ORIGINAL ARTICLE

CONTENTS

# Features of the clinical course of arterial hypertension in patients with vitamin D deficiency

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## ABSTRACT

**Aim:** To determine the peculiarities of the daily profile of blood pressure in patients with arterial hypertension (AH) and vitamin D deficiency and insufficiency, to evaluate the parameters of the lipid profile and quality of life in these patients.

**Materials and Methods:** A total number of 97 patients with uncomplicated AH stage 1 and 2 were divided into 3 groups depending on the level of vitamin D in the blood serum. All patients underwent office blood pressure (BP) measurement and daily ambulatory BP monitoring for 24 hours, biochemical blood test with the determination of indicators of lipid metabolism, questionnaires for quality of life indicators. Statistical processing of the study results was carried out using "IBM SPSS Statistics 22".

**Results:** "Non-dippers" are most often identified in groups 1 and 2. Their prevalence is 1.8 times higher than in group 3 ($p < 0.05$). The frequency of "night-peackers" in group 1 is 1.7 times higher than in group 2 and 2.6 times higher than in group 3 ($p < 0.05$). Patients with AH and vitamin D deficiency have severe lipid metabolism disorders ($p < 0.05$). The correlation analysis shows a direct relationship of average strength between them and average daily systolic and diastolic BP indicators ($p<0.05$).

**Conclusions:** Patients with AH and vitamin D deficiency has an increase in cardiovascular risk, which is manifested by increase in pressure load indicators, frequency of detection of "night-peakers" and lipid metabolism disorders which is worsens of vascular accidents prognosis.

**KEY WORDS:** quality of life, vitamin D, arterial hypertension, blood pressure monitoring, lipid metabolism

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## INTRODUCTION

Arterial hypertension (AH) is one of the most important risk factors for global mortality and morbidity and is associated with non-communicable diseases such as atherosclerosis, cardiomyopathy and acute myocardial infarction [1]. In addition, hypertension increases the risk of stroke, heart attack, and chronic renal failure, which imposes a large economic burden on society [2]. The prevalence of hypertension varies in different parts of the world and may depend on demographic factors such as age, race, gender, and socioeconomic status [3].

This problem remains extremely important for Ukraine. Thus, according to STEPS 2019 data, a third part of the population of Ukraine (34.8%, among those surveyed) had high blood pressure (BP) or hypertension or were taking antihypertensive drugs, and the prevalence of the population with high BP increases with age.

Several modifiable and non-modifiable risk factors, such as age, gender, genetics, high sodium intake, low potassium intake, obesity, lack of physical activity, and unhealthy diet are actively involved in the increase of BP and subsequent development of hypertension [4]. In recent years, another reason for a possible increase in blood pressure has been put forward: vitamin D deficiency [5].

Vitamin D deficiency or insufficiency is becoming a very common disease worldwide. Recent large-scale observational data indicate that about 40% of Europeans have vitamin D deficiency, and 13% – severe deficiency [6, 7]. Vitamin D is already considered not only as a vitamin itself, but also as a fat-soluble steroid hormone that is directly involved in maintaining the health of the musculoskeletal system and calcium-phosphorus metabolism. The two most important forms of vitamin D are ergocalciferol (vitamin D2), which enters the body with food products, and cholecalciferol (vitamin D3), which is also synthesized endogenously [8, 9]. The best marker for assessing vitamin D status is serum 25(OH) D, which reliably reflects free fractions of vitamin D metabolites, despite the fact that theoretically bioavailable fractions may be more clinically informative [10, 11].

A large number of studies, both in the field of basic science and clinical research, have highlighted the

strong connection of vitamin D deficiency with many chronic diseases, among which a significant percentage consider vitamin D deficiency as another cause of a possible increase in blood pressure [12-14]. These studies aim to reveal the potential positive effects of vitamin D use in patients with vitamin D deficiency and hypertension [15, 16]. The use of vitamin D supplements is being studied in the treatment of essential hypertension because they are safe and well tolerated by patients and can potentially reduce systolic and diastolic blood pressure [17, 18]. Antihypertensive benefits of vitamin D can be explained by renin-angiotensin-aldosterone system inhibition, prevention and reduction of proteinuria, direct effect on endothelial cells due to the expression of vitamin D receptors in endothelial cells, vascular smooth muscle cells, and cardiac cardiomyocytes [19, 20].

## AIM

To determine the peculiarities of the daily profile of blood pressure in patients with arterial hypertension against the background of vitamin D deficiency and its insufficiency, to evaluate the parameters of the lipid profile and quality of life in these patients.

## MATERIALS AND METHODS

The study was conducted on the basis of the therapeutic department of the University clinic, which is the clinical base of the department of propaedeutics of internal medicine No. 2 of Bogomolets National medical university. This work is a prospective study. To achieve the goal, we conducted instrumental and laboratory tests, as well as patient questionnaires.

Clinical trial was conducted in accorandce with the provisions of the Helsinki Declaration and the study protocol had been agreed with the Bioethics Commission of Bogomolets National Medical University. All patients signed an informed consent before the study.

97 patients with uncomplicated arterial hypertension degree 1 and 2 were examined in total between December 2022 and September 2023. Among patients with hypertension, 3 groups were distinguished depending on the level of vitamin D in the blood serum of patients according to the Endocrine Practice Guidelines Committee [17]. The first group – 33 patients with hypertension and vitamin deficiency D (below 20 ng/ml or 50 nmol/l); the second group - 32 patients with hypertension and vitamin D insufficiency (from 21 to 29 ng/ml or from 50.1 to 74.9 nmol/l); and the third group – 32 patients with hypertension and a sufficient level of vitamin D (above 30 ng/ml or 75 nmol/l). All groups of patients are comparable in age and sex, groups of patients with AH are comparable in the duration of AH.

Criteria for inclusion in the study: age from 45 to 74 years (middle and old age, according to WHO classification, 1968); the diagnosis of stage II hypertension of the 1st and 2nd degree is established (ESC/ESH Guidelines for the management of arterial hypertension, 2018, 2023); chronic kidney disease not higher than II stage (glomerular filtration rate 60-89 ml / min. / 1.73 m2); ejection fraction of the left ventricle is more than 40%; informed consent to participate in the study. All patients with uncomplicated hypertension received antihypertensive therapy: valsartan 80-160 mg in combination with a calcium channel antagonist (amlodipine 5-10 mg per day). In addition to existing combined antihypertensive therapy, patients received vitamin D3 in a dose of 4000 IU (in case of insufficiency) and 6000 IU (in case of deficiency) [21].

All patients with uncomplicated hypertension underwent office blood pressure (BP) measurement and 24-hour daily blood pressure monitoring (BPM). Office BP was measured according to ESH recommendations. Daily blood pressure monitoring was carried out using the ABPM-04 monitor of the Meditech company (Hungary). Blood pressure was recorded on the "non-working arm" of the patient, and when the asymmetry of the measurements on the right and left arm was more than 10 mm Hg. – on the arm with a higher blood pressure value. The cuff was fixed on the forearm 2 cm above the elbow bend. BP was measured periodically every 15 minutes from 6:00 to 23:00 and every 30 minutes from 23:00 to 6:00, which made it possible to comprehensively analyze its parameters both in the active and passive periods.

All patients underwent a biochemical blood test with the determination of indicators of lipid metabolism: total cholesterol and its fractions - high-density lipoproteins (HDL-C), low-density lipoproteins (LDL-C), very low-density lipoproteins (VLDL-C), triglycerides (TG).

Quality of life indicators were assessed using the SF-36 questionnaire. The 36-Item Short Form Health Survey questionnaire (SF-36) is a very popular instrument for evaluating Health-Related Quality of Life. The SF-36 measures eight scales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). There are two distinct concepts measured by the SF-36: a physical dimension, represented by the Physical Component Summary (PCS), and a mental dimension, represented by the Mental Component Summary (MCS). All scales do contribute in different proportions to the scoring of both PCS and MCS measures [22].

**Table 1.** Main indicators of daily blood pressure monitoring in patients with arterial hypertension depending on the concentration of vitamin D

| Parameter | Patients with arterial hypertension and vitamin D deficiency (group 1, n=33) | Patients with arterial hypertension and vitamin D insufficiency (group 2, n=32) | Patients with arterial hypertension and normal values of vitamin D (group 3, n=32) |
|---|---|---|---|
| 24-hour average SBP, mmHg | 146.4±3.98 * | 143.7±3,54 * | 133.2±2.35 |
| 24-hour average DBP, mmHg | 86.5±2.36 * | 84.8±2,08 * | 77.6±1.87 |
| Daytime SBP, mmHg | 151.8±4.06 * | 147.1±3.84 * | 135.1±1.86 |
| Daytime DBP, mmHg | 89.8±2.83 * | 86.7±2.18 * | 80.9±1.33 |
| Nighttime SBP, mmHg | 143.6±3.72 * | 138.2±3,27 * | 122.6±2.25 |
| Nighttime DBP, mmHg | 83.7±2.94 * | 81.1±2,19 * | 70.6±1.62 |
| Time index of the SBP, % | 78.2±3.76 * # | 69.4±3.18 * | 43.8±3.44 |
| Time index of the DBP, % | 54.7±3.68 * # | 48.6±2.98 * | 39.2±2.85 |
| Area index of the SBP, mmHg×h/24h | 296.1±44.6 * # | 272.8±49.5 * | 159.8±29.6 |
| Area index of the DBP, mmHg×h/24 h | 120.8±27.9 * # | 105.3±24.7 * | 61.1±12.8 |

Note: * – $p < 0.05$ compared to group 3;
# – $p < 0.05$ compared to group 2;
n – number of patients.

**Table 2.** The level of lipids in the blood of patients with arterial hypertension depending on the concentration of vitamin D

| Parameter | Patients with arterial hypertension and vitamin D deficiency (group 1, n=33) | Patients with arterial hypertension and vitamin D insufficiency (group 2, n=32) | Patients with arterial hypertension and normal values of vitamin D (group 3, n=32) |
|---|---|---|---|
| Total cholesterol, mmol/l | 7.24±0.31*# | 6.96±0.13* | 6.23±0.12 |
| Triglycerides, mmol/l | 2.81±0.14*# | 1.88±0.13* | 1.42±0.11 |
| LDL, mmol/l | 4.86±0.18*# | 4.24±0.12* | 4.08±0.10 |
| HDL, mmol/l | 0.96±0.07*# | 1.09±0.06* | 1.18±0.08 |
| VLDL, mmol/l | 0.98±0.06*# | 0.85±0.09* | 0.66±0.04 |
| Atherogenicity index | 4.89±0.11*# | 4.39±0.21* | 4.18±0,19 |

Note: * – $p < 0.05$ compared to group 3;
# – $p < 0.05$ compared to group 2;
n – number of patients.

Statistical processing of the obtained results was carried out using the program "IBM SPSS Statistics. Version 22". Given the normal distribution of the investigated characteristics, parametric statistical methods were used in the samples: for descriptive statistics, the mean value of the indicator (M), standard deviation (SD), standard error (SE), a confidence interval for the mean of 95% (95% CI). Group comparisons were performed using qualitative paired data using Pearson's $\chi 2$ test (with Yates correction), Fisher's exact test. Pearson's correlation coefficient was used to measure the association between variables (BP indicators and the lipidogram).

## RESULTS

Daily monitoring of BP makes it possible to assess not only the average, maximum and minimum values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at different times of the day, but also to detect the presence or absence of episodes of hypertension and hypotension, to analyze the severity of hypertension according to the time index (TI) and area index (AI), to evaluate the circadian dynamics of blood pressure, which is important for stratifying the risk of developing complications from the patient's target organs. We took these indicators as a basis for the analysis of BP indicators in our patients (Table 1).

As a result of the analysis of the obtained data, we found significantly increased ($p<0.05$) levels of average daily systolic, diastolic blood pressure in all groups of patients compared to the normal values. The same regularities were observed when analyzing day and night periods separately.

Indicators of pressure load - time index and area index of SBP and DBP - were also significantly higher in all groups of patients with hypertension ($p<0.05$).

**Table 3.** Indicators of life quality according to the SF-36 scale in patients with arterial hypertension and vitamin D deficiency and its insufficiency

| SF-36 scales | Patients with arterial hypertension and vitamin D deficiency (group 1, n=33) | Patients with arterial hypertension and vitamin D insufficiency (group 2, n=32) | Patients with arterial hypertension and normal values of vitamin D (group 3, n=32) |
|---|---|---|---|
| Physical Functioning, PF | 65.3±1.86 *# | 71.4±2.59 | 74.43±2.68 |
| Role Physical, RP | 74.4±1.97 *# | 79.8±2.35 | 85.1±2.47 |
| Bodily Pain, BP | 61.2±2.66 | 62.8±2.85 | 65.1±2.92 |
| General Health, GH | 68.7±2.14 | 70.4±2.36 | 73.7±2.28 |
| Vitality, V | 71.8±1.84 *# | 76.7±2.44 | 80.6±2.62 |
| Social Functioning, SF | 67.3±2.08 *# | 73.6±2.34 | 80.1±2.85 |
| Role Emotional, RE | 72.3±2.06 *# | 82.3±2.26 | 88.3±2.43 |
| Mental Heath, MH | 71.3±2.31 | 73.8±2.62 | 76.1±2.58 |

Note: * – $p < 0.05$ compared to group 3;
# – $p < 0.05$ compared to group 2;
n – number of patients.

**Table 4.** Assessment of the «currently» state of health in patients with arterial hypertension and vitamin D deficiency and its insufficiency

| «Currently" state of health | Patients with arterial hypertension and vitamin D deficiency (n=33) | Patients with arterial hypertension and vitamin D insufficiency (n=32) | Patients with arterial hypertension and normal values of vitamin D (n=32) |
|---|---|---|---|
| Distinctive | 0 | 0 | 0 |
| Very beautiful | 0 | 2 (6.3%) | 5 (15.6%) |
| Good | 5 (15.2%) | 12 (37.5%) | 15 (46.9%) |
| Mediocre | 21 (63.6%) | 15 (46.9%) | 11 (34.3%) |
| Bad | 7 (21.2%) | 3 (9.3%) | 1 (3.2%) |

Note: n – number of patients.

To assess the effect of vitamin D concentration on blood pressure, we compared indicators between three groups of patients.

Thus, the average value of SBP per day in patients with deficiency and insufficiency of vitamin D significantly exceeded the values of SBP in patients with arterial hypertension with a normal concentration of vitamin D by 9.91% and 7.89%, respectively ($p<0.05$). Similar results were observed for DBP indicators per day, which exceeded the indicators of the third group of patients by 11.46% and 9.28%, respectively ($p<0.05$). In the patients of the first and second groups, significantly increased levels of average values of blood pressure were also found when analyzing the active and passive periods of the day separately ($p<0.05$). It should be noted that the average daily BP values in patients with vitamin D deficiency were higher than in patients with insufficiency, but the difference between them was not statistically significant ($p>0.1$).

In the group of patients with vitamin D deficiency, a significant increase in the in the load of systolic and diastolic pressure per day was found for SBP and DBP. These indicators statistically significantly exceeded the corresponding values in patients with vitamin D insufficiency by 12.8% for SBP and 12.6% for DBP ($p<0.05$), as well as the indicators in the group patients with its normal concentration 78.5% for SBP and 39.5% for DBP ($p<0.05$).

We also studied the level of total cholesterol and its fractions in patients with arterial hypertension depending on their concentration of vitamin D (Table 2).

When analyzing the obtained data, we established a high frequency of increased levels of total cholesterol, LDL-C, TG, VLDL-C and a decrease in HDL-C content, which occurred both in patients with hypertension with a normal concentration of vitamin D and in the presence of its insufficiency and deficiency.

Thus, compared to patients with a normal concentration of vitamin D, hypertensive patients with vitamin D insufficiency had a significantly higher content of total cholesterol by 11.71% ($p<0.05$), TG – by 32.39% ($p<0.001$), VLDL-C - by 28.79% ($p<0.001$). The level of LDL cholesterol was higher than the data of the comparison group by 5.08% ($p<0.05$). It should be noted

that the level of HDL cholesterol was lower by 7.63% ($p<0.05$). At the same time, aterogenic index was higher by 6.02% ($p<0.05$).

Hypertensive patients with vitamin D deficiency had more severe lipid metabolism disorders. The level of cholesterol exceeded the value of the group 3 by 16.21% ($p<0.001$); the content of LDL cholesterol exceeded the data by 19.12% ($p<0.001$); the level of VLDL cholesterol also exceeded by 48.49% ($p<0.001$); the TG level was higher by 97.89% ($p<0.001$). The level of HDL cholesterol was significantly reduced by 18.64% ($p<0.001$) from the level of the comparing group. As a result of the above-mentioned violations of the main fractions aterogenic index in these patients was higher by 16.98% compared to the group 3. It should be noted that the above-identified changes statically reliably differed from the corresponding indicators in the group of patients with vitamin D insufficiency ($p<0.05$).

Based on the results of patient questionnaires using the SF-36 questionnaire, quality of life scores were obtained in the range from 0 to 100, according to which, the more limitations the patients experienced in everyday life, the lower the indicators demonstrated by this questionnaire. In patients with hypertension, depending on the concentration of vitamin D, the following distribution of indicators on the scales was recorded (Table 3).

A decrease in quality of life indicators was observed in patients on most scales.

To the greatest extent, the patients had reduced indicators of physical activity and pain syndrome was observed due to the presence of patients' complaints about headaches, which, according to the patients, "prevent them from working." These changes caused problems at work and in the performance of daily duties. Obviously, it is precisely with these circumstances, as well as with a decrease in vitality and indicators of general and psychological health that a sharp decrease in social functioning (SF) of patients is associated ($p < 0.05$).

Thus, in patients of group 1, a decrease in the physical component of health is observed significantly more often than in groups 2 and 3 (respectively, $\chi^2=5.1$ and $\chi^2=4.9$, $p<0.05$), and a decrease in the mental component of health in 2.8 times more often than in group 3 ($\chi^2=8.4$, $p<0.05$). The structure of the quality of life is dominated by a decrease in physical, role, emotional, social functioning and vitality. PF in patients with vitamin D deficiency was 8.6% lower than in patients with vitamin D insufficiency and 12.3% lower than in patients with normal concentration ($p<0.05$); RP – respectively lower by 6.8% and 12.6% ($p<0.05$); RE – respectively lower by 12.2% and 18.1% ($p<0.05$); SF – respectively lower by 8.5% and 15.9% ($p<0.05$); V – respectively lower by 6.4% and 10.9% ($p<0.05$).

One of the points of the SF-36 questionnaire, the so-called "transition point of health", which is not used in the processing of points on any of the scales, allowed to determine the state of health (in the opinion of the patient) at this moment in time (Table 4) .

The most indicative data were precisely in the case of a combination of hypertension and vitamin D deficiency. The majority of patients - 21 (63.6%) at the time of the survey noted their state of health as "mediocre"; 7 patients (21.2%) indicated "poor" and only 5 patients (15.2%) indicated "good" health. All patients with a daily BP profile of "Night-peackers" rated their condition as mediocre or poor.

## DISCUSSION

Having conducted a comprehensive assessment of the obtained results, we noted certain features of the clinical course of the combined pathology in our patients. During the analysis of the circadian profile of blood pressure, we established that "non-dippers" are most often identified in groups 1 and 2. Their prevalence does not differ among both groups ($p>0.1$), but is 1.8 times higher than in patients of group 3 ($\chi^2 = 4.2$, $p <0.05$). Among patients of group 1, the highest frequency of the most unfavorable circadian profile was found "night-peackers", which is 1.7 times higher than in group 2 ($\chi^2 = 3.9$, $p < 0.05$) and 2.6 times higher than in group 3 ($\chi^2 = 4.3$, $p < 0.05$). The high frequency of "non-dippers" found in patients with deficiency and insufficiency of vitamin D may indicate an increase in cardiovascular risk in these patients [19, 23].

We also established a high frequency of lipid metabolism disorders in patients with hypertension, as well as when it is combined with deficiency and insufficiency of vitamin D, in which the content of TG, LDL-C, VLDL-C and aterogenic index was significantly higher than in patients of the comparison group. This statement be due to a higher frequency of metabolic disorders in such patients and a higher percentage of people with excess body weight and obesity of the I-II degree [13, 22].

Correlation analysis to assess the relationship between blood pressure indicators and the lipidogram showed a direct relationship of average strength between average daily SBP indicators and the level of total cholesterol ($r=0.58$, $p<0.05$), LDL-C ($r=0.61$, $p<0.05$) and TG ($r=0.54$, $p<0.05$), as well as a negative relationship between average strength and HDL-C level ($r=-0.38$, $p<0, 05$) in the group of patients with hypertension with a deficiency of vitamin D. Similar changes were observed for indicators of average DBP. With its increase,

the levels of total cholesterol (r=0.56, p<0.05), LDL-C (r=0.57, p<0.05), and TG (r=0.53, p<0.05) increased, and the HDL-C level decreased (r=-0.36, p<0.05).

The study of indicators of life quality in patients with combined pathology is important for assessing the total impact of diseases on the physical, psychological and social state of a person through an integral assessment of the patient's subjective feelings. Based on the test data, we assume that vitamin D deficiency makes a significant contribution to the decrease in quality of life indicators of the studied patients. In patients of group 1, a decrease in the physical component of health is observed significantly more often than in groups 2 and 3 (respectively, $\chi^2$=5.1 and $\chi^2$=4.9, p<0.05), and a decrease in the mental component of health in 2.8 times more often than in group 3 ($\chi^2$=8.4, p<0.05). The structure of the life quality is dominated by a decrease in physical, role, emotional functioning and vitality (p<0.05). This can be explained by the fact that, in addition to the complaints inherent in hypertension, such as headache, dizziness, heart pain, patients experience unusual fatigue, bone and joint pain, muscle pain, and urination disorders. The combination of these characteristic complaints leads to a violation of the performance of even ordinary daily work. Since both hypertension and vitamin D deficiency are chronic diseases that lead to long-term physical deterioration, they also cause secondary problems of a psychological and social nature.

## CONCLUSIONS

Patients with hypertension in combination with vitamin D deficiency have more significant changes in the daily blood pressure profile, which are manifested by an increase in pressure load time index (statistically significantly exceeded the corresponding values in patients with vitamin D insufficiency by 12.8% for SBP and 12.6% for DBP (p<0.05), as well as the indicators in the group patients with its normal concentration 78.5% for SBP and 39.5% for DBP (p<0.05)) and also an increase in the frequency of detection of "night-peackers" by 1.7 and 2.6 times respectively (p<0.05), which may indicate an increase in cardiovascular risk in patients.

A high frequency of lipid metabolism disorders are established in patients with hypertension combined with a deficiency of vitamin D. The patients have a significantly higher level of cholesterol, TG, LDL-C and aterogenic index compared to patients with vitamin D insufficiency and with its normal concentration (p<0.05). The indicators of the daily profile of blood pressure, such as average daily SBP and average daily DBP have a direct relationship correlation with the level of cholesterol (r=0.58, r=0.56, respectively, p<0.05), LDL-C (r=0.61, r=0.57, respectively, p<0.05) and TG (r=0.54, r=0.53, respectively, p<0.05), as well as a negative relationship with the level of HDL-C (r=-0.38, r=-0.36, respectively, p<0.05).

The identified changes are also confirmed in the patients' subjective assessment of the indicators of the quality of life, which is manifested by a decrease in physical, role, emotional functioning and vitality (p<0.05), and is observed to the greatest extent in patients with hypertension with vitamin D deficiency – a decrease in the physical component of health is observed significantly more often than in groups 2 and 3 (respectively, $\chi^2$=5.1 and $\chi^2$=4.9, p<0.05), and a decrease in the mental component of health in 2.8 times more often than in group 3 ($\chi^2$=8.4, p<0.05).

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## CONFLICT OF INTEREST

The Authors declare no conflict of interest

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