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## Clinical and metabolic parameters, $Ca^{2+}$ , parathormone depending on serum 25(OH)D concentration in hypertensive patients in the West-Ukrainian population

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### Abstract

**Introduction.** Low plasma levels of 25-OH vitamin D (25(OH)D) have been associated with an increased prevalence of hypertension. **The purpose** of the research was to establish the association of clinical and metabolic parameters,  $Ca^{2+}$ , parathormone and serum 25(OH)D concentration in hypertensive patients in the West-Ukrainian population. **Material and method.** 100 subjects with essential arterial hypertension (EAH) and target-organ damaging (2<sup>nd</sup> stage), moderate, high, very high cardiovascular risk were involved in the case-control study. Among them, 70,84% females, 29,16% males, mean age  $57,86 \pm 7,81$  yo. The control group consisted of 60 healthy individuals. All recruited patients were examined for heart rate, systolic and diastolic blood pressure (SBP, DBP); SCORE, BMI, waist and hip circumference (WC, HC); lipid panel, serum glucose and ionized calcium, 25(OH)D, parathormone levels were studied. Patients were divided into groups depending on total serum 25(OH)D concentration. **Results.** Low 25(OH)D concentration ( $<30$  ng/ml) in patients with EAH was associated with arrhythmia, headache, sleep disturbance, weakness, fatigue, and increased total 10-year risk for fatal CVD SCORE  $>5,0\%$ . We found higher SBP and DBP by 9,12% ( $p=0,014$ ) and 5,17% ( $p=0,047$ ), higher BMI in men and women – by 20-28,11% ( $p<0,05$ ), as well as higher values of WC and HC by 8,69-11,92% ( $p<0,05$ ) in hypertensive patients with hypovitaminosis D. In addition, obesity ( $BMI \geq 30,0$  kg/m<sup>2</sup>), hyperglycemia, hypertriglyceridemia was more frequent – by 43% ( $p<0,05$ ), 43,13% ( $p<0,001$ ) and 59,37% ( $p=0,023$ ), respectively. The level of ionized  $Ca^{2+}$  was slightly higher in healthy individuals

( $p=0,047$ ) with low vitamin D concentration. PTH was compensatory increased by 31,85% ( $p=0,048$ ) in hypertensive patients with hypovitaminosis D.

**Conclusions.** Hypovitaminosis D is associated with more severe metabolic, hemodynamic disorders and clinical symptoms in hypertensive patients in the West-Ukrainian population.

**Key words:** 25(OH)D; essential arterial hypertension; clinical parameters; metabolic parameters;  $Ca^{2+}$ ; parathormone.

**Introduction.** Cardiovascular diseases (CVD) is the most common cause of death in the developed world and is forecasted to be the leading cause of death and morbidity in developing countries by 2020 [1]. Essential hypertension (EAH) is a complex, multifactorial and polygenic disease. Despite effective measures for control and modification of traditional risk factors, a significant amount of risk remains. Therefore, the identification of easily modifiable novel risk factors has been heavily investigated over the past few decades.

Recently a world-wide attention to biological effects of vitamin D in the humans' body and pathogenic changes in case of its shortage or deficiency has grown significantly. Vitamin D modulates growth, hypertrophy, collagen deposition, and differentiation of cardiomyocytes, pointing towards direct role of vitamin D levels and its receptor in cardiac pathophysiology. As hypovitaminosis D has been identified an independent risk factor for total mortality in general population, high prevalence of Vitamin D insufficiency remains an important public health issue.

Low plasma levels of vitamin D have been associated with an increased prevalence of hypertension [2, 3] and, in particular, diastolic hypertension [3, 4]. On the contrary, other studies do not endorse the association between vitamin D deficiency and increased susceptibility to high blood pressure [5, 6]. Vitamin D-mediated triglyceride abnormalities (also referred as dyslipidemia) have been linked with two-different mechanisms [7]. Vitamin D improves serum calcium by promoting calcium synthesis in the intestine. And by reducing hepatic triglyceride production and secretion, this calcium could lower serum triglycerides. Vitamin D has a suppressive effect on serum parathormone (PTH) concentration, which is the second mechanism. Low serum PTH can reduce serum triglycerides by increasing peripheral elimination, as elevated PTH concentration reduces plasma postheparin lipolytic activity. Another potential explanation for the connection between 25-hydroxyvitamin D and triglycerides is insulin resistance: while vitamin D deficiency exists, the risk of insulin resistance increases, which is linked to an increase in very low density lipoprotein cholesterol and triglyceride levels.

Despite observational studies support the concept that 25(OH)D is involved in the pathogenesis of cardiovascular diseases and arterial hypertension, the causal relationship and genetic basis of this association remains unclear and needs further diagnostic evaluations and research. **The purpose** of the research was to establish the association of clinical and metabolic parameters,  $Ca^{2+}$ , parathormone and serum 25(OH)D concentration in hypertensive patients in the West-Ukrainian population.

#### **Material and method**

The study was conducted according to the World Medical Declaration of Helsinki on the Ethical Principles of Medical Research involving human subjects and it was complied with basic international standards of good clinical and laboratory practices (GCP, GLP). The diagnosis of EAH was established as reported by the current Ukrainian (Order of 24.05.2012 № 384) and European guidelines (ESC, ESH 2018) [8, 9]. After screening for inclusion and exclusion criteria, that have been detailed in our publications [10, 11, 12, 13, 14, 15], 100 subjects with EAH and hypertensive-mediated organs damaging (2<sup>nd</sup> stage), moderate, high or very high CVR were involved in the case-control study. There were 70,84% of females,

29,16% of males among them, the mean age was 57,86±7,81 yo. The control group consisted of 60 practically healthy individuals: 62,5% women, 37,5% men, the average age was 46,37±6,77 yo, who did not differ by gender and age and from the group of patients (p>0,05). Patients were divided into groups depending on total serum 25(OH)D concentration.

All recruited patients underwent physical examination, gathering disease and life history, measuring of heart rate, systolic and diastolic blood pressure (SBP, DBP), height, body weight, body mass index (BMI), waist and hip circumference (WC, HC); total 10 year risk for fatal CVD (SCORE); were tested for serum level of fasting glucose (enzymatic method, "CORMAY", Poland), ionized calcium (Ca<sup>2+</sup>) (potentiometry, "SINNOWA", China), parathyroid hormone (PTH) and 25(OH)D (immune luminescent test "MAGLUMI", "SNIB", China).

Statistical analysis was performed using StatSoft Statistica v. 7.0 (USA) software. Pearson's criterion ( $\chi^2$ ) was used for the genotypes distribution comparison. Analysis of qualitative data (categorical variables), risk of pathology development was assessed by a binary logistic regression model using relative risk (RelR); risk ratio (RR) was estimated by odds ratio (OR) with 95% confidence interval [95% CI] using a chi-square test ( $\chi^2$ ) (df=1). Quantitative data was calculated using a Student's t-test (two-tail distribution and equal variances between the two samples) based on the triplicate values for each gene genotypes. The Wilcoxon-Mann-Whitney U-test applied in case of uneven data distribution (according to W-Shapiro-Wilk or Kolmogorov-Smirnov test results). Differences were regarded as significant at p values <0,05.

### Results

The frequency of complaints, clinical symptoms and total 10-year risk for fatal CVD (SCORE) considering levels of vitamin D are shown in table 1. Cardialgia, arrhythmia, headache, sleep disturbances, weakness were more often observed in hypertensive patients with low 25(OH)D concentration by 14,23% ( $\chi^2=2,17$ ; p>0,05), 20,86% ( $\chi^2=3,86$ ; p=0,049), 27,89% ( $\chi^2=7,34$ ; p=0,007), 29,77% ( $\chi^2=7,97$ ; p=0,005), 20,59% ( $\chi^2=3,88$ ; p=0,049), respectively. The frequency of patients with the total 10-year risk for fatal CVD – SCORE > 5,0 % with hypovitaminosis D dominated over the ones with normal concentration of 25(OH)D – by 20,94% ( $\chi^2=3,98$ ; p=0,046).

Table 1. Complaints, clinical symptoms and the total 10-year risk for fatal cardiovascular diseases (SCORE) considering serum 25(OH)D concentration

Complaints, clinical symptoms		N 25(OH)D, n=34	↓ 25(OH)D, n=66
Cardiac, n (%)	Cardialgia	7 (20,59)	23 (34,85)
	Arrhythmia	11 (32,35)	35 (53,03)
	Dyspnea	2 (5,88)	6 (9,09)
Cerebrovascular, n (%)	Headache	7 (20,59)	32 (48,48)
	Tinnitus	6 (17,65)	11 (16,67)
	Dizziness	10 (29,41)	20 (30,30)
	Sleep disturbances	11 (32,35)	41 (62,12)
Weakness, tiredness, n (%)		10 (29,41)	33 (50,0)
Peripheral edema, n (%)		6 (17,65)	9 (13,64)
Complaints from the gastrointestinal tract, associated with EAH, n (%)		10 (29,41)	14 (21,21)
Other: paresthesia, impaired vision, leg pain, unsteady gait, lameness, n (%)		13 (38,23)	21 (31,82)
SCORE, n (%)	<5,0 %	20 (58,82)	25 (37,88)
	>5,0 %	14 (41,18)	41 (62,12)

Alterations in clinical and laboratory parameters considering serum 25(OH)D concentration are shown in table 2. It is interesting to note that higher values of SBP and DBP values were recorded in EAH patients with hypovitaminosis D (<30 ng/ml) comparing to patients with normal concentration of 25(OH)D by 9,12% (p=0,014) and 5,17% (p=0,047), respectively. Equally important, BMI in both patients and healthy individuals, regardless the gender, with hypovitaminosis D exceeded BMI of those with normal serum 25(OH)D concentration: in healthy males and females by 20,0% (p=0,048) and in EAH patients by 28,11% (p=0,004) and 21,13% (p=0,042), respectively. Particularly, BMI did not differ between men and women in each group (p>0,05). We have found the similar changes in WC and HC values in individuals with vitamin D deficiency, that were greater than in individuals with normal concentration of 25(OH)D in both groups: for WC – by 10,53% (p=0,049) and 11,92% (p=0,007), for HC – by 10,37% (p=0,015) and 8,69% (p=0,028), accordingly. In addition, BMI and BP parameters in female patients exceeded the ones in the healthy group, but significant difference was found only in patients with hypovitaminosis D – by 22,99% (p<sub>c</sub>=0,002) and 11,80% (p<sub>c</sub>=0,001), respectively.

Blood glucose was higher in individuals with low 25(OH)D levels (Table 2) than in healthy individuals and patients with normal serum 25(OH)D concentration – by 42,03% and 43,13% (p<sub>c</sub>, p<sub>1</sub><0,001), as well as TG – by 59,37% (p<sub>1</sub>=0,023).

One of the pathogenetic links of metabolic disadaptation, in our opinion, is compensatory increase of ionized Ca<sup>2+</sup> and PTH concentration in the blood, that was found in subjects with hypovitaminosis D, regardless the group (control / study): Ca<sup>2+</sup> – by 3,54% (p<sub>1</sub>=0,047) in control group and by 1,74% (p<sub>1</sub>=0,056) in the study group, PTH – by 25,74% (p<sub>1</sub>=0,052) and 31,85% (p<sub>1</sub>=0,048), respectively (table 2).

Table 2. Clinical and laboratory parameters considering serum 25(OH)D concentration, M±m

Parameters		Control group		EAH patients	
		N 25(OH)D	↓25(OH)D	N 25(OH)D	↓25(OH)D
SBP, mm Hg		116,0±2,45	116,8±1,11	142,50±3,10 P <sub>C</sub> <0,001	155,50±1,77 P <sub>C</sub> <0,001 p <sub>I</sub> =0,014
DBP, mm Hg		76,01±2,45	76,30±1,37	90,0±2,24 p <sub>C</sub> =0,002	94,65±1,03 p <sub>C</sub> <0,001 p <sub>I</sub> =0,047
BMI, kg/m <sup>2</sup>	M	24,50±1,28	29,40±1,53 p <sub>I</sub> =0,048	24,90±0,97	31,90±1,28 p <sub>I</sub> =0,004
	F	20,90±1,49	26,10±1,44 p <sub>I</sub> =0,047	26,50±2,06 p <sub>C</sub> =0,052	32,10±0,78 p <sub>C</sub> =0,002 p <sub>I</sub> =0,042
Waist circumference, cm		83,60±5,38	92,40±2,73 p <sub>I</sub> =0,049	92,30±2,72 p=0,052	103,30±1,58 p <sub>C</sub> =0,001 p <sub>I</sub> =0,007
Hip circumference, cm		97,40±2,62	107,50±2,36 p <sub>I</sub> =0,015	103,50±2,99	112,50±1,35 p <sub>I</sub> =0,028
Blood glucose, mmol/l		5,0±0,34	5,21±0,14	5,17±0,09	7,40±0,39 p <sub>C</sub> ,p <sub>I</sub> <0,001
TC, mmol/l		5,64±0,53	5,58±0,19	5,38±0,79	5,77±0,14
TG, mmol/l		1,68±0,41	1,78±0,18	1,28±0,24	2,04±0,13 p <sub>I</sub> =0,023
HDL-C, mmol/l		1,58±0,30	1,34±0,07	1,37±0,14	1,24±0,03
LDL-C, mmol/l		3,80±0,48	4,10±0,19	3,90±0,53	4,30±0,13
Ionized Ca <sup>2+</sup> , mmol/l		1,13±0,02	1,17±0,01 p <sub>I</sub> =0,047	1,15±0,02	1,17±0,01 p <sub>I</sub> =0,056
Parathormone, pg/ml		47,0±6,01	59,10±3,84 p <sub>I</sub> =0,052	47,10±5,42	62,10±4,25 p <sub>I</sub> =0,048

Notes: 1. SBP, DBP – systolic, diastolic blood pressure; BMI - body mass index; TC – total cholesterol; TG – triglycerides; HDL-C – high density lipoprotein cholesterol, LDL-C – low density lipoprotein cholesterol;

2. p<sub>C</sub> – significance of differences with control group, according to 25(OH)D concentration; p<sub>I</sub> – significance of differences in the group of normal 25(OH)D concentration of each group.

The relative frequency of patients with normal weight and overweight prevailed among individuals with normal concentration of 25(OH)D by 43% (p = 0,049) (Fig. 1). Whereas, obese patients (BMI≥30,0 kg/m<sup>2</sup>) dominated among patients with hypovitaminosis D by 43% (p<0,05).

The relative frequency of diabetes mellitus 2, tobacco smoking, increased WC in EAH patients did not depend on total serum 25(OH)D concentration (Fig. 2).

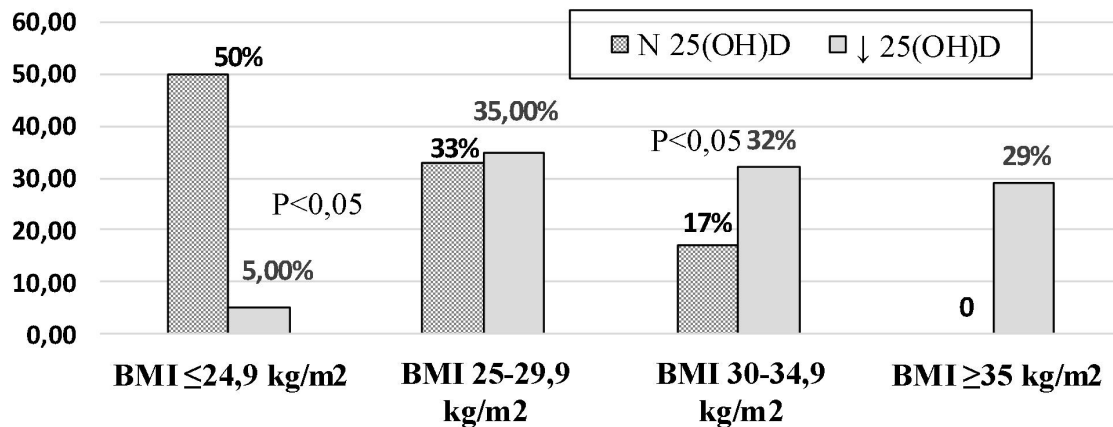


Fig. 1. Distribution (%) of body mass index (BMI) in patients with essential hypertension considering the total serum 25(OH)D concentration.

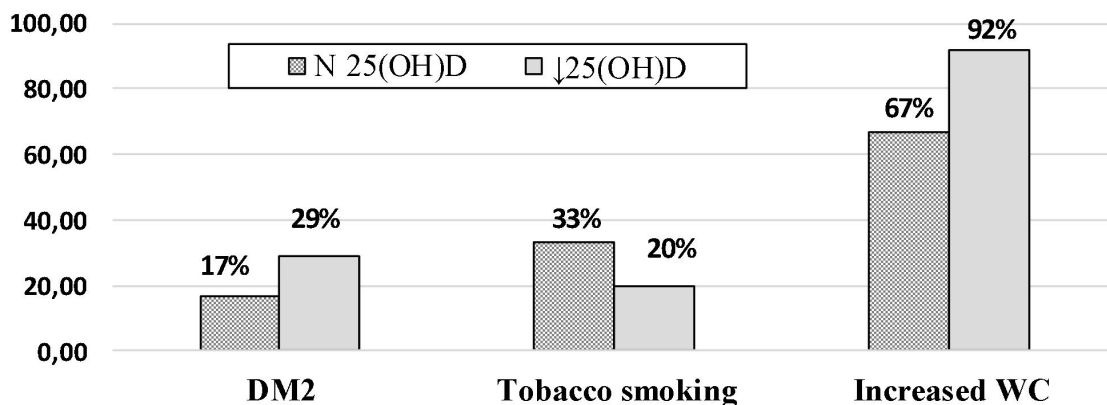


Fig. 2. Frequency (%) of diabetes mellitus 2, tobacco smoking, increased waist circumference (WC) in patients with essential hypertension depending the total serum 25(OH)D concentration.

### Discussion

The current study partially confirmed findings of the role of vitamin D in metabolic disorders (development of insulin resistance, incidence of type 2 diabetes and obesity, effects on lipids), antioxidant protection (reducing of glucose-mediated oxidative stress), inflammation (high concentration of inflammatory biomarker, such as C-reactive protein), regulation of intracellular Ca<sup>2+</sup> concentration [16, 17, 18, 19]. However, no such links have been established in some works. In contrast, Lerchbaum E et al. [20] did not show significant changes in metabolic parameters of insulin resistance and lipid panel in healthy men additionally taking vitamin D supplements. Other authors also did not find the effect of vitamin D supplements (short-term use – 3-4 months) on HbA1c, insulin resistance, lipid panel, C-reactive protein, markers of oxidative stress in patients with diagnosed type 2 diabetes or increased risk for it, as well as their association with individual anthropometric parameters [21, 22, 23]. The above was not entirely consistent with the results of our study, however, it should be noted that we studied the association of total metabolites of vitamin D in the blood with clinical, anthropometric, metabolic and hormonal parameters, with no prescription of Vitamin D supplements and evaluations of treatment outcomes.

### Conclusions

Hypovitaminosis D is associated with more severe metabolic, hemodynamic disorders and clinical symptoms in hypertensive patients in the West-Ukrainian population: higher

values of SBP and DBP by 9,12% i 5,17%; higher BMI in men and women – by 20-28,11% and WC and HC – by 8,69-11,92%, as well as more frequent cases of obesity (BMI  $\geq$ 30,0 kg/m<sup>2</sup>) – by 43%; elevation of blood glucose by 43,13% and hypertriglyceridemia – by 59,37%. Compensatory increase of PTH in EAH patients is associated with low serum 25(OH)D concentration. Additionally, these patients were most complained on arrhythmia – by 20,86%, headache – by 27,89%, sleep disturbance – by 29,77%, weakness, fatigue – 20,59%.

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