D's neuroprotective function are scarce. Menopause may lead to memory impairment, according to an experimental investigation examining the impact of menopause on behavioral status. Cholecalciferol was found to have anxiolytic effects in rats with ovariectomies in addition to its effects on the hippocampus [18]. It is evident from these results that the psychological conclusion of our study is supported.

In the deficient group, the subjects' scores for irritation and depressed mood were significantly greater. Additionally, although it was not statistically significant, this group's anxiety level was higher. There was already a noticeable difference in the deficient group when looking at the overall psychiatric score. Similarly, it was noted that depression scores were high in the postmenopausal era and 25-OH vitamin D levels were low in a report discussing vitamin D and menopausal symptoms with a large patient group [19]. Despite considerable differences

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between patient groups, all groups had a severe psychological score (more than six). The high BMIs of our patients may be the cause of this score's harshness.

The elevated urogenital subscale ratings in the deficit and insufficiency groups were another finding in our investigation. The bladder issues area of this subscale in particular had a noticeably high score. According to the literature, there may be a correlation between low vitamin D levels and symptoms of the urinary tract. because low vitamin D levels may have an impact on the strength of the pelvic floor muscles. A study that included patients from both premenopausal and postmenopausal periods found that postmenopausal women with vitamin D levels below 20 ng/mL had reduced pelvic floor muscular strength. According to the same study, women with vitamin D insufficiency had greater urinary incontinence scores, although no statistically significant difference was seen. Our findings on vitamin D levels and symptoms related to the urinary system were statistically significant, in contrast to that study. Menopausal women may find somatic symptoms like hot flashes difficult to manage. The majority of women complain of these symptoms regardless of their vitamin D levels [20]. Vitamin D levels and somatic scores were found to be negatively correlated in our study. In rats, vitamin D has been shown to stop seratonin depletion. A decrease in seratonin levels may result in hot flashes because it is a neurotransmitter that plays a part in thermoregulation. In this sense, elevated vitamin D levels might provide protection against hot flashes and other menopausal physical symptoms. Furthermore, a recent study noted that women with normal vitamin D levels are less likely than those with vitamin D insufficiency to experience menopausal symptoms. The purpose of this study was to determine whether specific menopausal symptoms were brought on by vitamin D insufficiency. To do this, we employed the validated MRS questionnaire and excluded individuals with any other comorbidities in an effort to reduce outside factors that might have an impact on scale rates. In terms of demographics and hormones, our patient groups were comparable. In addition, we provided a cutoff 25-OH vitamin D level for women with adequate vitamin D levels who experience menopause-related symptoms. Our patients' period since menopause was brief, in contrast to the literature. Notwithstanding these advantages, the study had drawbacks. There was only one geographic area within our patient population. We were unable to assess the patients' parathormone levels or determine if supplementation would be effective in treating menopausal symptoms linked to vitamin D deficiency.

CONCLUSIONS AND RECOMMENDATIONS. Insufficient vitamin D levels during the menopausal phase may make menopausal symptoms worse. One may argue that menopausal Vitamin D supplementation may be beneficial for

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women whose symptoms are severe. It will need more prospective research to fully illuminate this intricate and multifaceted relationship.

In women with natural menopause and those of perimenopausal age, when laboratory test results indicate low levels, it is recommended to prescribe vitamin D preparations (500 IU of vitamin D and 500 mg of Klimadinon) for the prevention of osteoporosis. Klimadinon should be taken at a dose of 30 drops in the morning and evening for 12 months. In addition, healthy and balanced nutrition as well as regular physical activity are recommended.

To assess the dynamics of the effectiveness of preventive therapy, it is advisable to repeat laboratory testing of biochemical markers of bone turnover after 3 or 6 months, and to perform a follow-up densitometry examination after one year.

For evaluating risk factors of osteoporosis development in peri- and postmenopausal women, it is advisable to use a predictive screening model. This model helps identify a group of women with a high risk of developing osteoporosis and ensures their early preventive monitoring.

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