Original article:

Investigation of calcium metabolism in patients with coronary heart disease complicated by chronic heart failure, stage ii-a

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Abstract:

Objective: This study aims to to investigate calcium metabolism indices and bone mineralization in patients with coronary heart disease complicated by stage II-A chronic heart failure. ***Materials and Methods:*** The study involved 33 men with coronary heart disease (CHD) complicated by Stage II-A chronic heart failure (according to the classification by N.D. Strazhesko, V.H. Vasilenko and G.F. Lung (1935). Bone mineral density was measured using dual energy x-ray densitometry of lumbar region of spine. The level of 25-hydroxyvitamin D (25(OH)D) has been detected by ELISA method using commercial Vitamin D3 screening kit (Switzerland). The level of ionized calcium was measuring by ion selective method using analyser of electrolytes AEK-01 (QuertiMed, Ukraine). ***Results and Discussion:*** Structural and functional changes of bone tissue of the lumbar spine have been found in 49,2 percent patients with coronary heart disease complicated by Stage II-A chronic heart failure, in particular, I stage of osteopenia – in 44,6 %, II stage of osteopenia – in 27,7 %, III stage of osteopenia – in 10,8 % and osteoporosis – in 16,9 %. It was established the same type of downward trend for BMD decreasing in L_1 of patients with different stages of osteopenia, but in case of osteoporosis mineralization decreased equally in all vertebrae. The analysis of calcium metabolism indices indicate that concentration of ionized calcium significantly decreased in patients with CHD complicated by Stage II-A chronic heart failure vs control (1.26±0.02 mmol/l) by 11.1 % (I stage of osteopenia), 18.3 % (II stage of osteopenia) and 31.7 % (III stage of osteopenia). Similar tendency was observed towards concentration of 25(OH)D. ***Conclusion:*** In patients with CHD complicated by Stage II-A chronic heart failure we have established statistically significant decrease in serum level of ionized calcium and 25-hydroxyvitamin D concentration. However, we didn't find the relationship between serum calcium, 25-hydroxyvitamin D concentration and bone mineral density. Structural and functional changes of bone tissue of the lumbar spine have been found in 49,2 percent patients with coronary heart disease complicated by Stage II-A chronic heart failure. It was established the same type of downward trend for BMD decreasing in L_1 of patients with different stages of osteopenia, but in case of osteoporosis mineralization decreased equally in all vertebrae.

Keywords: coronary heart disease, ionized calcium, 25-hydroxyvitamin D, bone mineral density.

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Introduction: Cardiovascular diseases (CVD) and osteoporosis are important causes of morbidity and mortality in the elderly [1, 2]. Osteoporosis is a serious public health concern with an estimated worldwide incidence of over 200 million. Approximately 30% of postmenopausal women in developed countries have osteoporosis and at least 40% of women and 15–30% of men will sustain a fracture; the risk of a further fracture is increased by 50–100%. The worldwide annual incidence of hip fracture is 1.7 million [3].

Traditionally osteoporosis and CVD were considered unrelated and their coexistence has been attributed to independent processes exclusively related to age. However, the majority of the studies have shown that individuals with CVD have a higher risk of experiencing bone loss and thus greater predisposition to risk of fracture [4]. On the other hand there is growing evidence that individuals with low bone mass have higher mortality for cardiovascular events compared to patients with cardiovascular disease with normal bone mass [2].

The nature of the putative link between osteoporosis and CVD remains unclear. It could be firstly explained by their common risk factors such as age, smoking, alcohol consumption, physical activity and menopause [3].

Moreover, vascular calcification is an independent risk factor for CVD. Potential links underlying both diseases may be related to the calcification process that is involved in atherosclerosis and bone mineralization. Mineralization is of particular interest because numerous noncollagenous bone-related proteins mediating bone resorption have also been implicated in calcification and ossification in the vascular intima [1]. Calcification of any artery or cardiac valve increases the risk of cardiovascular events and mortality threefold to fourfold and is accepted as a predictor of coronary heart disease (CHD) [5].

To identify targets for early diagnosis and therapeutic intervention, it is essential to understand the molecular and cellular basis of calcium handling and the signaling pathways governing the functional remodeling associated with HF in humans. Calcium (Ca^{2+}) cycling is an essential mediator of cardiac contractile function, and remodeling of calcium handling is thought to be one of the major factors contributing to the mechanical and electrical dysfunction observed in HF [6].

This study aims to investigate calcium metabolism indices and bone mineralization in patients with CHD complicated by stage II-A chronic heart failure.

Material and Methods: The study involved 33 men with CHD complicated by Stage II-A chronic heart failure (according to the classification by N.D. Strazhesko, V.H. Vasilenko and G.F. Lung (1935).

The average age of patients was 57.91±9.30 years. Their BMI exceeded normal range (set at less than 25 kg/m^2) and was in the range of subcompensated obesity, 28.04± 2.12 kg/m^2. Clinical characteristics of the patients were as follows: the disease duration ranged from 2 to 20 years, the underlying disorder mainly was cardiosclerosis. In patients' history were found bad habits: 16 - smoking, 4 - alcohol abuse, 7 - caffeine abuse (4-5 cups of coffee per day). A history of fractures was found in 4 persons.

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 corroborate 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 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 according to the WHO guidelines (WHO, Geneva, 1994): BMD >1.2 g/sm^2 is classified as osteosclerosis; a T-score ≥ –1 is regarded as normal, and T-score between –2.5 and -1 is classified as osteopenia.

The level of 25-hydroxyvitamin D (25(OH)D) has been detected by ELISA method using commercial Vitamin D3 screening kit (Switzerland). The level of ionized calcium was measuring by ion selective method using analyser of electrolytes AEK-01 (QuertiMed, Ukraine).

The control population samples were selected from a densitometric database of healthy individuals maintained at the medical diagnostic center of Ternopil State Medical University and designated as Young Adults and Age Matched groups [7].

The results were analysed using Statistica 7.0 software and presented as mean with standard deviations. To evaluate the distribution of the character together by sampling data we have used Lillieforsa and Kolmogorov-Smirnov tests. The differences between all groups were determined using one-way ANOVA, followed by post hoc Least Significant Difference test. A p-value of <0.05 was considered statistically significant.

Results and Discussion: Densitometry analysis of lumbar segment of patients with CHD complicated by Stage II-A chronic heart failure showed normal BMD or signs of osteodeficiency. Thus, at L_1 level osteopenia was diagnosed in 51,5 % patients, L_2 – 51,5 %, L_3 – 48,5 % and L_4 – 45,5 %. Among the osteodeficient states frequently was observed osteopenia I stage in 44,6 %, osteopenia II stage – in 27,7 %, osteopenia III stage – in 10,8 % and osteoporosis was noted in 16,9 % patients .

The data presented in Table 1, have showed large number of patients with CHD complicated by Stage II-A chronic heart failure with normal BMD (50,8 %). Herewith practically identical mineralization in all vertebrae was observed. The indices of bone tissue state, expressed in units of standard deviation determined by densitometric method and analyzed comparatively to young healthy people (T), and in accordance with their age group (Z), have confirmed this statement. The average value of BMD in T-score was (-0,17±0,08), which was not significantly differed (P>0,05) of mineralization due to Z -score (-0,11±0,06).

Densitometry analysis of lumbar segment of patients with CHD complicated by Stage II-A chronic heart failure showed that in case of osteopenia I stage BMD was significantly higher (P<0,001) at the L_1 level compared with three other vertebrae. Although according to T-score mineralization equally decreased in all investigated vertebrae approximately by 7.4 times vs normal BMD of this group patients (table 1). It should be noted that in case of osteopenia I stage the indices of BMD are changing samely due to young healthy people (Young Adult) and their age group (Age Matched), because there is no significant difference (P>0,05). The average value of BMD in T-score was (-1,26±0,02), that in fact not differ from mineralization in Z-score (-1,19±0,07).

Densitometry analysis of lumbar segment of patients with CHD complicated by Stage II-A chronic heart failure showed that in case of osteopenia II stage BMD was the lowest at the L_1 level. The lowest index in Young Adult (T-score) was established at the L_4 level, which is significantly different from data of 2 patients at L_2 level ((-1,70); (-1,80)) and 4 patients at L_3 level (P<0,05) (table 1). However investigated values do not correlate with BMD indices compared with those of age, since the minimum values were in the third lumbar vertebra. Moreover, comparing the indices of "T" and "Z" score, it was established that maximum values of BMD were diagnosed in L_4, herewith the value of mineralization due to Young Adult was significantly lower (P<0,01) due to age. Besides, value of Age Matched (Z-score) at the L_4 level did'nt correspond to osteopenia II stage (-1,20±0,15) and was significantly higher compared to those of other vertebrae. The average value of BMD in T-score was (-1,75±0,05), that in fact not differ from mineralization in Z-score (-1,55±0,13).

Table 1. BMD of the lumbar spine of male patients with CHD complicated by Stage II-A chronic heart failure with normal bone tissue and osteopenia (M±m)

Vertebra number	BMD, g/cm²	Young Adult		Age Matched	
		%	T	%	Z
	normal bone tissue				
L_1 (n=16)	1,16± 0,02	100,18±1,79	0,02± 0,17	101,59± 2,17	-0,14± 0,21
P_1	>0,05	>0,05	>0,05	>0,05	>0,05
L_2 (n=16)	1,20±0,02	97,20± 1,77	-0,28± 0,18	98,87± 2,04	0,04±0,27
P_2	>0,05	>0,05	>0,05	>0,05	>0,05
L_3 (n=17)	1,21±0,02	99,35± 1,60	-0,09± 0,17	100,82± 2,08	-0,24±0,20
P_3	>0,05	>0,05	>0,05	>0,05	>0,05
L_4 (n=18)	1,19±0,02	96,88± 1,30	-0,32± 0,13	98,12± 1,76	-0,11±0,23
P_4	>0,05	>0,05	>0,05	>0,05	>0,05
	I stage of osteopenia				
L_1 (n=6)	1,00± 0,01	86,33± 0,71	- 1,30± 0,06	88,67± 2,03	-1,10± 0,21
P_1	<0,001	<0,05	>0,05	>0,05	>0,05
L_2 (n=9)	1,09±0,01	88,22± 0,36	-1,21± 0,05	88,78± 1,50	-1,18±0,18
P_2	>0,05	>0,05	>0,05	>0,05	>0,05
L_3 (n=10)	1,09±0,01	87,90± 0,43	-1,23± 0,05	89,60± 1,36	-1,09±0,16
P_3	>0,05	>0,05	>0,05	>0,05	>0,05
L_4 (n=4)	1,08±0,01	87,25± 0,75	-1,28± 0,08	87,00± 2,58	-1,38±0,30
P_4	>0,05	>0,05	>0,05	>0,05	>0,05
	II stage of osteopenia				
L_1 (n=7)	0,95± 0,01	82,14± 0,40	-1,71± 0,03	83,43± 1,96	-1,60± 0,23
P_1	<0,001	>0,05	>0,05	>0,05	>0,05
L_3 (n=4)	1,02±0,01	82,25± 0,63	-1,88± 0,06	81,75± 1,65	-1,85±0,21
P_2	>0,05	>0,05	<0,01	<0,05	<0,05
L_4 (n=5)	1,03±0,01	82,80± 0,20	-1,66± 0,02	87,80± 1,53	-1,20±0,15
P_3	<0,001	>0,05	>0,05	>0,05	>0,05

Note:

1. P_1 – significance of difference between indices L_1 and L_2.
2. P_2 – significance of difference between indices L_2 and L_3.
3. P_3 – significance of difference between indices L_3 and L_4.
4. P_4 – significance of difference between indices L_4 and L_1.

Densitometry analysis of lumbar segment of patients with CHD complicated by Stage II-A chronic heart failure showed that III stage of osteopenia was detected in a small number of patients (n=7), moreover III stage of osteopenia was not determined at L_3 level. Assessing the level of mineralization we have found that BMD is the lowest at L_1 level: from 0,89 to 0,91 g/cm². Considering the index Young Adult (T-score), it should be noted that its values at all levels practically did not differ from each other. Thus, at L_1 level T-score was (-2,10)-(-2,20), at L_2 and L_4 level – (-2,10)- (-2,30).

It was established that in case of III stage of osteopenia the indices of BMD are changing samely due to young healthy people (Young Adult) and their age group (Age Matched), because there is no significant difference (P>0,05). The average value of BMD in T-score was (-2,18±0,02), that in fact not differ from mineralization in Z-score (-2,11±0,09).

Densitometry analysis with established osteoporosis

showed that in all lumbar vertebrae mineralization decreases vs patients with III stage of osteopenia about by 8,0 % ($p<0,05$). Thus, BMD in patients ranged from 0,80 to 0,88 g/cm^2. Analysis of Age Matched indices showed, that bone mass loss in case of Stage II-A chronic heart failure and osteoporosis based on age regarding healthy people of similar age was almost the same, as compared with group of young healthy people Young Adult ($P>0,05$). The average value of BMD in T-score was (-3,12±0,14), that in fact not differ ($P>0,05$) from mineralization in Z-score (-2,60±0,22).

The analysis of data presented in table 2 indicate that concentration of ionized calcium significantly decreased in patients with CHD complicated by Stage II-A chronic heart failure vs control (1.26±0.02 mmol/l) by 11.1 % (I stage of osteopenia), 18.3 % (II stage of osteopenia) and 31.7 % (III stage of osteopenia). Similar tendency was observed towards concentration of 25(OH)D.

Table 2. Indices of serum calcium metabolism in male patients with CHD complicated by Stage II-A chronic heart failure (M±m)

Index	State of bone mineralization			
	normal bone tissue (n=16)	I stage of osteopenia (n=6)	II stage of osteopenia (n=7)	III stage of osteopenia (n=4)
Ca^{2+}, mmol/l	1.19±0.01	1.12±0.02*	1.03±0.05	0.86±0.03^
25(OH)D, ng/ml	47.52±2.62	36.24±2.26*	32.47±2.45	22.17±3.11^

Note:

1.* – significance of difference between normal bone tissue and I stage of osteopenia.

2. # - significance of difference between I and II stage of osteopenia.

3. ^ - significance of difference between II and III stage of osteopenia.

In our study we have not determined relationship between low serum level of Ca^{2+} and 25(OH)D with BMD. In study of V. Kamineni et al., there is no correlation between serum 25(OH)D levels and BMD [8]. In earlier studies Harinarayan et al. [6] also demonstrated that BMD had no relation to serum 25(OH)D status. On the contrary, few studies have shown a positive correlation of serum 25(OH)D levels and BMD [6, 10].

A number of studies have investigated the association between BMD and cardiovascular morbidity [11]. Chen S.J. et al. 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 are those without treatment. Their findings suggest that osteoporosis is significantly associated with the risk of CHD in an Asian population [12]. 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 [13].

Potential mechanisms for the link between osteoporosis and cardiovascular disease remain unknown. One hypothesis puts forth that the coexistence of osteoporosis and CVD is due to their shared etiological factors (such as smoking, physical activity, alcohol intake, menopause, hypertension, etc), which may simultaneously promote or inhibit atherosclerosis and bone demineralization. However, in many epidemiologic studies, the association between osteoporosis and CVD 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 [14].

Thirdly, coexistence of osteoporosis and CVD may be due to common genetic factors. Genome-wide association studies have identified several genes and single nucleotide polymorphisms associated with BMD, and CVD risk factors or metabolic traits, including high density lipoprotein, low density lipoprotein, triglycerides, type 1 diabetes, type 2 diabetes, systolic blood pressure, diastolic blood pressure and waist hip ratio [13, 15, 16, 17]. Furthermore osteoprotegerin and receptor activator of nuclear factor kappa B ligand regulate osteoclast activation and function but are also involved in the vascular calcification process and atherosclerosis. Bone morphogenetic protein (BMP2) is involved in osteoblastic differentiation by the stimulation of

Runx2 expression; in humans, atherosclerotic lesions show an increased expression of BMP2 and Runx2 with respect to normal arteries and this may be responsible for arteries wall calcification [18].

Conclusions. 1. In patients with CHD complicated by Stage II-A chronic heart failure we have established statistically significant decrease in serum level of ionized calcium and 25-hydroxyvitamin D concentration. However, we didn't find the relationship between serum calcium, 25-hydroxyvitamin D concentration and bone mineral density.

2. Structural and functional changes of bone tissue of the lumbar spine have been found in 49,2 percent patients with coronary heart disease complicated by Stage II-A chronic heart failure, in particular, I stage of osteopenia – in 44,6 %, II stage of osteopenia – in 27,7 %, III stage of osteopenia – in 10,8 % and osteoporosis – in 16,9 %.

3. It was established the same type of downward trend for BMD decreasing in L_1 of patients with different stages of osteopenia, but in case of osteoporosis mineralization decreased equally in all vertebrae.

Conflict of interest statement. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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