

12. Littlefield A, Lenahan C. Cholelithiasis: Presentation and Management. J Midwifery Womens Health. 2019 May; 64(3):289–297. doi: 10.1111/jmwh.12959.
13. Prykhidko RA, Dudchenko MO, Kravtsiv MI, Zaiets SM, Ivashchenko DM, Chelishvili AL, et al. A three-stage therapeutic and diagnostic algorithm in mechanical jaundice of different genesis and the most effective mini-invasive method of its treatment. World of Medicine and Biology. 2022; 2(80):119–124 doi 10.26724/2079-8334-2022-2-80-119-124
14. Qayed E, Shah R, Haddad YK. Endoscopic Retrograde Cholangiopancreatography Decreases All-Cause and Pancreatitis Readmissions in Patients With Acute Gallstone Pancreatitis Who Do Not Undergo Cholecystectomy: A Nationwide 5-Year Analysis. Pancreas. 2018 Apr; 47(4):425–435. doi: 10.1097/MPA.0000000000001033.
15. Yildirim M, Dasiran F, Ozsoy U, Daldal E, Kocabay A, Okan I. The Efficiency of Laparoscopic Common Bile duct exploration in endoscopic retrograde–cholangiopancreatography–limited setting in a peripheral university hospital. J Laparoendosc Adv Surg Tech A. 2020 Sep 9; doi: 10.1089/lap.2020.0525.

Стаття надійшла 25.08.2022 р.

DOI 10.26724/2079-8334-2023-3-85-91-96

UDC 616.71-007.234-06:616.12-008.46

O.M. Ignatiev, O.I. Paniuta, T.I. Prutian
Odessa National Medical University, Odessa

FEATURES OF STRUCTURAL AND FUNCTIONAL DISORDERS OF BONE TISSUE IN CHRONIC HEART FAILURE

e-mail: tatyana.prut@ukr.net

The purpose of the study was to assess the effect of loop diuretic therapy on the structural and functional condition of bone tissue and phosphorus-calcium metabolism in patients with chronic heart failure and moderately reduced ejection fraction. 109 patients between the ages of 65 and 74 were examined, 86 of them had chronic heart failure, and 23 were practically healthy. The 1st group received basic therapy; the 2nd group – basic therapy and loop diuretics. The examination includes the following: the collection of anamneses, anthropometric measurements, laboratory (determination of natriuretic hormone (B-type), N-terminal polypeptide, C-terminal telopeptide, osteocalcin, osteoprotegerin, 25-hydroxyvitamin D, parathormone, phosphorus) and instrumental (heart ultrasound examination, ultrasound densitometry) investigations. In patients with chronic heart failure, a violation of the processes of bone remodeling with a predominance of bone resorption against the background of slowed bone tissue formation was revealed. In patients with chronic heart failure, structural and functional changes in bone tissue were revealed, which are manifested by an imbalance of bone remodeling processes with a predominance of bone resorption and slowed bone formation, vitamin D deficiency, and significantly low indices of bone mineral density. Moreover, significantly pronounced changes were revealed in the group of patients who were on basic chronic heart failure therapy and loop diuretics comparing with the same indices in patients with chronic heart disease who received only basic therapy.

Key words: chronic heart failure, mineral density of bone tissue, markers of bone remodeling, vitamin D.

O.M. Ігнат'єв, O.I. Панюта, T.I. Прутіян

ОСОБЛИВОСТІ СТРУКТУРНО-ФУНКЦІОНАЛЬНИХ ПОРУШЕНЬ КІСТКОВОЇ ТКАНИНИ ПРИ ХРОНІЧНІЙ СЕРЦЕВІЙ НЕДОСТАТНОСТІ

Метою роботи було оцінити вплив терапії петлевими діуретиками на структурно-функціональний стан кісткової тканини та фосфорно-кальцієвий обмін у пацієнтів із хронічною серцевою недостатністю та помірно зниженою фракцією викиду. Обстежено 109 пацієнтів віком від 65 до 74 років, із них 86 (основна група) мали хронічну серцеву недостатність та помірно знижену фракцію викиду, 23 – практично здорові. Пацієнти 1-ї групи отримували базову терапію хронічної серцевої недостатності; 2-ї групи – базову терапію хронічної серцевої недостатності та петлеві діуретики. Обстеження включало збір анамнезу, антропометричні вимірювання, лабораторні (визначення натрійуретичного гормону (В-типу) N-кінцевого поліпептиду, С-термінального телопептиду, остеокальцину, остеопротегерину, 25-гідроксिवітаміну D, паратгормону, фосфору) та інструментальні (ультразвукове дослідження серця, ультразвукова денситометрія) дослідження. Отримані результати показали, що у пацієнтів з хронічною серцевою недостатністю виявлено порушення процесів кісткового ремоделювання з переважанням кісткової резорбції і уповільненням кісткоутворення, дефіцитом вітаміну D та редукцією показників щільності кісткової тканини. Достовірно ($p < 0,05$) виражені зміни виявлені у групі хворих, які перебували на базовій терапії хронічної серцевої недостатності та петлевих діуретиків у порівнянні з групою хворих, які приймали лише базову терапію хронічної серцевої недостатності.

Ключові слова: хронічна серцева недостатність, мінеральна щільність кісткової тканини, маркери кісткового ремоделювання, вітамін D

The study is a fragment of the research project “The use of cytological and molecular genetic methods of the musculoskeletal system investigation in the professional selection of the transport and marine economic complex workers”, state registration No 0121U109467.

The modern medicine has to increase the life expectancy of the population and at the same time contributed to the spread of age-related diseases, which are a global burden for the health care system [6]. In the most countries the prevalence of chronic heart failure (CHF) among the adult population in general 1.5–5.5% [8]. Spreading of CHF has a tendency to progressive growth and includes 10 % people over 70

years old. According to epidemiological data, almost 75–80% of all cases of CHF are caused by coronary heart disease (CHD) or arterial hypertension (AH) by itself or in combination [3].

Ukraine remains one of the world leaders in cardiovascular diseases among men with 772.1 cases per 100,000, and the five-year mortality of patients with manifest CHD reaches almost 50 % [9]. The prognosis of survival for patients with CHF worsens with the progression of this disease, which prompts treatment of CHF, including diuretics, as early as possible [3].

The number of patients with CHF combined with multiple pathologies is increasing [13, 15]. Disorder of bone tissue metabolism in the elderly occupies a special place in connection with CHF, which is associated with common pathophysiological mechanisms of development, as well as similar social, economic and medical consequences [14]. A number of studies have shown a connection between cardiovascular diseases and a high risk of bone loss [11].

It was established that reduced bone mineral density (BMD) was a predictor of CHF [4]. Angiotensin II activates the proliferation of osteoblasts, which stimulates the synthesis of collagen and removal calcium from the body. They recommend a BMD screening for patients with CHF, because of the T-criterion index and the functional classes of the NYHA correlation [3].

According to the 2021 Recommendations of the European Association of Cardiology (ESC), the most CHF patients should be given long-term loop diuretics therapy [1]. A relationship between the use of loop diuretics, BMD decrease and the risk of fractures was shown in many studies [5, 7, 10, 13].

However, taking into account the heterogeneity of patient cohorts, the inconsistency of the obtained data, depending of the effect of different diuretics, large dispersion on the characteristics of CHF, what results the task of controlling bone tissue status remains unresolved.

The purpose of the study was to assess the effect of loop diuretic therapy on the structural and functional condition of bone tissue and phosphorus-calcium metabolism in patients with chronic heart failure and moderately reduced ejection fraction.

Materials and Methods. The research has a prospective nature. On the basis of the Odesa Regional Clinical Medical Centre, a clinical and laboratory examination of 109 male patients aged from 65 to 74 years (mean age – 67.4±2.7) was carried out. Among them, 86 patients had CHF stage “C: with a moderately reduced left ventricular EF functional class III according to NYHA, which occurred against the background of CHD and arterial hypertension (AH) and were divided into groups: the 1st group included 41 patients who received constant basic therapy for CHF; The 2nd group consisted of 45 patients who were on constant basic CHF therapy and used loop diuretics (torasemide 10–20 mg/day or furosemide 40–80 mg/day) during the last year.

The control group or group III consisted of 23 patients who had no complaints or clinical abnormalities from the cardiovascular and bone systems.

Verification of the diagnosis of CHF, and determination of the stage and functional class was carried out on the basis of anamnestic, clinical, laboratory and instrumental studies in accordance with the guidelines for the diagnosis of acute and chronic heart failure developed in 2021 by the European Society of Cardiology and the Heart Failure Association [2].

All patients underwent a complete clinical examination, which included: collection of complaints, history (disease and life), anthropometric examination (measurement of height, body weight, calculation of body mass index (BMI)), objective examination according to generally accepted methods: blood pressure measurement and pulse rates.

Highly sensitive and specific IRMA method was used to measure plasma natriuretic hormone (B-type) N-terminal polypeptide (NT-proBNP) level. Instrumental researches include: ultrasound examination of the heart (EchoCG) on a stationary device of the Sonoline G50 type. No. GEE2528, manufacturer “Siemens Medical Systems Inc.”, Germany; ultrasound densitometry (USD) using a bone densitometer on the AOS-100NW device, Aloka (Japan). According to the criteria of WHO (1994), the value of the T-criterion up to “-1 SD” corresponds to a normal BMD index; from “-1 SD” to “-2.5 SD” - indicates the presence of osteopenia (Op); more than “-2.5 SD” indicates osteoporosis (OP).

A decrease in BMD is the condition what can be assessed by determining the markers of bone remodeling, namely: the marker of bone tissue resorption β -CrossLaps – C-telopeptide of type I collagen (CTx), the marker of bone formation – osteocalcin (OC), osteoclastogenesis marker – osteoprotegerin (OPG). Phosphorus-calcium exchange indices were assessed by determining total and ionized calcium, phosphorus, parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D) in blood serum.

Deficiency of vitamin D (DVD) was diagnosed with a level of 25(OH)D below 20 ng/ml, severe DVD – below 10 ng/ml, insufficiency of vitamin D (IVD) – at the level of 20–30 ng/ml, optimal vitamin D (OVD) – over 30 ng/ml [7].

The work was carried out with the provision of safety measures for life and health, with in compliance of human rights and moral and ethical norms, which correspond to the principles of the Helsinki Declaration of Human Rights and the order of the Ministry of Health of Ukraine No. 693 dated October 1, 2015.

Inclusion criteria: male patients suffering from arterial hypertension and coronary heart disease, complicated by CHF stage "C" with a moderately reduced left ventricular EF III according to NYHA, who provided written informed consent to participate in the study.

Exclusion criteria: CHF with EF ≥ 50 and $\leq 40\%$, acute heart failure, acute myocardial infarction, diabetes, chronic kidney and liver diseases, thyroid disease, diabetes, oncological pathology, autoimmune diseases, taking drugs affecting metabolism of bone tissue (glucocorticoids, hormone replacement therapy, anticonvulsants, drugs for the treatment of osteoporosis).

Statistical processing of the research results was carried out using the Statistica 10.0 software package, Student's t-test (the results were considered statistically significant at $p < 0.05$), correlation and regression analyses.

Results of the study and their discussion. The mean age of patients in the 1st group was 68.7 ± 2.8 years, in the 2nd group – 68.1 ± 2.1 , and in the 3rd group – 67.9 ± 2.4 years. Therefore, according to age indices, all groups of examined men were homogeneous ($p > 0.05$).

Based on the results of the analysis of risk factors for the development and progression of CHF, the following factors were identified in the study groups: AH, CHD, obesity, excess body weight, dyslipidemia, permanent form of arterial fibrillation, impaired glucose tolerance in Table 1.

Table 1

Risk factors for the development and progression of chronic heart failure in groups of study

Risk factors	The 1 st group, n=41		The 2 nd group, n=45	
	Absolute	Relative	Absolute	Relative
Arterial hypertension	12	29.3	11	24.4
Coronary heart disease	18	43.9	21	46.7
Arterial hypertension and coronary heart disease	11	26.8	13	28.9
Obesity	20	48.8	17	37.8
Excessive body weight	16	39.0	19	42.2
Dyslipidemia	31	75.6	29	64.4
Permanent form of atrial fibrillation	14	34.1	16	35.6
Violation of glucose tolerance	23	56.1	21	46.7

The BMI was significantly lower ($p < 0.01$) in patients of the 1st group 28.3 ± 1.6 kg/m² compared to the 2nd group – (31.7 ± 1.4) kg/m². The mean level of systolic blood pressure (sBP) and diastolic blood pressure (dBP) in the study groups did not differ significantly ($p > 0.05$): in the 1st group sBP was 155 ± 1.9 and dBP 89 ± 2.3 against 158 ± 2.3 and 91 ± 2.53 mm in patients of the 2nd group. The groups of patients did not differ significantly in terms of the duration of AH and/or CHD ($p > 0.05$). The duration of AH and/or CHD in the 1st group was 18.2 ± 2.7 years, in the 2nd group – 19.5 ± 2.3 years. Edema syndrome in the form of pasty feet up to the level of the shins was registered in 30 (73.1%) patients of the 1st group, and in 16 (35.6%) of the patients of the 2nd group.

The level of NT-proBNP was significantly higher in the 1st group – 398.4 ± 26.8 pg/ml ($p < 0.05$) and the 2nd group – 345.2 ± 26.8 pg/ml ($p < 0.05$) compared to the control group – 112 ± 11.4 pg/ml. However, the level of NT-proBNP was significantly higher in patients of the 1st group compared to patients of the 2nd group ($p < 0.05$).

The left ventricular EF in patients of both groups with CHF was significantly lower ($p < 0.05$) compared to the control group: in the 1st group it was equal to 43.1 ± 2.3 % ($p < 0.05$), in the 2nd group – 46.9 ± 1.9 % ($p < 0.05$), in the control group – 59.3 ± 2.8 %. Also, the EF index was significantly lower ($p < 0.05$) in men of the 1st group compared to men of the 2nd group.

A significantly lower ($p < 0.05$) frequency of edema, a significantly lower ($p < 0.05$) level of NT-proBNP, and a significantly higher ($p < 0.05$) EF in patients of the 2nd group compared to patients of the 1st group may indicate effectiveness of constant use of basic therapy with loop diuretics by patients with CHF.

The mean index of the T-criterion in the control group was (-0.78 ± 0.12) SD. In the 1st group was significantly lower ($p < 0.05$) compared to the 2nd group: (-2.72 ± 0.10) SD vs (-2.54 ± 0.12) SD, respectively.

The index of the T-criterion in 19 (46.3%) of the 1st group was (-2.83 ± 0.09) SD, which corresponded to the OP, in 18 (43.9%) – the T-criterion was (-2.35 ± 0.08) SD, which indicated the presence of Op in 4 (9.8%) patients. BMD corresponded to a normal index (-0.92 ± 0.08) SD. In the 2nd group, 15 (33.4%) patients with OP had a T-criterion of (-2.69 ± 0.07) SD, 24 (53.3%) men had a T-criterion of OP (-2.04 ± 0.11) SD and in 6 (13.3%) BMD was normal (T-criterion – (-0.81 ± 0.09) SD) (Fig. 1 A).

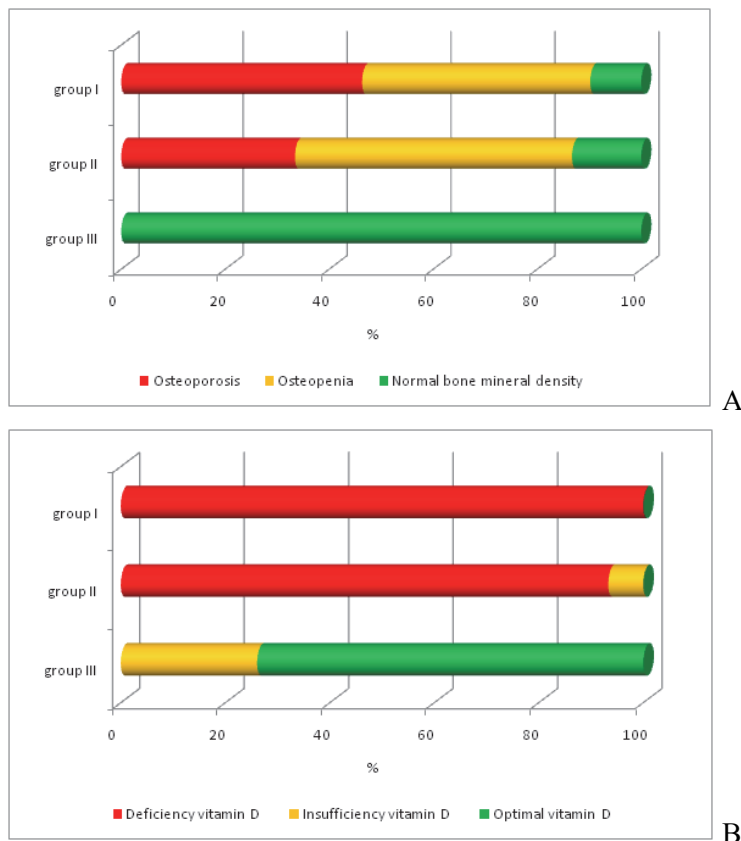


Fig. 1. Condition of bone mineral density in the study groups (A) and frequency of deficiency and insufficiency of vitamin D in the study groups (B)

and the 2nd groups did not have a significantly significant difference ($p > 0.05$), but it indicated suppression of bone tissue formation processes in patients with CHF.

The level of OPG in the control group was 2.43 ± 0.12 pmol/l, in the 1st group – 1.23 ± 0.13 pmol/l, which is by 49.3 % lower ($p < 0.01$) index of the 3rd group, in the 2nd group – 1.56 ± 0.12 pmol/l, which is 36.8% lower ($p < 0.01$) compared to the 3rd group.

The mean level in the 1st group was 13.1 ± 1.4 ng/ml, ($p < 0.05$), in the 2nd group – (16.3 ± 1.2) ng/ml, ($p < 0, 05$), in the 3rd group – 30.5 ± 2.1 ng/ml. The level of 25(OH)D in the 1st group corresponded to DVD in 41 (100 %) patients. In the 2nd group DVD was registered in 42 (93.3 %) patients, 3 (6.7 %) men had IVT. In the control group, 6 (26.1 %) men had IVD and 17 (73.9 %) men had OVD (Fig. 1B).

The level of PTH was significantly higher in the groups of patients with CHF: the 1st group – 49.7 ± 1.6 pg/ml, ($p < 0.05$), in the 2nd group – 47.7 ± 1.5 ng/ml, ($p < 0.05$) compared to the 3rd group – 32.740 ± 1.5 pg/ml. However, it was not different in both groups ($p > 0.05$).

The study of indices of phosphorus-calcium metabolism did not reveal a significant ($p > 0.05$) increase in the level of total and ionized calcium in the blood serum of patients with hypertension and coronary heart disease complicated by CHF. The content of total calcium in the 1st group was 2.26 ± 0.03 mmol/l ($p > 0.05$), in the 2nd group – 2.24 ± 0.02 mmol/l ($p > 0.05$), in the 3rd group – 2.29 ± 0.02 mmol/l. Ionized calcium in the 1st group – 1.23 ± 0.02 mmol/l ($p > 0.05$), in the 2nd group – 1.22 ± 0.01 mmol/l ($p > 0.05$), in the 3rd group – 1.25 ± 0.02 mmol/l.

Phosphorus level in patients of the 1st and the 2nd groups was significantly reduced – 0.84 ± 0.01 mmol/l ($p > 0.05$) and 0.96 ± 0.02 mmol/l ($p > 0.05$), respectively, compared to the 3rd group – 1.12 ± 0.02 mmol/l. A significant difference was found between the level of phosphorus in the 1st and the 2nd groups ($p < 0.05$), a lower level of phosphorus was recorded in men of the 1st group.

Correlation analysis showed the presence of a moderate direct relationship between the EF index and the level of OC ($r = 0.585$; $p = 0.012$), a strong direct relationship between the EF index and the OPG level ($r = 0.751$; $p = 0.001$), the level of NT-proBNP and the level of CTx ($r = 0.564$; $p = 0.001$), a weak inverse relationship between the level of NT-proBNP and the level of OC ($r = -0.351$; $p = 0.002$), a weak inverse relationship between the level of NT-proBNP and T -criterion ($r = -0.325$; $p = 0.008$).

The performed correlation analysis permits to believe that the EF index has a reliable direct very strong influence on the level of 25(OH)D in the examined patients, as evidenced by the correlation index ($r = 0.876$; $p = 0.001$).

Against the background of reduced BMD in the groups of patients with CHF, a significant ($p < 0.05$) increase in the bone tissue resorption marker (CTx) was found. In the control group, the CTx level was 0.31 ± 0.03 ng/ml, in the 1st group – 0.69 ± 0.04 ng/ml, which is 55.1% higher compared to the 3rd group ($p < 0.05$), in the 2nd group – 0.54 ± 0.03 ng/ml, which is 42.6% higher than the CTx level of the control group ($p < 0.05$). An increase in the CTx marker indicates accelerated bone tissue resorption in the study groups. However, more pronounced bone tissue resorption was found in the group of patients who were on basic CHF therapy and used loop diuretics ($p < 0.05$).

The concentration of the bone formation marker (OC) in the first group of patients was 12.8 ± 1.7 , which is 29.2% lower ($p < 0.05$) than the index of the control group 18.1 ± 1.5 ng/ml, in the 2nd group – 13.1 ± 1.8 ng/ml and was 27.6 % lower ($p < 0.05$) compared to the 3rd group. The level of OC in the 1st

Correlation analysis for the purpose of investigating the effect of EF on the CTx level showed the presence of a reliable inverse strong direct relationship between the studied indices, as evidenced by the coefficient of determination ($r = -0.832$; $p = 0.001$). In order to study the influence of EF on the state of BMD, a reliable moderate direct relationship was established, as evidenced by the correlation index ($r = 0.613$; $p = 0.014$).

Correlation analysis suggests that the level of NT-proBNP has a reliable strong inverse relationship with the level of 25(OH)D in blood serum, the index of determination ($r = -0.775$; $p = 0.015$). Correlation analysis to investigate the effect of NT-proBNP level on OPG level showed the existence of a reliable moderate inverse relationship between the studied indices, as evidenced by the coefficient of determination ($r = -0.598$; $p = 0.018$), (Fig. 2).

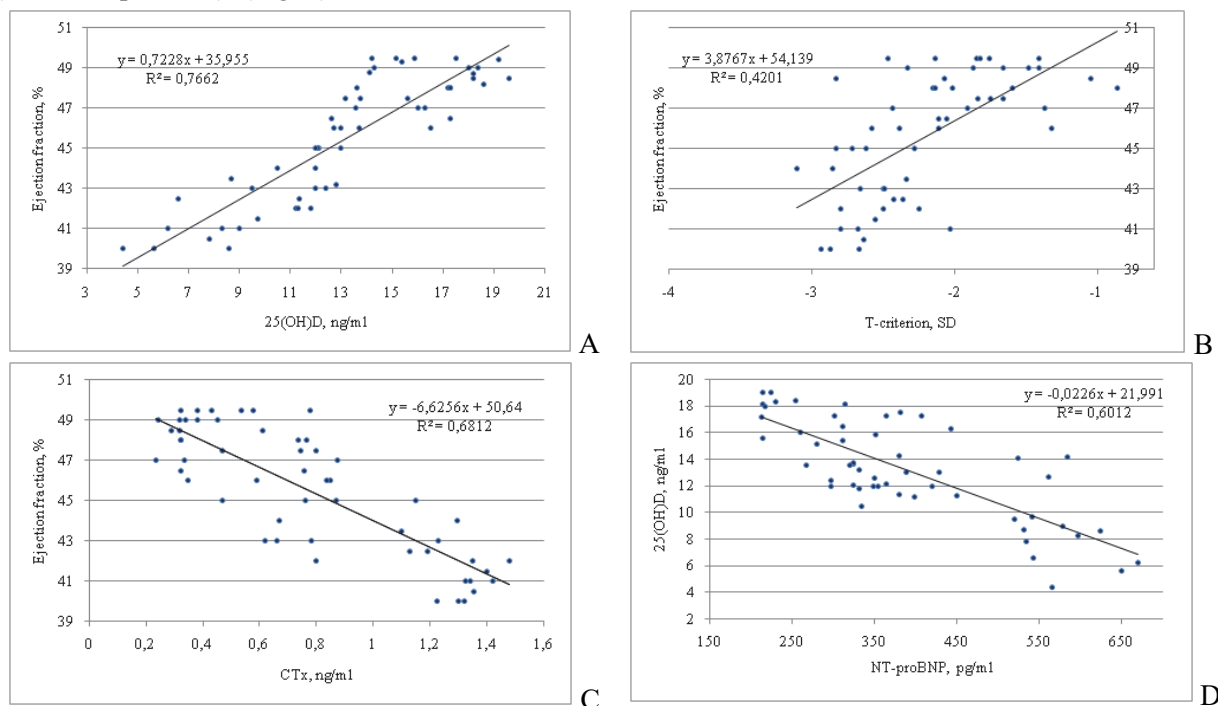


Fig. 2. Linear regression of the ejection fraction and level dependence 25-hydroxyvitamin D (A), the level of type I collagen C-telopeptide (B) and the T-criterion index (C) and of the level of natriuretic hormone N-terminal polypeptide and the level of 25-hydroxyvitamin D in patients with chronic heart failure

A violation of bone remodeling processes with a predominance of bone resorption against the background of slowed bone tissue formation was found ($p < 0.05$) for men with hypertension and coronary heart disease, complicated by CHF stage “C” with moderately reduced left ventricular EF functional class III according to NYHA. Significantly ($p < 0.05$) pronounced changes were found in the group of patients, who took loop diuretics, compared to the group of patients who received only basic therapy for CHF. The results may indicate diuretics' negative effect on BMD and bone remodelling processes.

The revealed imbalance in the system of osteoclastogenesis is manifested by a significant ($p < 0.05$) decrease in the level of OPG in men with CHF. However, significantly lower ($p < 0.05$) OPG indices were recorded in men who were on basic CHF pharmacotherapy and loop diuretic therapy.

The obtained inverse moderate correlation between the level of OPG and the level of NT-proBNP ($r = -0.598$; $p = 0.018$) and a strong inverse relationship between the level of CTx and the left ventricular EF ($r = -0.832$; $p = 0.001$) demonstrate common pathogenetic the mechanisms of influence on the processes of bone remodeling in patients with CHF.

The frequency of OP in patients of the I group was significantly higher compared to the II group – 46.3 % and 33.4 % ($p < 0.05$), respectively, and the frequency of Op was significantly lower – 43.9 % and 53.3 % ($p < 0.05$) respectively, indicating lower BMD values in patients who received basic therapy and loop diuretics. The presence of a moderate correlation between the left ventricular EF index and the T-criterion ($r = 0.613$; $p = 0.014$), an inverse relationship between the level of NT-proBNP and the T-criterion ($r = -0.325$; $p = 0.008$) indicates a negative influence CHF on the state of BMD.

Deficiency of vitamin D and IVD, a significantly higher ($p < 0.05$) level of PTH and a low level of phosphorus demonstrate the presence of disturbances in phosphorus-calcium metabolism and indicate the presence of an imbalance in the system of hormonal regulation of calcium homeostasis in patients with AH and CHD complicated by CHF. A significant direct correlation was established between the level of 25(OH)D and the left ventricular EF index ($r = 0.876$; $p = 0.01$), a significant inverse relationship between

the level of 25(OH)D and by the level of NT-proBNP ($r=-0.775$; $p=0.015$), which indicates the adverse effect of a low level of 25(OH)D on the state of the cardiovascular system, where DVD is an independent risk factor for the severe course of CHF.

Therefore, the obtained results are generally consistent with those previously published. This is also true in relation to changes in the structure of bone tissue in cardiac patients [2, 14] and in relation to the effect of diuretics [11, 13]. However, in our work, both theses were studied simultaneously on the basis of data obtained from similar groups of patients under the same conditions. Also, the correlation was calculated on a wider range of indices. This makes possible to better understand the bones reactions for patients with heart diseases.

Conclusion

In patients with chronic heart failure, a violation of bone remodeling processes with a predominance of bone tissue resorption against the background of slowed bone formation was found ($p<0.05$). The level of osteoprotegerin is a predictor of bone mass loss and indicates a violation of bone remodeling processes.

The frequency of osteoporosis and osteopenia in patients with arterial hypertension and coronary heart disease complicated by chronic heart failure, who were on basic therapy and took loop diuretics was 46.3 % and 43.9 %, respectively, in patients who were only on basic therapy - 33, 4 % and 53.3 %, respectively.

Vitamin D deficiency is an independent risk factor for the severe course of chronic heart failure and requires timely diagnosis and correction.

Basic therapy of chronic heart failure in combination with loop diuretics for a long time has a negative effect on the state of mineral density of bone tissue, indices of bone remodeling and phosphorus-calcium metabolism.

Prospects for further research are aimed at the development of algorithms for timely diagnosis and correction of identified structural and functional disorders of bone tissue in patients with chronic heart failure in order to prevent the development of osteoporotic fractures.

References

1. Adamo M, Gardner RS, McDonagh TA, Metra M. The 'Ten Commandments' of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2022; 43(6): 440–441. doi: 10.1093/eurheartj/ehab853.
2. Bhatta L, Cepelis A, Vikjord SA, Malmo V, Laugsand LE, Dalen H. et al. Bone mineral density and risk of cardiovascular disease in men and women: the HUNT study. *Eur J Epidemiol*. 2021; 6(11): 1169–1177. doi:10.1007/s10654-021-00803-y
3. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017; 19(12): 1574–1585. doi: 10.1002/ehfj.813.
4. Fang Y, Wang L, Xing W, Qing W, Qian T, Yanbo Yu. et al. Bone mineral density in older patients with chronic heart failure is related to NYHA classification: a retrospective study. *Eur Geriatr Med*. 2018; 9(2):183–189. doi:10.1007/s41999-018-0027-5
5. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP. et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline *J Clin Endocrinol Metab*. 2011; 96(7):1911–1930. doi:10.1210/jc.2011-0385
6. Kadam UT, Roberts I, White S, Bednall R, Khunti K, Nilsson PM, Lawson CA. Conceptualizing multiple drug use in patients with comorbidity and multimorbidity: proposal for standard definitions beyond the term polypharmacy. *J Clin Epidemiol*. 2019; 106: 98–107. doi: 10.1016/j.jclinepi.2018.10.014.
7. Paik JM, Rosen HN, Gordon CM, Curhan GC. Diuretic Use and Risk of Vertebral Fracture in Women. *Am J Med*. 2016; 129(12): 1299–1306. doi: 10.1016/j.amjmed.2016.07.013.
8. Špinar J, Špinarová L, Vítovec J. Pathophysiology, causes and epidemiology of chronic heart failure. *Vnitr Lek*. 2018; 64(9): 834–838.
9. Shaposhnyk OA, Prykhotko NP, Savchenko LV, Shevchenko TI, Sorokina SI, Yakymyshyna LI, et al. Clinical and diagnostic aspects of managing patients with valvular heart disease. *World of medicine and biology*. 2022; 80(2): 178–183. <http://dx.doi.org/10.26724/2079-8334-2022-2-80-178-183>
10. Shevroja E, Cafarelli FP, Guglielmi G, Hans D. DXA parameters, Trabecular Bone Score (TBS) and Bone Mineral Density (BMD), in fracture risk prediction in endocrine-mediated secondary osteoporosis. *Endocrine*. 2021; 74(1): 20–28. doi: 10.1007/s12020-021-02806-x.
11. Velliou M, Sanidas E, Zografou A, Papadopoulos D, Dalianis N, Barbetseas J. Antihypertensive Drugs and Risk of Bone Fractures. *Drugs Aging*. 2022;39(7):551–557. doi:10.1007/s40266-022-00955-w
12. Voronkov LH, Berezin OE, Zharinov OI. Comorbidity in chronic heart failure. Recommendations of the All-Ukrainian Association of Cardiologists of Ukraine and the All-Ukrainian Association of Heart Failure Specialists. *Heart failure. Klinichna praktyka*. No. Vyd. Kyiv „ART STUDIa DRUKU“, 2020; (2): 54–57
13. Xiao F, Qu X, Zhai Z, Jiang C, Li H, Liu X, Ouyang Z, Gu D. Association between loop diuretic use and fracture risk. *Osteoporos Int*. 2015; 26(2):775–784. doi: 10.1007/s00198-014-2979-8.
14. Xing W, Lv X, Gao W, Wang J, Yang Z, Wang S. et al. Bone mineral density in patients with chronic heart failure: a meta-analysis. *Clin Interv Aging*. 2018; 13: 343-353. doi: 10.2147/CIA.S154356.
15. Zhang Y, Zhang J, Ni W, Yuan X, Zhang H, Li P. et al. Sarcopenia in heart failure: a systematic review and meta-analysis. *ESC Heart Fail*. 2021; 8(2):1007–1017. doi:10.1002/ehf2.13255

Стаття надійшла 30.07.2022 р.