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## **MATHEMATICAL MODELING AND THE ASSESSMENT OF THE STRUCTURAL AND FUNCTIONAL STATE OF BONE TISSUE IN WOMEN WITH ARTERIAL HYPERTENSION AND OBESITY**

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### **Abstract**

140 postmenopausal women aged 48 - 60 y. o. were examined. They had stage I - II arterial hypertension of the 1-2 degree and obesity of the I degree. All of them worked under the adverse labour conditions. The relationship between bone mineral density, osteoprotegrin level and additional factors that have an adverse effect on the state of bone tissue were studied. A correlation analysis of the relationship between T-criterion, the level of osteoprotegrin and the length of service, the duration of the postmenopausal period, the duration of arterial hypertension, the level of systolic blood pressure, markers of bone remodeling, the level of 25 (OH) D<sub>3</sub> and lipid metabolism was performed. Using the linear multiple regression model and taking into account the influence of several factors on the indicator modeled, mathematical models were created for the T-criterion and osteoprotegrin as the most informative indicators for assessing the state of bone tissue. Mathematical modeling allows with a high degree of confidence, using available laboratory indicators, which, when undergoing medical examinations, are obligatory for determination, to determine quickly, without special equipment and significant economic costs, evaluate the structural and functional state of bone tissue in this category of women.

**Key words: bone mineral density; osteoprotegrin; arterial hypertension; obesity; adverse labour factors.**

**Urgency of the problem.** Arterial hypertension (AH) is one of the most common chronic noncommunicable disease. According to the data of Ukrainian Ministry of Health, hypertension is registered in 12 million people or 32.2% of the adult population. The most common comorbid state in the development and progression of hypertension is obesity (OB) [2]. About half of the adult Ukrainian population has overweight and obesity. In women the frequency of obesity is 1.7 times higher compared to men [1].

Increased frequency of hypertension and obesity in women older than 45 years is associated with the onset of the postmenopausal period (PMP) [3]. It is known that the hormonal restructuring of a woman's body during the PMP is accompanied not only by lipid and carbohydrate metabolism disorders, but also by changes in calcium-phosphorus metabolism and bone remodeling. To date, a huge number of works devoted to studying the effect of hormonal ovarian dysfunction on the state of bone tissue in PMP women have been published [3, 5].

Hypertension, obesity and PMP act as independent clinical risk factors in the development of bone tissue structural and functional changes and this is confirmed by a number of studies [7, 9]. Osteoporosis (OP) is the most common metabolic bone disease, which is characterized by bone mineral density (BMD) decrease, its microarchitectonics disturbances, and further increase in its fragility and increased risk of low-energy fractures [4].

It is known, that in women over 50 y. o. OP fractures occur in every third person [10]. The risk of vertebral compression fracture in PMP increases by 15.5%, proximal femur fracture by 17.5%, and distal forearm - by 16% [6].

Adverse labour factors have a separate negative impact on the state of bone tissue. Adverse conditions of the production process (physical overstrain, physical inactivity, noise, vibration, influence of chemical agents, etc.) act as provocative and modifying factors, catalyst for natural involutive processes that lead to premature aging of bone tissue [7]. If only because PMP begins earlier than the retirement age, women continue to work at adverse labour conditions.

The occurrence of low-energy fractures leads to exclusion from the labor process for a long period of treatment and rehabilitation of working age women. However, in many cases it is still impossible to achieve the previous working capacity in connection with the onset of

disability. In the medico-social and economic aspect, the consequences of osteoporosis are difficult to assess, since they include the frequency of cases of urgent hospitalization, the number of disability days, treatment, rehabilitation, etc.

AH, obesity, PMP and, at the same time, the effect of harmful factors of the working environment on a female body significantly worsen the prognosis of such patients. Therefore, the forecasting and osteoporosis early diagnosis at the preclinical stage of its development continues to be the issue of priority.

**The objective:** to create models for assessing the structural and functional state of bone tissue in PMP women with AH and obesity working under adverse labour conditions.

**Materials and methods.** 140 PMP women (duration of PMP  $5.4 \pm 1.5$  years) aged 48-60 (average age  $56.2 \pm 1.3$  years) were examined. All the women under examination had AH stage I - II of 1-2 degrees and the first degree of obesity (AH duration -  $7.6 \pm 3.4$  years) and work under the adverse factors of the labour environment (work experience -  $26.2 \pm 5.7$  years). The diagnosis of hypertension was established in accordance with the Unified Clinical Protocol of Primary, Emergency and Specialized Medical Care for Hypertension (2012), and Ukrainian Ministry of Health orders( N 384 dated 05.24.2012). To assess the degree of obesity, the body mass index (BMI) was determined by the ratio of body weight to growth ( $\text{kg} / \text{m}^2$ ) in accordance with the recommendations of the international obesity group (WHO, 1997). The criterion for an abdominal or central type of obesity was considered the index of the waist circumference to the circumference of the hips (CW / CH) of more than 0.8 or 80 cm.

All the workers were measured systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR). Laboratory examination included: to assess the state of lipid metabolism, the blood serum was determined for total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL cholesterol), low density lipoprotein cholesterol (LDL cholesterol), very low density lipoprotein cholesterol (VLDL cholesterol) and atherogenic index (AI). Bone tissue status was assessed using bone remodeling markers: a marker for bone resorption of type C collagen telopeptide type 1 (CTx), a bone marker for osteocalcin (OK) and osteoprotegrin (OPG), the level of 25-hydroxyvitamin D3 (25 (OH) D3) was determined. Mineral density of bone tissue was studied by determining T-criterion using ultrasonic densitometry ( AOS-100NW Aloka, Japan).

Statistical data processing was performed with Microsoft Office Excel and Statistica 6.0 applications. The construction of mathematical models was carried out in two stages. At the first stage a correlation analysis of the indicators studied was used. In view of correlation

analysis results, only indicators with strong correlation relationships were included in mathematical models. Based on the revealed close correlations, the correlation coefficients were calculated. The second step was to build a model based on a linear multiple regression model, with which one can take into account the influence of several factors on the indicator that is being modeled.

**The results.** The following indicators were considered for the correlation analysis: work experience, PMP duration, diastolic arterial blood pressure, BMI, systolic arterial blood pressure, level 25 (OH) D<sub>3</sub>, CTx, osteocalcin, OPG, total cholesterol, TG, HDL cholesterol, LDL cholesterol, VLDL cholesterol, AC, T-criterion. The value of the correlation coefficients between the pairs of indicators under study are presented in Table 1.

Table 1

**THE VALUE OF THE CORRELATION COEFFICIENTS BETWEEN PAIRS OF INDICATORS UNDER STUDY**

	OPG		T-criterion
Length of service	-0.7	Length of service	-0.66
PMP duration	-0.44	PMP duration	-0.49
Arterial blood pressure, diastolic	-0.68	Arterial blood pressure, diastolic	-0.7
Body mass index	-0.5	Body mass index	-0.34
Arterial blood pressure, systolic	-0.48	Arterial blood pressure, systolic	-0.57
25(OH)D <sub>3</sub>	0.88	25(OH) D <sub>3</sub>	0.66
CTx	-0.77	CTx	-0.61
Osteocalcin	0.5	Osteocalcin	0.47
T-criterion	-0.6	T-criterion	0.6
Total cholesterol	-0.65	Total cholesterol	-0.79
Triglycerids	-0.1	Triglycerids	-0.07
HDL cholesterol	0.19	HDL cholesterol	0.07
LDL cholesterol	-0.53	LDL cholesterol	-0.68
Very low density lipoprotein cholesterol	-0.1	Very low density lipoprotein cholesterol	-0.1
Atherogenic index	-0.55	Atherogenic index	-0.56

Based on the correlation analysis, mathematical modeling of the most important indexes regarding the assessment of the structural and functional state of bone tissue was performed: osteoprotegrin (OPG) and T - criterion.

Of particular interest in the construction of the model is the determination of the possibility of OPG predicting through indicators of lipid metabolism and level 25 (OH) D, as the most affordable laboratory indexes.

Before the start of mathematical modeling, the values of all indicators under study were normalized. This was a must for building a model in connection with the maximum assessment of the influence of each factor on the indicator that is being modeled. The linear multiple regression equation used was of the form:

$$y = \alpha_0 + \alpha_1x_1 + \alpha_2x_2 + \alpha_3x_3 + \dots + \alpha_nx_n,$$

where y is an indicator that is modeled,

$\alpha_0, \alpha_1, \alpha_2, \alpha_3, \dots, \alpha_n$  are the coefficients of the linear multiple regression equation,

$x_1, x_2, x_3, \dots, x_n$  - factors that affect the value of the indicator under modeling.

The model was considered reliable when R-squared ( $R^2$ ) value was equal to or greater than 0.5. Models in which  $R^2$  value was less than 0.5 were not used due to their poor displacement of the simulated process.

To simulate the values of OPG and T-criterion, the initial indicators were evaluated in a group of hypertension and obesity women and did not depend on the labor conditions and treatment methods.

Models with which one can evaluate the value of OPG are presented in Table 2.

Table 2

**MODELS FOR ASSESSING THE VALUE OF OPG ACCORDING TO  
LABORATORY DATA IN WOMEN WITH ARTERIAL HYPERTENSION AND  
OBESITY**

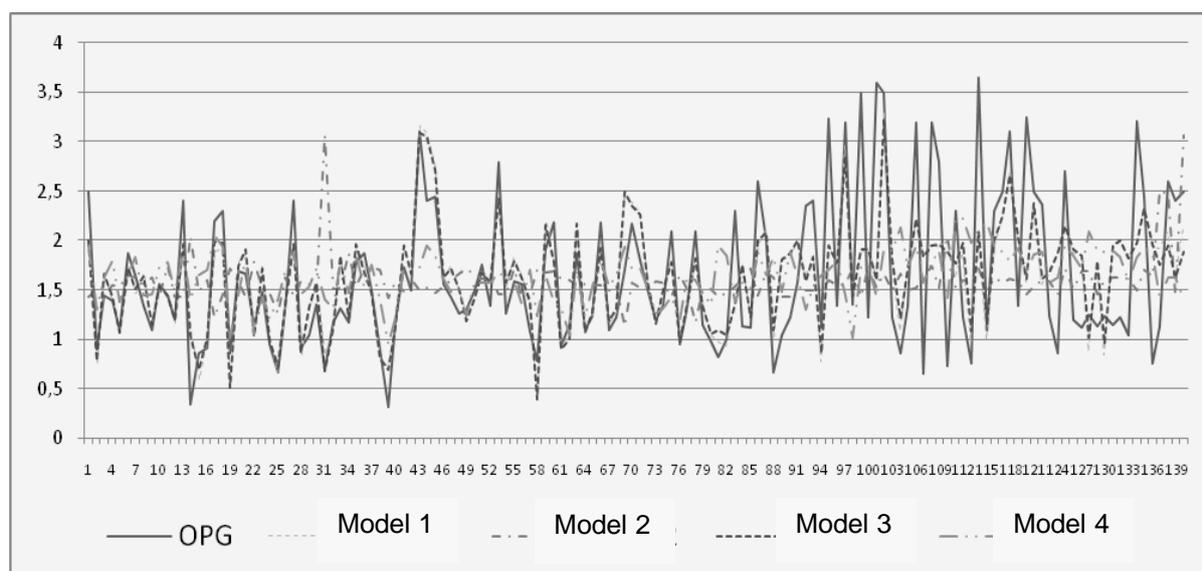
Model (y)	$R^2$	Factors (x), coefficients ( $\alpha$ )			
		$\alpha_0$	25(OH)D <sub>3</sub> , $\alpha_1$	Total cholesterol, $\alpha_2$	LDL cholesterol, $\alpha_3$
1	0.91	-	0.099	0.08	-0.127
2	0.8	-	-	0.599	-0.537
3	0.47	0.635	0.092	- 0.044	-0.066
4	0.12	3.374	-	- 0.259	-0.055

As Table 2 shows, model 2 and 4 were built without the inclusion of the primary indicator 25 (OH) D<sub>3</sub>:

$$\text{OPG} = 0.599 \cdot \text{TC} - 0.537 \cdot \text{LDL cholesterol}, R^2 = 0.8 \text{ (2)};$$

$$\text{OPG} = 3.374 + 0.259 \cdot \text{TC} - 0.055 \cdot \text{LDL cholesterol}, R^2 = 0.12 \text{ (4)}$$

In contrast to model 2, in model 4, in addition to 25 (OH) D<sup>3</sup>, TC, LDL cholesterol, another additional unknown factor ( $\alpha_0$ ) was taken into account. In model 2  $R^2 = 0.8$ , and in model 4  $R^2 = 0.12$ . Due to the low (less than 0.5)  $R^2$  of model 4, it can be excluded from the study. In addition, these models showed weak sensitivity to the initial modeling index OPG (Fig. 1).



**Fig. 1. OPG value: primary and calculated using models 1 – 4**

Models 1 and 3 were built taking into account indicator 25 (OH) D<sup>3</sup>:

$$\text{OPG} = 0.099 \cdot 25 \text{ (OH) D}_3 + 0.083 \cdot \text{TC} - 0.127 \cdot \text{LDL cholesterol}, R^2 = 0.91 \text{ (1)}$$

$$\text{OPG} = 0.635 + 0.092 \cdot 25 \text{ (OH) D}_3 - 0.044 \cdot \text{TC} - 0.066 \cdot \text{LDL cholesterol}, R^2 = 0.47 \text{ (3)}$$

Compared to model 1, an additional unknown factor ( $\alpha_0$ ) was also included in model 3. The results obtained indicate that the models in which 25 (OH) D<sub>3</sub> is included accurately reflect the behavior of the modeling indicator OPG, therefore, models 2 and 4 can be discarded. Therefore, the choice remains between model 1 and 3. If we compare the value of  $R^2$  in these models, then in model 1  $R^2 = 0.91$ , and in model 3  $R^2 = 0.47$ , which is less than 0.5 and indicates the exclusion of this model from research. Along with this, the advantage is given to model 1.

In fig. 1 is a graphical representation of the OPG value compared with the data obtained during the initial examination and the data calculated in accordance with the constructed models 1 - 4.

Fig. 1 shows how model OPG values reproduce these values obtained at the initial examination of the women under observation. In accordance with the graphic image, the closest model is model 1. Therefore, this model can be used in practice.

Models with which one can evaluate the value of the T-criterion are presented in Table 3.

Table 3

**MODELS FOR ASSESSING THE VALUE OF T-CRITERION IN WOMEN WITH ARTERIAL HYPERTENSION AND OBESITY**

Model (y)	R <sup>2</sup>	Factors (x), coefficients (α)						
		α	DBP, α <sub>1</sub>	BMI, α <sub>2</sub>	25(OH)D <sub>3</sub> , α <sub>3</sub>	CTx, α <sub>4</sub>	TC, α <sub>5</sub>	LDL cholesterol, α <sub>6</sub>
1	0.88	-	-0.017	- 0.00009	0.066	-1.466	-0.203	-0.187
2	0.6	1.199	-0.015	-0.023	0.055	-1.458	-0.272	-0.156
3	0.85	-	-0.036	-0.042	0.111	-	-0.193	-0.246
4	0.53	1.413	-0.034	-0.069	0.098	-	-0.274	-0.209

As Table 3 shows, model 1 and 2 are built with the inclusion of CTx resorption marker, but they differentiate by presence in model 2, in addition to DBP, BMI, 25 (OH) D<sub>3</sub>, TC and LDL cholesterol, an additional independent factor (α<sub>0</sub>):

$$\text{T-criterion} = -0.017 \cdot \text{DBP} - 0.00009 \cdot \text{BMI} + 0.066 \cdot 25 \text{ (OH) D}_3 - 1.466 \cdot \text{CTx} - 0.203 \cdot \text{TC} - 0.187 \cdot \text{LDL cholesterol}, R^2 = 0.88 \text{ (1)};$$

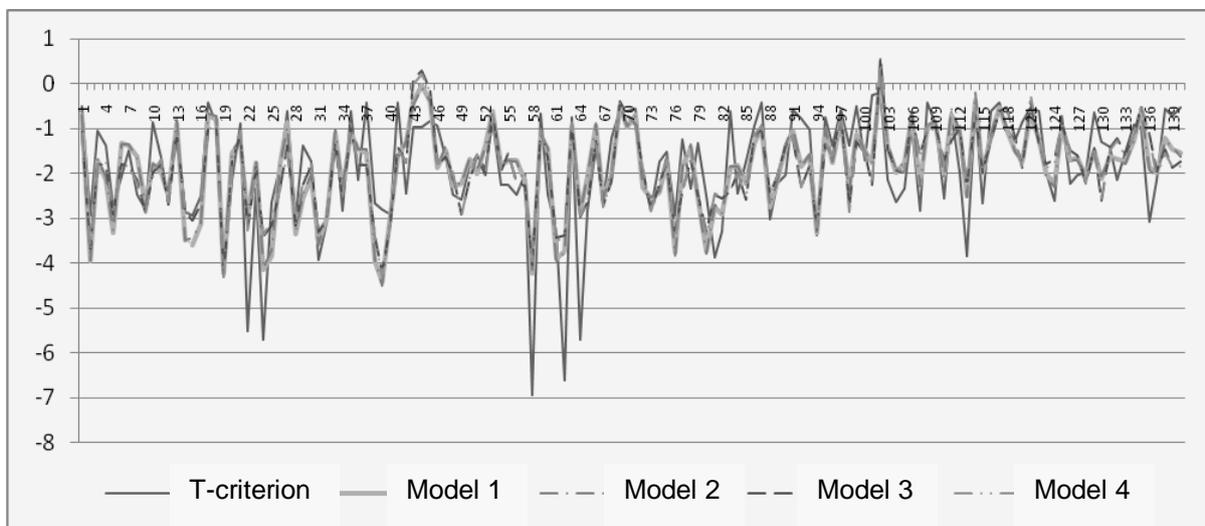
$$\text{T- criterion} = 1.199 - 0.015 \cdot \text{DBP} - 0.023 \cdot \text{BMI} + 0.055 \cdot 25 \text{ (OH) D}_3 - 1.458 \cdot \text{CTx} - 0.272 \cdot \text{TC} - 0.156 \cdot \text{LDL cholesterol}, R^2 = 0.6 \text{ (2)}$$

If we compare R<sup>2</sup> value, then in model 1 R<sup>2</sup> = 0.88, and in model 2 - R<sup>2</sup> = 0.6, in this regard, one can refuse from model 2. Models 3 and 4 are built without taking into account the CTx indicator:

$$\text{T-criterion} = -0.036 \cdot \text{DBP} - 0.042 \cdot \text{BMI} + 0.111 \cdot 25 \text{ (OH) D}_3 - 0.193 \cdot \text{TC} - 0.246 \cdot \text{LDL cholesterol}, R^2 = 0.85 \text{ (3)};$$

$$\text{T-criterion} = 1.143 - 0.034 \cdot \text{DBP} - 0.069 \cdot \text{BMI} + 0.098 \cdot 25 (\text{OH}) \text{D}_3 - 0.274 \cdot \text{TC} - 0.209 \cdot \text{LDL cholesterol}, R^2 = 0.53 \quad (4)$$

Model 4 differs from model 3 by the presence of an additional unknown factor ( $\alpha_0$ ).  $R^2$  in model 3 was equal to 0.85, which is higher compared to model 4 ( $R^2 = 0.53$ ). Since  $R^2$  in models 1 and 3 are almost the same, one can give an advantage to both models. This allows to calculate the value of T-criterion both taking into account (model 1) and without taking into account the CTx marker (model 3). In Fig. 2 the graphical creation of T-criterion in comparison with the primary indicators and values calculated using models 1 – 4 is presented.



**Fig. 2.** *T - criterion value: primary and calculated using models 1-4*

The graph shows that the constructed models 1 and 3 maximally reproduce the primary indicators of T - criterion and can be recommended for practical use.

**Conclusions.** Mathematical modeling allows with a high degree of reliability using available laboratory indicators, which are obligatory when undergoing medical examinations, quickly and without special equipment and significant economic costs to evaluate the structural and functional state of bone tissue in postmenopausal women with arterial hypertension and obesity

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