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MINERALIZATION OF BONES IN PATIENTS WITH CORONARY HEART DISEASE COMPLICATED BY CHRONIC HEART FAILURE AND PHARMACOLOGIC MANAGEMENT

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Abstract

Our study aims to investigate the effect of combined calcium with vitamin D3 supplement called "calcemin-advance" and calcitonin in the prophylaxis and treatment of osteopenia and osteoporosis in patients with coronary heart disease complicated by chronic heart failure with the establishment of their influence on the bone mineral density.

Totally 59 patients with coronary heart disease complicated by chronic heart failure. Interventions: The physical examination findings, Dual-energy X-ray absorptiometry findings and treatment results were assessed.

The results of the calcemin-advance usage in patients with osteopenic changes showed a positive dynamics of the studied parameters, both in the lumbar spine and in the femoral bone. In patients with osteoporosis the usage of osteoprotective therapy (calcemin-advance+miacalcic) contributed to the increasing of bone mineral density in lumbar spine and in the femoral bone vs patients who received only combined calcium with vitamin D3 supplement.

Our results suggest that bone density screening could be recommended in patients with prevalent chronic heart failure. Moreover, the results of our investigation substantiate the necessity and effectiveness of osteoprotective therapy in patients with chronic heart failure with osteoporosis by calcitonin (miacalcic), in combination with combined calcium and vitamin D3 supplement (calcemin-advance), and by only calcemin-advance in patients with chronic heart failure and osteopenia.

Keywords: *chronic heart failure, osteopenia, osteoporosis, therapy.*

Introduction

Cardiovascular disease remains a leading cause of morbidity and mortality, despite improvements in outcomes [*Benjamin E et al., 2016; Piepoli M et al., 2016; Mozaffarian D, 2017; Marushchak M et al., 2019a*]. It accounts for 31% of mortality, the majority of this in the form of coronary heart disease (CHD) and cerebrovascular accident [*Stewart J et al., 2017*].

Chronic heart failure (CHF) is a syndrome rather than a disease, the cause of which may be structural or functional. Whatever be the underlying cause, the cardinal symptoms are dyspnea and fatigue leading to a progressive decrease in exercise capacity [*Pai S et al., 2016*]. The prevalence of CHF is ~2% of the general population in the developed countries, increasing to ~10% among people >70 years of age; moreover, the prevalence increased with age in both men and women. CHF is a chronic multisystem disorder associated with a myriad of metabolic disturbances. Moreover, CHF may adversely affect bone metabolism and induce a severe bone loss, increasing susceptibility to fractures and osteoporosis [*Krynytska I et al., 2017; Xing W et al., 2018*]. It should be noted that

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CHF and osteoporosis are often diagnosed in the same patient [*Schulz E et al., 2004*].

Therefore, both chronic heart failure and osteoporosis are common causes of loss of function and independence and have become a heavy burden on the health care system [*Yarema N et al., 2020*]. Our previous studies showed that structural and functional changes in the bone tissue of the lumbar spine were found in 75.9% of patients with stage 1 of CHF caused by ischemic heart disease: 64.4% of patients had osteopenic syndrome, and 11.5% - osteosclerotic changes. In 75.8% of CHF patients we have found structural and functional changes in the bone tissue of proximal right femur [*Marushchak M et al., 2018*]. Structural and functional changes of bone tissue of the lumbar spine have been found in 49.2% of patients with CHD complicated by stage 2-A CHF, in particular, 1st stage of osteopenia – in 44.6%, 2nd stage of osteopenia – in 27.7%, 3th stage of osteopenia – in 10,8 % and osteoporosis – in 16.9% [*Krynytska I et al., 2017*].

This study aims to investigate the effect of combined calcium with vitamin D3 supplement called "calcemin-advance" and calcitonin in the prophylaxis and treatment of osteopenia and osteoporosis in patients with CHD complicated by CHF with the establishment of their influence on the bone mineral density (BMD).

MATERIAL AND METHODS

The study involved 59 patients with CHD complicated by CHF (according to the classification by N.D. Strazhesko ND and coautors (1935).

The average age of patients was 57.91±9.30 years. Their BMI exceeded normal range (set at less than 25 *kg/m²*) and was in the range of subcompensated obesity - 28.04±2.12 *kg/m²*. Clinical characteristics of the patients were as follows: the disease duration ranged from 2 to 20 years, the underlying disorder mainly was cardiosclerosis. In patient's history were found bad habits: 16 – smoking, 4 – alcohol abuse, 12 – caffeine abuse (4-5 cups of coffee per day). A history of fractures was found in 9 persons.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

The patients did not have other severe comorbidities that could have caused changes in bone tissue. All study participants were hospitalized patients and had given written consent for their clinical data to be used in the study. All reported research conducted in accordance with the principles set forth in the Helsinki Declaration (2008).

Diagnosis of CHD was confirmed using a set of characteristic anamnestic, clinical (typical angina attacks with physical and psycho-emotional stress), biochemical (increased total cholesterol and total lipids levels) and ECG (ST segment depression below the baseline, T-wave inversion) data. To confirm the diagnosis, we also used data obtained during physical examination, such as enlarged to the left heart boundaries, weakened sound of the top tone, stress of the second tone above the aorta, changes in blood pressure and heart rate.

In order to verify the diagnosis of heart failure we have used main limiting factors of physical performance and clinical symptoms: dyspnea, tachycardia, and fatigue after exertion. The final diagnosis of chronic heart failure with systolic dysfunction was given, based on the results of echocardiography test.

Dual-energy X-ray absorptiometry (DXA) is widely used for measuring bone mineral density (BMD), because of its recognized precision. The method utilizes two measurements, T-score and Z-score. The first one is calculated when the patient's BMD is subtracted from mean BMD of a population of healthy young adults, matched The T-score is calculated as a number of SDs the patient's measured BMD is above or below the mean for population of healthy 30-year adults, matched for sex and ethnicity. The Z-score is expressed in units of the population SD, but instead of comparing the patient's BMD to the mean of young adult population, it is compared with the mean BMD of a healthy population matched for age, sex and ethnicity. In this study, we evaluated the scores ac-

cording to the WHO guidelines (WHO, Geneva, 1994): BMD >1.2 *g/sm²* is classified as osteosclerosis; a T-score ≥ –1 is regarded as normal, and T-score between –2.5 and -1 is classified as osteopenia [*Smiyan S et al., 2002*].

Standard therapy for patients with CHF included the use of an angiotensin-converting enzyme inhibitor, β-adrenoblocker, diuretic, cardiac glycoside according to the recommendations of the Ukrainian Association of Cardiologists for the diagnosis, treatment and prevention of CHF. Patient's therapy was as standardized as possible. Before the survey, patients did not receive antiresorptive drugs for the prophylaxis and treatment of osteoporosis.

To study the effects of the combined calcium with vitamin D3 supplement (calcemin-advance) and calcitonin (miacalcic) on bone tissue, the patients were distributed as follows. We have used Calcemin-Advance (Sagmel, Inc. USA), which consist of Calcium Carbonate 1312 *mg*, Vitamin D3 200 *IU*, Magnesium Oxide 40 *mg*, Zinc Oxide 7.5 *mg*, Copper 1.0 *mg*, Sodium Borate 2.45 *mg*).

The first group (12 persons) consisted of patients with normal BMD, which was carried out only standardized therapy.

The second group of patients (13 persons) received the same standardized therapy as the first group, but there BMD was characterized by osteopenic changes.

The third group of patients (15 persons) with osteopenic changes, in addition to standard therapy, was prescribed combined calcium with vitamin D3 supplement - calcemin-advance. Calcemin-advance therapy was performed for 3 months (1 tablet 2 times per day).

The fourth group of patients (10 persons) received the same therapy as the third one, but changes in bone tissue were consistent with osteoporosis.

The fifth group of patients (9 persons) with diagnosed osteoporosis received the same therapy as the fourth group, and calcitonin (miacalcic). Miacalcic (salmon calcitonin, Switzerland) was administrated according to the scheme, depending on the degree of osteogenic changes (100 *IU* per day intramuscularly every other day during the first month, 200 *IU* per day every day intranasal – second and third month). In parallel, patients received calcemin-advance for 1 tablet 2 times per day for 3 months. The effectiveness of therapy with was evaluated after 3 months.

Results and discussion

The analysis of the therapy effectiveness showed that standard therapy does not decrease bone resorption processes, and leads to loss of 1.6 % of bone mass in patients with normal BMD and 3.8 % in patients with osteopenic changes. The results of the calcemin-advance usage in patients with osteopenic changes showed a positive dynamics of the studied parameters, both in the lumbar spine and in the femoral bone. Thus, an additional therapy with calcemin-advance in patients with CHF and osteopenia of different stage caused a statistically significant increase in BMD in the first two lumbar vertebrae with a simultaneous decrease in the manifestations of the toxic component and pain syndrome in the heart failure clinical manifestations (table 1). Modified therapy with the inclusion of calcemin-advance to standard therapy enhances bone mineralization in patients of third group in the femoral neck by 3.3 %, in Ward's triangle – by 10.8 %, in greater trochanter – by 8.6 % and in proximal femur – by 1.0 % vs BMD indices in these patients before treatment (table 2).

In patients with osteoporosis the usage of osteoprotective therapy (calcemin-advance + miacalcic) contributed to the increasing of bone mineral density at L_1 region by 16.0 % ($p<0.01$), L_2 – by 9.5 % ($p<0.05$) vs patients who received only combined calcium with vitamin D3 supplement (table 1).

Modified therapy with the inclusion of calcemin-advance and miacalcic to standard therapy enhances bone mineralization in patients of 5th group in the femoral neck by 7.4 %, in Ward's triangle – by 11.1 %, in greater trochanter – by 9.8 % and in proximal femur – by 8.1 % vs BMD indices in patients of 4th group who received only combined calcium with vitamin D3 supplement (table 2).

Also it should be noted that the rate of BMD reduction and its restoring with the use of osteoprotective therapy depends on the stage of osteodeficiency. So, in the presence of osteoporosis patients

Table 1

BMD of lumbar vertebrae in patients with CHF and osteopenia, before and after the therapy (M±m).

Status	Before therapy	After therapy
2nd group (n=13)		
L_1	1.02±0.02	0.96±0.02*
L_2	1.10±0.03	1.06±0.03
L_3	1.12±0.02	1.05±0.02*
L_4	0.98±0.03	1.02±0.03
3rd group (n=15)		
L_1	0.97±0.02	1.05±0.03*
L_2	1.05±0.02	1.12±0.02*
L_3	1.10±0.02	1.14±0.02
L_4	1.12±0.02	1.15±0.02
4th group (n=9)		
L_1	0.81±003	0.75±0.02
L_2	0.85±0.03	0.84±0.03
L_3	0.92±0.03	0.90±0.03
L_4	0.94±0.03	0.92±0.04
5th group (n=9)		
L_1	0.78±0.03	0.87±0.02*
L_2	0.87±0.04	0.92±0.04
L_3	0.92±0.03	0.94±0.03
L_4	0.87±0.02	0.89±0.03

Note: ** – significant difference before vs after therapy.*

lose more bone mass faster, but bone tissue faster is restored with the application of adequate treatment.

The research made by Lewiecki E. and co-authors have indicated that bone microarchitectural changes associated with bone loss are largely irreversible. Although, treatment can increase BMD and reduce the risk of fracture, it is unlikely to fully restore the quality and strength of bone to normal. BMD in adults is determined by peak bone mass (PBM), which is the maximum bone mass achieved in life, and the subsequent rate of bone loss. The prevention of osteoporosis or low BMD is directed to maximizing PBM and minimizing the rate of bone loss, with the ultimate goal of maintaining bone strength and preventing fractures. Stabilizing BMD or reducing the rate of bone loss is the primary objective in the prevention of osteoporosis [*Lewiecki E, Silverman S, 2006*].

Osteoporosis is a systemic metabolic bone disease, which is characterized by decrease of bone mass, as well as degeneration of bone microstructure and is prone to lead to fracture due to increasing bone fragility. Increased osteocyte apoptosis has been correlated with sites of rapid bone turnover [*Hock J et al., 2001; Marushchak M et al., 2017*]. In Europe, osteoporosis accounts for more disability-adjusted life years than many non-communicable diseases including rheumatoid arthritis, Parkinson's disease, breast cancer and prostate cancer [*Johnell O, Kanis J, 2006*]. Although plenty of studies on osteoporosis and cardiovascular diseases have been carried out there are still some

Table 2

BMD of femoral bone in patients with CHF and osteopenia, before and after the therapy (M±m).

Status	Before therapy	After therapy
2nd group (n=13)		
neck	0.92±0.02	0.94±0.03
Ward triangle	0.82±0.03	0.74±0.02*
trochanter	0.89±0.03	0.90±0.03
total	1.04±0.02	1.04±0.03
3rd group (n=15)		
neck	0.91±0.03	0.94±0.03
Ward triangle	0.74±0.02	0.82±0.03*
trochanter	0.81±0.03	0.88±0.02*
total	0.99±0.03	1.00±0.03
4th group (n=9)		
neck	0.78±0.04	0.81±0.05
Ward triangle	0.57±0.04	0.63±0.05
trochanter	0.72±0.04	0.71±0.04
total	0.86±0.05	0.86±0.05
5th group (n=9)		
neck	0.86±0.02	0.87±0.02
Ward triangle	0.65±0.01	0.70±0.03
trochanter	0.77±0.03	0.78±0.04
total	0.92±0.03	0.93±0.03

Note: ** – significant difference before vs after therapy.*

controversies on the findings [*Lian X et al., 2017*].

Li S. and co-authors suggest that patients with osteoporosis have higher risk of CHD than those without osteoporosis. Patients who have osteoporosis and have received treatment with bisphosphonates have a significantly lower risk for CHD than those without treatment [*Li S et al., 2014*]. In the placebo branch of the MORE study, osteoporosis (T-score< -2.5 at the spine or the femoral neck) was associated with a fivefold higher risk of cardiovascular event (for example, stroke, myocardial infarction). In a group of 6800 men and women (MONICA and Västerbotten Intervention Programme databases), low hip BMD was associated with higher risk of myocardial infarction [*Farhat G, Cauley J, 2008*].

Potential mechanisms for the link between osteoporosis and cardiovascular disease remain unknown. One hypothesis puts forth that the coexistence of osteoporosis and cardiovascular disease is due to their shared etiological factors (such as smoking, physical activity, alcohol intake, menopause, hypertension, etc) [*Chernatska O, Demikhova N, 2018*], which may simultaneously promote or inhibit atherosclerosis and bone demineralization. However, in many epidemiologic studies, the association between osteoporosis and cardiovascular disease remained even after the adjustment of some of these risk factors. Secondly, common pathophysiological mechanisms are implicated in the progression of the two conditions: inflammatory cytokines, endogenous sex hormones, oxidized lipids, vitamin K deficiency, and vitamin D. Thirdly, coexistence of osteoporosis and cardiovascular disease may be due to common genetic factors. Genom-wide association studies have identified several genes and single nucleotide polymorphisms associated with BMD, and CVD risk factors or metabolic traits [*Estrada K et al., 2012*].

Calcium supplements marginally reduce the risk of fracture and observational studies suggest that high calcium intake might protect against vascular disease, and the findings are consistent with those of interventional studies of calcium supplements that show improvement in some vascular risk factors [*Bolland M et al., 2012*]. On another hand calcification in the aorta and coronary arteries may increase cardiovascular risk through the activation of bone morphogenetic protein, alkaline phosphatase, osteopontin and matrix GLA protein [*Uyl D et al., 2011*].

CONCLUSION

Our results suggest that bone density screening could be recommended in patients with prevalent chronic heart failure. Moreover, the results of our investigation substantiate the necessity and effectiveness of osteoprotective therapy in patients with CHF with osteoporosis by calcitonin (miacalcic), in combination with combined calcium and vitamin D3 supplement (calcemin-advance), and by only calcemin-advance – in patients with CHF and osteopenia.

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