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ORIGINAL ARTICLE

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GENDER AND AGE ASPECTS IN THE PATHOGENESIS OF BONE MINERAL DENSITY DISORDERS

Nataliia I. Chekalina, Viktoriia M. Plaksa, Yurii M. Kazakov, Tetiana A. Tribrat, Svitlana V. Shut, Yevhen Ye. Petrov, Tetiana A. Ivanytska

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ABSTRACT

The aim: To assess the structural and functional state of bone tissue in terms of gender and age.

Materials and Methods: 108 people aged 54.7±14.8 years, who were divided into two groups according to gender, participated in the retrospective cohort study. All patients underwent ultrasound densitometry to assess bone mineral density (BMD) on the radial bone with an assessment of T-score, Z-score, and speed of ultrasonic wave propagation (SoS).

Results: The study found that T-score and Z-score values, which corresponded to osteoporosis, were recorded in the age group > 50 years, regardless of the gender of the subjects. All women older than 35 years had a decrease in BMD below -1.0 SD by T-score. It was determined that osteoporosis criteria clearly prevail in women of the > 50-year-old group. In osteoporosis, the SoS is significantly lower than in individuals with normal indicators of the T-criterion. According to the results of the T-score comparison, BMD disorders were determined in postmenopausal women which emphasize the importance of the level of female sex hormones in the formation of osteopenic syndrome, in contrast to men, in whom no changes in the state of bone tissue were recorded.

Conclusions: The results of the research prove the prevalence of osteopenic syndrome in terms of age and gender, with an emphasis on women aged 50 years and older. Screening for BMD disorders using ultrasound densitometry is appropriate and allows taking measures to prevent the progression of osteoporosis in the early stages.

KEY WORDS: osteoporosis, osteopenia, bone mineral density, ultrasound densitometry, gender and age aspects, postmenopause

INTRODUCTION

Osteoporosis is a systemic progressive disease of the musculoskeletal system, caused by the loss of bone mass with the disrupted microarchitectonics of bone tissue, which leads to an increase in bone fragility and the risk of fractures [1]. This disease is observed in all age groups, regardless of gender and race, but the highest prevalence is observed in Caucasians (white race), postmenopausal women, and the elderly. With an aging population and a decrease in life expectancy, osteoporosis is increasingly becoming a global epidemic [2, 3]. Currently, it is estimated that more than 200 million people suffer from osteoporosis [3, 4]. According to the latest statistics from the International Osteoporosis Foundation, 1 in 3 women over 50 years of age and 1 in 5 men worldwide experience osteoporotic fractures during their lifetime [5]. Osteoporosis is a significant risk factor for fractures in the same way that hypertension is a risk factor for stroke [4]. According to estimates, it has been established that 40% of women suffer from osteoporosis, of which 30% are postmenopausal women. 30% of men experience osteoporotic fractures during their lifetime [6]. According to the International Osteoporosis Foundation (IOF), the number of postmenopausal women in Ukraine with osteoporosis and osteopenia is 7 million (28% of the total number of women) [7]. Today, about 2.5 million women and 900.000 men suffer from osteoporosis in Ukraine, 50% of osteoporosis patients become disabled as a result of the disease, and 20% die. According to the prognosis, by 2050, the number of hip fracture cases among men will increase by 310%, and among women – by 240%, compared to the indicators as of 1990 [8].

An imbalance between the formation of bone tissue and the speed of its resorption, where the latter prevails, underlies the development of osteoporosis. Modeling of bone tissue occurs from birth to adulthood, it reaches its peak during puberty, and is called peak bone mass (PBM). PBM is determined by genetic factors, the balance of sex hormones, the state of health during the development of bone tissue, concomitant pathology, and taking medications (in particular, glucocorticoids, cytostatics, and anticonvulsants) [9].

Glucocorticoids are used to treat a wide range of diseases, and an estimated 1-2% of the population receives long-term glucocorticosteroid therapy [8, 10]. Glucocorticoids affect bone resorption by increasing the production of macrophage colony-stimulating factor (M-CSF) and RANKL, which leads to a decrease in the production of osteoprotegerin (OPG) by osteoblastic cells and osteocytes, and, as a result, an increase in both the number and activity of osteoclasts [11-14].

The indisputable cause of the formation of osteoporosis is considered to be a deficiency of estrogens – the main hormonal regulators of bone resorption. They have an

osteoprotective effect on bone tissue, acting through specific receptors or local mediators, starting a cascade of growth and differentiation of bone tissue cells.

Densitometry is considered the gold standard in the diagnosis of osteoporosis. Densitometry is an equipment-based non-invasive method of determining bone mineral density (BMD), whose main task is to detect osteoporosis in the early stages of development. There are several types of densitometry: quantitative ultrasonic densitometry (QDM), dual-energy X-ray absorptiometry (DRA or DXA) and quantitative computer tomography [15].

Along with ultrasonic (US) densitometry, the FRAX scale is used. FRAX is a computer algorithm created in 2008 by the World Health Organization (WHO) Collaborating Center in Sheffield. The FRAX instrument consists of seven dichotomous clinical risk factors that include previous fractures, parental hip fractures, smoking, systemic glucocorticoid use, excessive alcohol consumption, rheumatoid arthritis, and other causes of secondary osteoporosis. In addition to age, gender, and body mass index (BMI), these risk factors contribute to the estimation of the 10-year probability of fracture, regardless of bone mineral density (BMD) [16, 17].

The WHO criteria for osteoporosis are based on BMD values compared to a control population of healthy young people. According to this, two main criteria are distinguished: T-score and Z-score. The diagnosis of osteoporosis is made if BMD values are below the average peak bone mass by no more than 2.5 SD (standard deviation) (T ≤ -2.5). Osteopenia (low bone mass) is verified if BMD values are more than 1 SD below the mean peak bone mass, but not more than 2.5 SD (-2.5 T ≤ -1). Depending on the T-score distribution, 3 degrees of osteopenia are distinguished: I degree (T ≤ -1.0 – > -1.5), II degree (T ≤ -1.5 – > -2.0); III degree (T ≤ – 2.0 – > -2.5). Normal values of BMD correspond to a range of more than 1 SD from the average value of peak bone mass of a young adult (T> -1) [18].

Using the method of ultrasound densitometry with a screening purpose in combination with the FRAX scale, whose functioning consists in calculating the individual 10-year probability of damage to the hip joint and large osteoporotic fractures, makes it possible to establish the state of bone tissue in the early stages of the formation of the disease, depending on gender, and predict and prevent progression of complications [19].

THE AIM

The aim of the research is the assessment of the structural and functional state of bone tissue in terms of gender and age.

MATERIALS AND METHODS

This study is a part of the initiative research project of the Department of Propaedeutics of Internal Medicine "Peculiarities of the course of cardiovascular pathology in patients of different age categories depending on the presence of components of the metabolic syndrome and comorbid conditions, the ways of correcting the detected disorders and prevention", state registration No. 0119U1028.

We conducted a retrospective cohort study. The object of the research is bone mineral density according to ultrasound densitometry data. Inclusion criteria: women (of reproductive and postmenopausal age) and men. Exclusion criteria: diabetes, rheumatic diseases, oncological diseases, including in the anamnesis, diseases of the endocrine glands, heart defects, chronic kidney and liver failure, and diseases of the blood system.

A total of 108 people aged 54.7±14.8 years, who were divided into two groups according to gender, took part in the study. The study group, which consisted of women, in turn, was divided into a subgroup of postmenopausal age – IA (74% of women) and reproductive age IB (26% of women). Group II (men) made up 8% of all studied subjects (Fig. 2). The average age of women of reproductive age (subgroup IB) was 36.2±7.0; postmenopausal women (subgroup IA) – 62.2±8.5; men – 48.5±22.7. As to the age, the distribution was carried out according to the criterion:

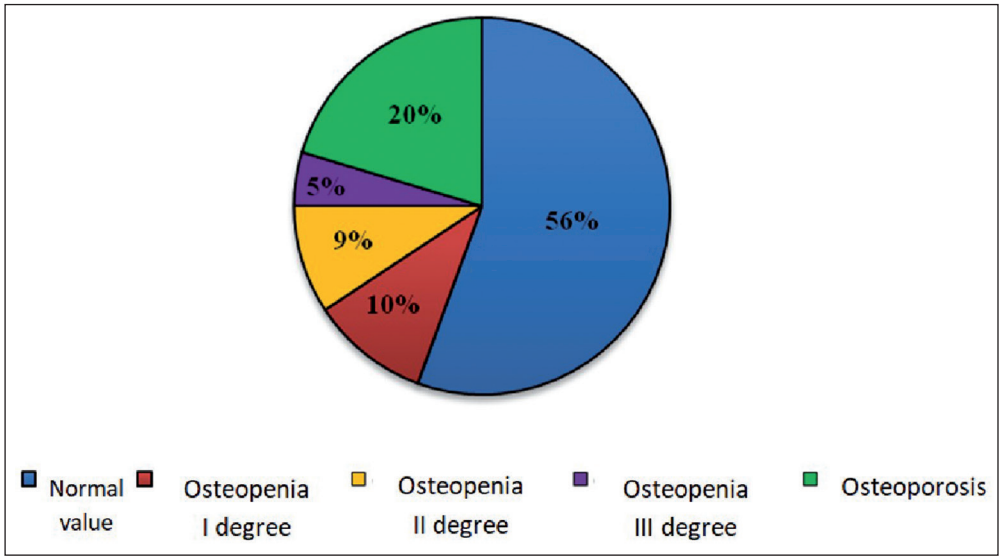


Fig. 1. Percentage distribution of patients according to the frequency of detection of abnormalities in bone mineral density (BMD).

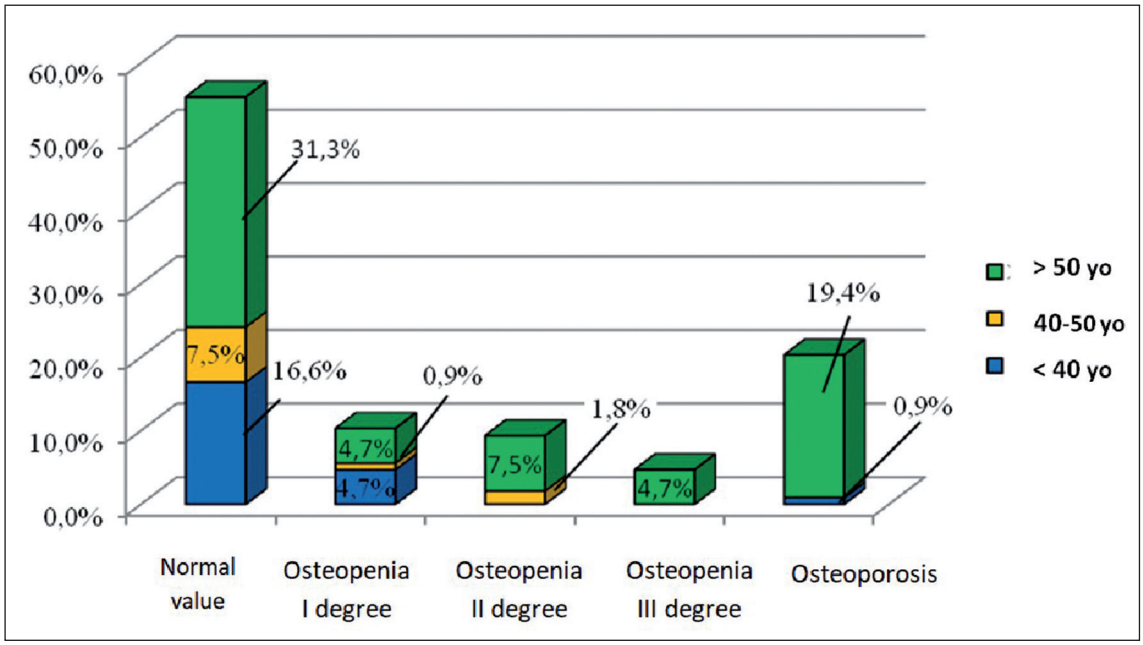


Fig. 2. Distribution by indicators of the mineral density of bone tissue in the age aspect.

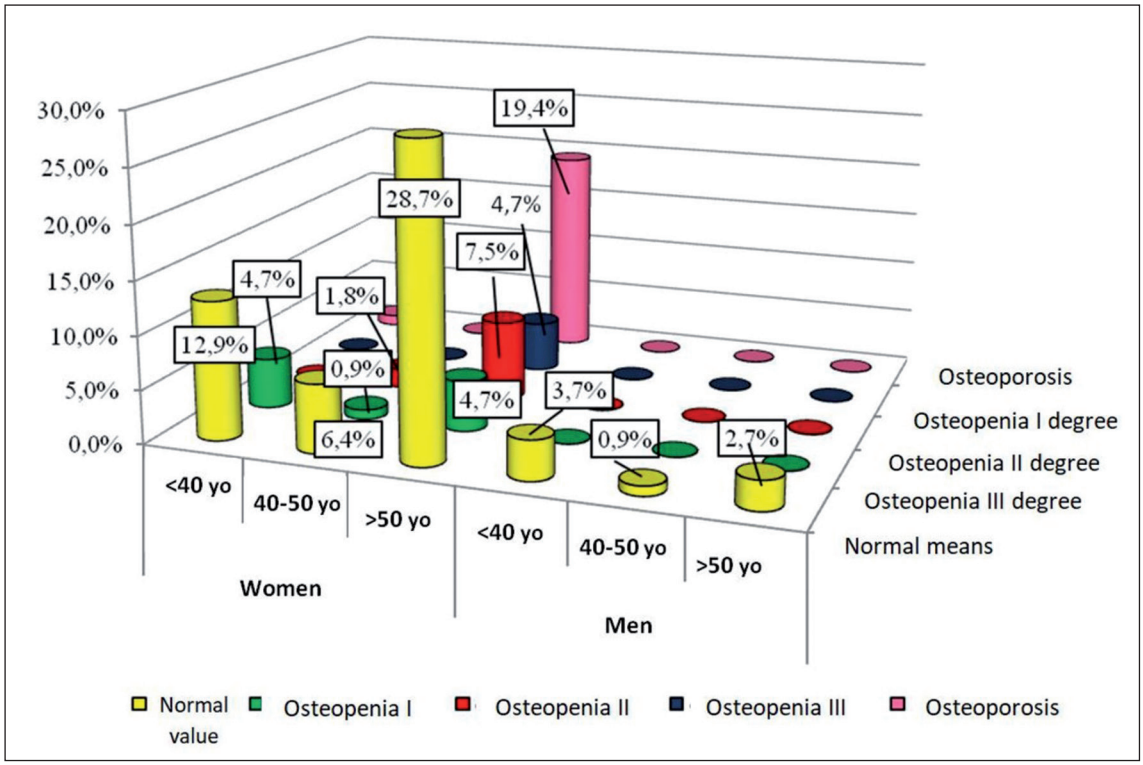


Fig. 3. Features of the distribution of BMD indicators according to age and gender.

< 40 years – 22.2% of the studied persons, 40-50 years – 11% of persons, > 50 years – 67.6% of persons.

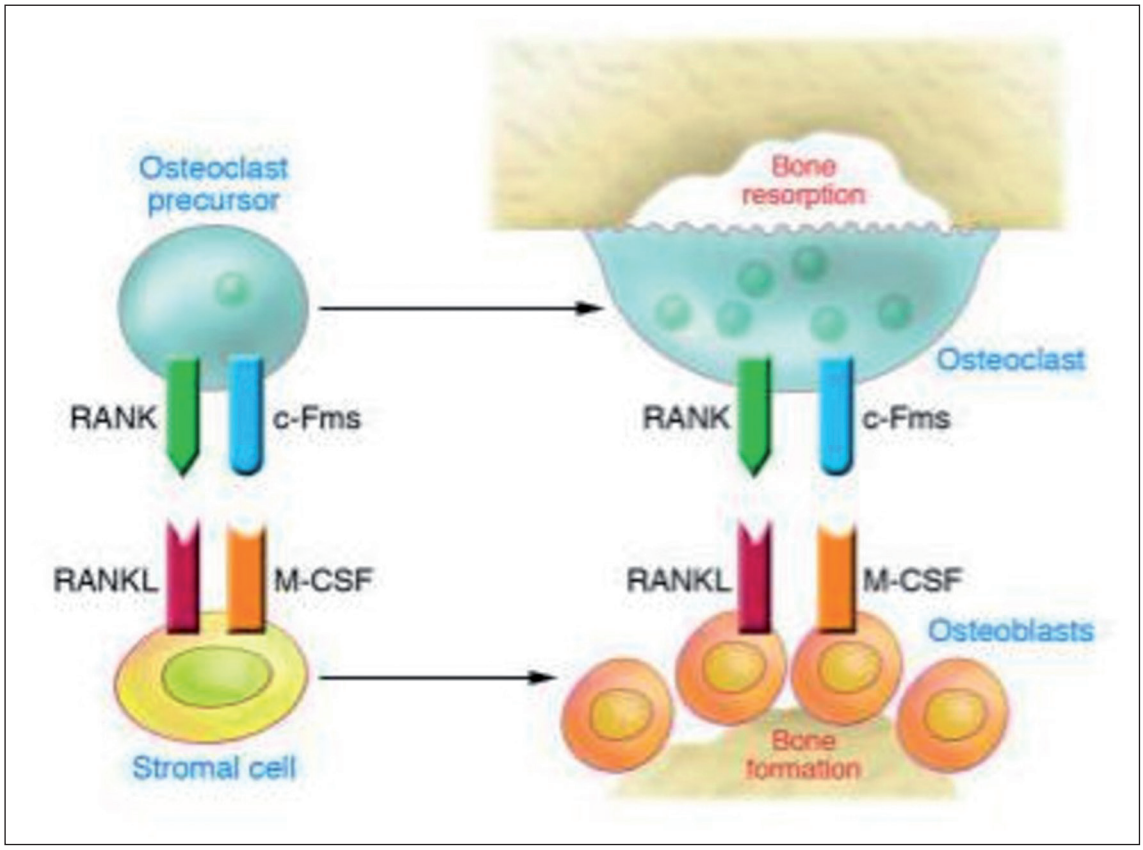
All patients underwent ultrasound densitometry to assess the structural and functional state of bone tissue. Determination of BMD was performed using an ultrasonic bone densitometer Sunlight MiniOmni on the radial bone.

T-score (T-criterion) was determined by comparing the obtained results of bone tissue density with the normal average "peak" bone mass for an adult.

Z-score (Z-criterion) was obtained by comparing the density of bone tissue with the average indicator of the norm in a given age group.

In addition, the speed of ultrasonic wave propagation (SoS) in m/sec was determined. In compliance with the T-criterion of BMD, according to WHO indicators, the character of the bone tissue structure disruption was determined.

Before conducting the study, all patients signed an informed voluntary consent to participate in this study. The research



Notes: RANK – nuclear factor κB receptor activator; C-fms – a specific receptor for M-CSF.

Fig. 4. The role of nuclear factor κB, RANKL and macrophage colony-stimulating factor (M-CSF) in the differentiation and regulation of osteoblastic activity under physiological conditions (adapted from M.N. Weitzmann, 2006 [26]).

Table 1. Indicators of the ultrasound wave propagation speed

Distribution according to the T-score/(M±σ)	Study group IA	Study group IB	Study group II
Normal value	4181.3±119.7	4128.6±16.7	4124.1±67.2
Osteopenia I degree	4036.1±23.7	4067.4±116.5	–
Osteopenia II degree	3980.2±33.2	–	–
Osteopenia III degree	3916.3±64.6	–	–
Osteoporosis	3832.5±109.9*	–	–

Notes: M – the sample mean, σ – standard quadratic deviation.
** – p <0.05 comparing study group IA with osteoporosis and groups IB and II with normal indices.*

Table 2. Indicators of bone mineral density of the radial bone according to ultrasound densitometry data

	Study group IA	Study group IB	Study group II
T-score (M±σ)	-1.55±0.29	-0.48±0.14*	0.30±0.17*
Z-score (M±σ)	-0.38±0.26	-0.21±0.13	0.56±0.15

Notes: M – the sample mean, σ – standard quadratic deviation.
** – p <0.05 significant differences in BMD in comparison with group IA.*

was conducted in accordance with the requirements of the Helsinki Declaration of 1975 and the Order of the Ministry of Healthcare of Ukraine No. 690 of 23.09.2009 "On approval of the Procedure for conducting clinical trials of medicinal products and examination of clinical trial materials".

Statistical processing of the results was carried out using KyPlot 6.0 and Microsoft Excel software. The hypothesis about the normality of the distribution was tested using the Shapiro-Wilk test. The belonging of the samples to the same population was determined using the Kruskel-

Table 3. The value of mineral density of the bone tissue of the radial bone according to the data of ultrasound densitometry by the T-criterion.

	Normal value (M±σ)	Osteopenia I degree (M±σ)	Osteopenia II degree (M±σ)	Osteopenia III degree (M±σ)	Osteoporosis (M±σ)
Study group IA	0.25±1.16	-1.12±0.13	-1.68±0.09	-2.18±0.13	-4.31±2.7
Study group IB	-0.08±0.43	-1.26±0.2	-1.7±0.14	–	–
Study group II	0.30±0.50	–	–	–	–

Notes: M – the sample mean, σ – standard quadratic deviation.

Table 4. The value of the mineral density of bone tissue of the radial bone according to the data of ultrasound densitometry by the Z-criterion.

	Normal value (M±σ)	Osteopenia I degree (M±σ)	Osteopenia II degree (M±σ)	Osteopenia III degree (M±σ)	Osteoporosis (M±σ)
Study group IA	0.8±1.06	-0.8±0.18	-0.17±0.53	-0.48±0.55	-2.36±3.13
Study group IB	0.15±0.42	-0.85±0.13	-1.7±0.14		-
Study group II	0.56±0.44	-	-	-	-

Notes: M – the sample mean, σ – standard quadratic deviation.

Wallis rank test. Data were presented as arithmetic mean and standard deviation (M+σ). Independent samples were compared using Student's t-test. Statistical significance was established under the condition that the level of statistical significance p was less than 0.05.

RESULTS

During the study, regardless of age and gender, part of the examinees (56%) had normal BMD indicators, osteopenia was registered in 24% of people: I degree – in 10%, II degree – 9%, III degree – in 5% of the examined subjects (Fig. 1). Osteoporosis was determined in 20% of the subjects.

In the group demarcated by the age criterion of < 40 years, the share of examinees who corresponded to normal T-score values was 16.6%, in the group of 40-50 years – 7.5%, in the group > 50 years – 31.3% (Fig. 1).

In addition, it was found that all women older than 35 years had a decrease in BMD below -1.0.

Values corresponding to osteoporosis were recorded in the age group > 50 years and accounted for 19.4% of the studied cohort, which is probably due to changes in the hormonal status of the subjects (Fig. 2).

Comparing the gender characteristics of the BMD of the examined subjects, we found that the criteria of osteoporosis according to the T-score clearly prevail in women of the group > 50 years old, which is shown in Figure 3.

Evaluating the speed of ultrasonic wave propagation (SoS) in m/sec, we found that in osteoporosis the value of this indicator is significantly lower than in individuals of all studied groups with normal indicators of the T-criterion ($p<0.05$) (Table 1)

According to the results of the T-score comparison, BMD disorders were observed in women of study groups IA and IB, which emphasizes the importance of the level of female sex hormones in the formation of osteopenic syndrome, unlike men (group II), in whom no changes in the state of bone tissue were recorded (Tables 2, 3, 4).

DISCUSSION

According to the data of the conducted research, the most vulnerable category in terms of BMD disorders are women in the perimenopausal, and especially, postmenopausal period. The decisive role of estrogens in relation to the state of bone tissue relies on ligand-dependent mechanisms that mediate an increase in the functional activity of osteoblasts and osteocytes, as well as in the inhibitory effect on osteoclastogenesis by activating osteoblast apoptosis [20]. Since osteoclasts are of monocyte-macrophage origin, they are specialized cells of the immune system in bone tissue and have phagocytic activity. Taking an active part in the immune response, they are capable of secreting pro-inflammatory cytokines (IL-1, IL-6, IL-17 and others), which increase the resorption of bone tissue [21].

The central role in the regulation and differentiation of osteoclasts belongs to such cytokines (CK) as the precursor of macrophage colony-stimulating factor (M-CSF) and the ligand-activator of the receptor of nuclear factor kappa B (NF-kB) – RANKL. M-CSF is an effective stimulator of RANK receptor expression and osteoclast proliferation, it also regulates apoptosis, increasing the viability of these cells [22, 23].

RANKL belongs to the family of tumor necrosis factor α (TNF-α), it is expressed by osteoblasts, stromal cells and activated immune cells. Its activation leads to the expression of the RANK receptor on osteoblasts and their progenitors. The effect of the formed RANKL-RANK complex on cell activity is carried out through signaling pathways involving NF-kB, the early response gene (c-Fos) and the transcriptional nuclear factor of activated T cells c1 (NFATc1) [24, 25].

In the RANKL-RANK-OPG system, osteoprotegerin (OPG) belongs to the CK of the TNF superfamily, it provides a protective role in bone tissue resorption and osteoclast activation, being a soluble "trap receptor" for RANKL [26] (Fig. 4).

It has been proven that estrogens can suppress the production of RANKL and M-CSF, as well as stimulate the synthesis of OPG, while under the conditions of hypoestrogenia caused by menopause, these mechanisms work in the opposite direction. Since the expression of RANKL is controlled by estrogens, the lack of formation of the corresponding hormones leads to an increase in the concentration of RANKL due to the activation of cells of the immune system, which is one of the mechanisms of postmenopausal osteoporosis and it occupies one of the leading links in the development of this pathology.

Women in the period of early hypoestrogenia lose about 5-15% of bone tissue, which affects the quality and length of life with the mediated formation of comorbid pathology. The relationship between hypoestrogenia, osteoporosis and cardiovascular events has been established [27, 28].

Hypoestrogenia is considered one of the predictors of cardiovascular risk with the formation of heart failure with the preserved systolic function of the left ventricle. Its typical clinical manifestation in postmenopausal women is diastolic dysfunction, which is caused by estrogen deficiency and the loss of its cardioprotective effect [29].

Under physiological conditions, estrogens and their receptors modulate the expression of circulating catecholamines, regulating inotropic and chronotropic effects, by signaling through β-adrenergic receptors (βAR). In conditions of hypoestrogenia, the above-mentioned factors are associated with the initiation and progression of heart failure with the preserved systolic function of the left ventricle [30, 31]. Thus, a lower incidence of the disease is observed in premenopausal women than in postmenopausal women and men in all age groups, which will be the subject of our further studies.

Unlike postmenopausal women, men retain cancellous bone integrity longer, although their bone trabeculae become thinner. During puberty, men develop larger bones than women due to periosteal appositional growth. On the other hand, in women, on the contrary, estrogens have an inhibitory effect on periosteal bone tissue formation, and a stimulating effect on endocortical bone tissue. Estrogens, by their properties, stimulate the early closure of the epiphyseal bone growth zones, which is why shorter bones are formed in women than in men. Since the amount of the formed periosteal surface of the bone tissue is greater in men than in women, endocortical resorption prevails in women [19, 26].

For women with pronounced osteopenia and osteoporosis, subject to confirmation by laboratory and other evidence-based methods, we plan to prescribe a program for the treatment of bone metabolism disorders, as well as pathogenetically related cardiometabolic complications, as the basis of preventive medicine [32, 33].

CONCLUSIONS

The results of the research prove the prevalence of osteopenic syndrome in terms of age and gender, with an emphasis on women aged 50 years and older. According to the obtained data, early detection of signs of bone mineral density disorders by screening with the help of ultrasound densitometry is appropriate and allows taking measures to prevent the progression of osteoporosis in the early stages, even before the appearance of clinical signs and its consequences. This will allow us to prevent the formation of complications, in particular, low-traumatic fractures, to develop pathogenetically based gender-oriented treatment methods to improve the quality and increase the length of life. The pathogenetic basis of postmenopausal osteoporosis is the basis for our further studies in the aspect of comorbidity.

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