Structural and functional state of bone in patients with arteriovenous malformations of the lower extremities


Abstract. Background. Disruption of regional blood flow in patients with arteriovenous malformations (AVMs) of the lower extremities changes the conditions of bone tissue functioning. The purpose was to study the structural and functional state of bone tissue and its metabolism in patients with AVMs of the lower extremities using dual-energy X-ray absorptiometry and the markers of bone turnover. Materials and methods. Fifteen patients with AVMs had been examined. The clinical class of chronic venous disease (CVD) was evaluated according to CEAP; patients were divided into 2 subgroups: the first one was with CVD C1-C3 and the second one was with CVD C4-C6. Bone mineral density (BMD) was studied based on the X-ray absorptiometry. The level of bone metabolism markers, such as procollagen type 1 N-terminal propeptide (P1NP), C-terminal cross-linking telopeptide of type I collagen (β-CTx) and osteocalcin, 25-hydroxyvitamin D (25(OH)D) and parathyroid hormone were studied. Results. Disturbances of the bone tissue indices of the affected limb were found in 70 % of the patients. Also, the statistically significant difference in BMD of the affected limb compared to the healthy limb was established (p = 0.005). A multidirectional level of P1NP was detected; β-CTx exceeded norm in 80 % of the patients; osteocalcin exceeded norm in 33 % of the cases. In 67 % of the patients, a decrease in serum level of 25(OH)D was noted. Increase of the β-CTx level in the first subgroup and its decrease in the second one was associated with stabilization of the AVMs course and age-related changes in the hormonal background of the patients. Conclusions. Disturbances in the structural state of bone tissue of the affected limb were found in 70 % of the patients; statistically significant difference between the BMD of the affected and healthy limb obviously caused by the influence of regional hemodynamic disturbances. Various deviations of the metabolism markers were found, which indicates the need to develop a system of drug therapy. Keywords: arteriovenous malformation; bone mineral density; bone metabolism
In our opinion, a number of questions remain unsolved and relevant regarding research of the “life” of bone tissue as a result of regional blood flow disorders in patients with AVMs, namely: what are the quantitative indices and degree of disturbances of the structural state and metabolism of bone tissue in this exact form of the disease? How does the process of bone formation, bone resorption and speed of bone tissue remodeling change with AVMs? Whether the detected changes will depend on the severity of the disorders of regional hemodynamics? Do the detected changes require medication correction?

The **purpose** was to investigate the structural and functional state and metabolism of bone tissue in the patients with AVMs of the lower extremities using X-ray densitometry and markers of bone remodeling.

**Materials and methods**

**Population**

In the single-center cross-sectional study, 15 patients with AVMs of the lower limbs were examined (5 male, 10 female patients). The age of the subjects was from 5 up to 50 years old (median 12.0 [8.0–31.0] years old). All patients underwent embolization of arteriovenous shunts and corrective operations on the superficial and deep venous net in order to eliminate venous hypertension. The clinical class of chronic venous disease (CVD) was evaluated according to the CEAP classification (Table 1).

The patients were divided into 2 subgroups: the first one — without trophic disorders (CVD, class C1-C3; 10 patients, median age of the patients 9.0 [7.0–12.0] years), the second subgroup — with trophic disorders (CVD, class C4-C6; 5 patients, median age was 32.0 [31.0–39.0] years).

**Methods**

The study of biochemical markers of bone remodeling was carried out in 15 patients, among them 10 patients underwent dual-energy X-ray absorptiometry (DXA) to study bone mineral density (BMD). It was measured using DXA (Hologic Discovery, USA). BMD and Z-score were evaluated, the last one reflected the fraction of the mean square deviation of the BMD of the person under examination compared to the age norm.

BMD indices were studied at the total body, the lumbar spine (total index) and the hip. For interpretation of the results, we were guided by the recommendations of the International Society of Clinical Densitometry (ISCD) [6].

A decrease in BMD in pediatric patients according to the Z-score equal to or below 2 sigma deviations (≥ –2.0 SD) was considered as BMD below the expected value at this age. In adult patients, a decrease in BMD of more than 1 SD (≥ –1.0 SD) was considered osteopenia [6, 7].

The level of biochemical markers of bone remodeling in blood serum was studied and compared with age norms: N-terminal propeptide of type I collagen (P1NP), C-terminal cross-linked telopeptide of type I collagen (β-CTx), osteocalcin. The level of total 25-hydroxyvitamin D (25(OH)D), as well as the level of parathyroid hormone, was studied. The research was carried out by the enzyme immunoassay method on the Roche Elecsys analyzer (Roche Diagnostics, Germany) in the Laboratory of clinical physiology and pathology of the musculoskeletal system of the State Institution “D.F. Chebotarev Institute of Gerontology of the National Academy of Sciences of Ukraine” using the Cobas test system (Table 2). The results were compared with the reference bases of bone remodeling markers according to the age (interval of normal β-CTx is 0–1.734 ng/ml; P1NP is 8–194 ng/ml; osteocalcin is 4.9–238.9 ng/ml; 25(OH)D is 30–50 ng/ml; parathyroid hormone is 15.0–65.0 ng/ml) [8–10]. The conditions for blood sampling in the patients were standard for biochemical examination of the blood.

The dependence of BMD and the level of biochemical markers of bone metabolism on the clinical class of CVD in the subgroups were determined.

**Statistical analysis**

The results, analyzed using the methods of descriptive statistics, were presented in the distribution of the patients (%), the calculation of the median (Me) and the interquartile range (IQR: 25–75%). Comparison between hip BMD indices of the healthy and affected limbs was carried out according to the Wilcoxon test for dependent samples. The standardized mean difference (SMD) and correlation coefficients between indices of metabolism and the structural state of bone tissue were also determined using Spearman’s rank correlation coefficients. Statistical analysis was performed using the Stata 12.1 license package.

**Results**

The analysis of the Z-score revealed its decrease in 3 out of 7 children with AVMs (43 %), the changes in Z-score were from –2.1 to –3.2 SD; Me –2.5 SD. The decreased lumbar spine BMD was noted only in 2 patients (20 %), Z-score was –1.3 and –1.6 SD, respectively. The measurement of hip BMD revealed a decrease in Z-score in 7 patients (70 %) on the affected side (from –1.1 to –3.8 SD). At the same time, a decrease in BMD at the hip of the healthy limb was found only in two patients (20 %), Z-score was –1.6 and –1.4 SD, respectively.

The comparison of the average BMD indices of the affected and healthy hip in accordance with Wilcoxon’s test revealed the presence of statistically significant differences of the indices (healthy and affected limbs, respectively, 0.89 [0.73–0.90] and 0.88 [0.68–0.95] (Me [IQR: 25–75 %]).
In the comparison of BMD indices of the lumbar spine and the hip of a healthy limb, no significant differences were found.

The analysis of the BMD in the affected limb revealed that one patient had the clinical grade of CVD C2 with a Z-score of −1.7 SD; 4 patients had class CVD C3 with a Z-score from −1.1 to −2.8 SD; 2 patients had class CVD C4 with Z-score of −1.7 and −3.8 SD, respectively.

Thus, a decrease in BMD and deterioration of the bone tissue of the affected limb in the patients is obviously a consequence of the progressive course of the disease. In addition, a moderate correlation was established between the indices of the Z-score and the clinical class of CVD, which indicates the influence of the interruption of regional hemodynamics on BMD of the affected limb (R = −0.46).

In the first subgroup, 5 patients (83 %) had a decreased BMD of the hip on the side of AVMs damages (Z-score from −1.6 to −2.8 SD). Additionally, the hip BMD of the healthy limb was below the norm in only one of the patients (Z-score −1.6 SD). In the second subgroup (with trophic disorders), 2 subjects (50 %) showed a decrease in hip BMD of the affected limb (Z-score −1.2 and −3.8 SD, respectively). At the same time, the hip BMD of the healthy limb was decreased in only one of the patients (Z-score −1.4 SD).

Thus, 70 % of the patients with AVMs of lower extremities showed a decrease in BMD of the affected limb. Statistically significant differences in BMD of the limb affected by vascular malformation compared to the parameters of the healthy limb had been established.

The analysis of biochemical markers of bone metabolism established multidirectional changes in the P1NP level (both a decrease and an increase from the limits of the age norm) in 5 subjects (33.4 %), the fluctuation of the increase of the level of P1NP was from 93.4 to 1127 ng/ml; Me [IQR: 25−75 %] = 439.4 [100.0−627.7] ng/ml; the level of β-CTx exceeded the age norm in 12 patients (80 %), increased fluctuations of the level of β-CTx from 0.69 to 4.24 ng/ml; Me [IQR: 25−75 %] = 1.22 [0.78−1.73] ng/ml; the level of osteocalcin exceeded the meaning of age norm in 5 patients (33.3 %), the fluctuation of the increase of the level of osteocalcin was from 2.72 to 115.3 ng/ml; Me [IQR: 25−75 %] = 11.76 [3.60−14.3] ng/ml. Ten patients (67 %) had a decrease in 25(OH)D; among them, 2 subjects (14 %) had vitamin D deficiency; 8 patients (53 %) had its insufficiency. Parathyroid hormone was increased only in one case.

The increase of the β-CTx serum level prevailed in the first subgroup (Me [IQR: 25−75 %] = 0.612 [0.224−0.912] ng/ml) in relation to the patients from second subgroup (Me [IQR: 25−75 %] = 0.346 [0.110−0.520] ng/ml), which indicates a significant dependence on the clinical class of CVD and the level of β-CTx (SMD = 0.57).

Fig. 1 represents a clinical example of a patient with orthopedic manifestations of congenital vascular malformation of the lower limb. The results of measuring the level of the biochemical markers of bone metabolism in blood serum: P1NP — 439.5 ng/ml; β-CTx — 1.22 ng/ml; osteocalcin — 13.3 ng/ml; 25(OH)D — 19.65 ng/ml, intact parathyroid hormone — 24.01 ng/ml. X-ray densitometry indices: total body (BMI 0.598 g/cm²; Z-score −3.2 SD); lumbar spine (BMI 0.597 g/cm²; Z-score −1.3 SD); the proximal part of the affected limb (BMI 0.573 g/cm²; Z-score −2.8 SD); proximal part of the healthy limb (BMI 0.652 g/cm²; Z-score −1.6 SD). An increase in the marker of bone resorption (β-CTx) and changes in the BMD of the left limb of this patient indicate a progressive loss of bone in the limb affected by congenital AVM.

Table 2. Indices of the bone turnover markers and X-ray densitometry indices in patients with AVMs of the lower extremities

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, years</th>
<th>Gender</th>
<th>β-CTx, ng/ml</th>
<th>P1NP, ng/ml</th>
<th>Osteocalcin, ng/ml</th>
<th>25(OH)D, ng/ml</th>
<th>Parathyroid hormone, ng/ml</th>
<th>The stage of CVD (CEAP)</th>
<th>Total body BMD</th>
<th>Lumbar spine BMD</th>
<th>Hip BMD of the affected limb</th>
<th>Hip BMD of the healthy limb</th>
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<td>W</td>
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<td>27.62</td>
<td>43.29</td>
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<td>28.65</td>
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<td>24.65</td>
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<td>1.147</td>
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<td>100</td>
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<td>24.23</td>
<td>23.35</td>
<td>4</td>
<td>1.000</td>
<td>0.735</td>
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Discussion

In accordance with current literature data, congenital vascular malformation is a rare disease that occurs with a frequency of about 1 case per 100,000 subjects [11]. The specific gravity of arteriovenous forms of diseases with limb damage is 36–43 % [12]. Clinical manifestations of AVMs in 40–60 % of the cases are diagnosed at birth, up to 7 years — in about 86 % [2].

Pathological blood shunting leads to the phenomena of vascular stealing in the distal parts of the limb, secondary hypertension occurs in the venous system. Also, AVMs can have a mechanical influence on the surrounding tissues. The severity of clinical manifestations depends on the number of shunts, their localization, and the volume of arteriovenous shunting of blood [3, 13].

AVMs belong to progressing diseases, the progression is provoked by internal (change in the hormonal background) and external (trauma, undergone surgery, etc.) factors. Progression of the disease unavoidably leads to the complications, both, from the side of regional and systemic hemodynamics, and changes the conditions of functioning of bone tissue.

The scientific data from the literary sources regarding the structural bone state in patients with AVMs are quite generalized, limited only by the description of radiological features; and with regard to the metabolism of bone tissue in this nosology, they are absent at all [14]. According to various data, the frequency of radiological changes in bone tissue ranges from 20 to 74 % [15]. Local osteoporosis, erosive changes of the cortical layer, peristomal layering, and limited areas of thinning of bone tissue had been described. It was noted that disturbances in bone tissue in AVMs patients can be associated with both intraosseous localization of the damage and secondary mediated effects. In the case of intraosseous localization of the AVMs, there is a mechanical and autolytic effect of the malformation on bone tissue, which leads to its lysis [16]. Secondary mediated damages can occur in cases of involvement in the pathological process of tissues surrounding the bone (periosteum, muscles) or direct adhesion of the AVMs to the cortical layer. The changed bone structure in AVMs leads to a violation of its mechanical characteristics, which is the cause of pathological fractures, that contribute to the progression of AVMs and significantly worsen their clinical course [17]. It is noted the complexity of surgical treatment of such fractures due to the risk of uncontrolled bleeding, as well as the slowing down of consolidation of the fractures [18, 19].

In order to provide assistance for patients with AVMs, a multidisciplinary approach to diagnosis and treatment has been proposed [20]. The coordinated work of specialists (vascular surgeon, plastic surgeon, dermatologist, radiologist, orthopedist, etc.) makes it possible to improve significantly the results of diagnostics, carry out correction of arteriovenous shunting in time, and stabilize the course of the disease. It is noted that during the assessment of the clinical course of AVMs, lytic changes in bone tissue are characteristic of the patients with clinical manifestations of decompenation of the regional blood flow of the affected limb [21]. The specified clinical features emphasize the importance of timely comprehensive diagnosis and treatment of patients with AVMs.

According to the recommendations of the ISCD, DXA of the proximal femur (hip) is uninformative in children (in contrast to studies of BMD in adult patients) because of the

![Figure 1. Clinical case: patient G., 11 years old; diagnosis: congenital vascular malformation of the left lower limb, arteriovenous microfistulous form, elongation of the left lower limb of 7.5 cm: a) appearance of the patient; b) panoramic X-ray of the lower limbs with segmental measurement of the length of the extremities](image-url)
significant variability of the indices of this area of the body and the low reproducibility of the results of the studied areas [6]. Therefore, in children and adolescents, the BMD should be evaluated based on the indices of the lumbar spine and the total body (the last one excluding the BMD of the skull bones). However, the determining of BMD indices of the hip in children allows doing a comparative assessment of the local structural state of the bone tissue of healthy and affected limbs.

The results of our study, namely the absence of significant differences between the BMD of the lumbar spine and the hip of a healthy limb, are explained by the lack of influence of regional hemodynamics on the structural state of bone tissue of a healthy limb. Statistically significant differences in the BMD of the limb affected by vascular malformation compared to the indices of the healthy limb are, in our opinion, related to the influence of the disturbance of regional hemodynamics and its underload.

The increase in the level of β-CTx in the first subgroup and its decrease in the second subgroup are considered to be related to the surgical correction of arteriovenous shunting and venous hypertension in the previous stages of the treatment, and as a result, increasing the stabilization of the AVMs course in the mentioned clinical stages of the disease; age-related changes in the hormonal background are provided by the peculiarities of bone tissue metabolism for different ages. The detected increase in the level of P1NP and osteocalcin in the examined patients is noted less often, the exceeding of the reference levels of indices is less significant, which did not allow to conduct a statistically significant comparison in the subgroups.

Regarding changes in the level of 25(OH)D in the patients with AVMs, in our opinion, its insufficiency and deficiency are due to the limitation of the patients’ exposure under direct sunlight. An increase in the level of parathyroid hormone is not informative in this study.

The analysis of the relationship between BMD indices of the affected limb and biochemical markers of bone metabolism established that the level of β-CTx, P1NP, osteocalcin has a weak relationship with BMD (R = 0.37, R = 0.42 and R = 0.71, respectively), however, a significant one was established between the level of osteocalcin and BMD of a healthy limb (R = 0.94; p = 0.004). In our opinion, this is due to discordant patterns between indices in patients of the first subgroup (without trophic disorders) and the second one (with trophic disorders). In the initial period of the formation of pathological changes (clinical class of CVD C1–C3), correlation dependences are significant (correlation coefficients 0.41–0.78 for the individual comparisons). In the clinical stages with trophic disorders, there are additional factors affecting the dependencies between the investigated indices (in particular, surgical interventions performed by vascular surgeons), which lead to an imbalance of correlation dependences between the indices as a whole (low values of correlation coefficients). 25 (OH)D does not show its influence on the stages of CVD C1–C3 (younger age), but in general shows an average level of correlation dependence: r = 0.500–0.504. This was, probably, formed at the expense of older patients with clinical stages of CVD C4–C6, who had vitamin D deficiency increased.

Our study of the structural state of bone tissue in the patients with AVMs is the result of a multidisciplinary approach to the diagnosis of pathology of the musculoskeletal system for this contingent of the patients. The revealed changes in the structural state of bone tissue and its metabolism in the patients with AVMs of the lower limb indicate their significant disturbance, strengthening of the processes of bone resorption, and the speed of bone tissue remodeling, which requires the development of a system of medical correction with the use of modern anti-osteoporotic drugs. Hypoxia of bone, metabolic acidosis, and increased venous pressure can most likely be considered as the reasons for established changes in the metabolism and structure of bone tissue.

To the limitations of the study, we can refer to a small quantity of subjects in the groups and a large variability of patients in terms of age. For a more in-depth study of the structural state and metabolism of bone tissue in AVMs, which is a rather rare disease, there is a need to conduct multicenter studies with an increase in the number of clinical observations.

Conclusions

In 70 % of the patients with AVMs of the lower extremities, a violation of the structural state of the bone tissue of the affected limb was found; a statistically significant difference between the BMD of the limb affected by AVM compared to the healthy one, because of the influence of regional hemodynamic disturbances. A statistically significant relationship between the osteocalcin index and BMD of a healthy limb is noted; there is a low correlation between P1NP, β-CTx, and osteocalcin indices with BMD of a healthy limb. In the patients with AVMs, various deviations of the level of markers of bone tissue metabolism from the limits of the age norm were found, which indicates the need to develop a system of antosteoporotic drug therapy in the early clinical stages of the disease.

References


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Conflicts of interests. Authors declare the absence of any conflicts of interest and own financial interest that might be construed to influence the results or interpretation of the manuscript.

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Oригінальні дослідження / Original Researches
Структурно-функціональний стан кісткової тканини у хворих з артеріовенозними мальформаціями нижніх кінцівок

Резюме. Актуальність. Порушення регіонарного кровотоку в пацієнтів з артеріовенозними мальформаціями (АВМ) нижніх кінцівок змінює умови функціонування кісткової тканини. Мета: дослідити структурно-функціональний стан і метаболізм кісткової тканини у хворих з АВМ нижніх кінцівок за допомогою двохенергетичної рентгенівської абсорбціометрії та вивчення маркерів кісткового метаболізму.

Матеріали та методи. Обстежено 15 пацієнтів з АВМ. Оцінювали клінічний клас хронічного захворювання вен (ХЗВ) за класифікацією CEAP. Обстежені були розподілені на дві підгрупи: першу — із ХЗВ С1–С3 і другу — із ХЗВ С4–С6. Досліджували показники мінеральної щільності кісткової тканини (МЩКТ) за даними двохенергетичної рентгенівської абсорбціометрії, рівень маркерів кісткового обміну в сироватці крові: N-термінального пропептиду колагену 1-го типу (P1NP), C-термінального телопептиду колагену 1-го типу (β-CTx), остеокальцину, 25-гідроксивітаміну D (25(OH)D) і паратормону.

Результати. У 70% хворих виявлено порушення статусу кісткової тканини ураженої кінцівки. Встановлено достовірно нижчі показники МЩКТ ураженої судинною мальформацією кінцівки порівняно зі здоров'юю (p = 0.005). Сироватковий рівень β-CTx перевищував норму у 80% пацієнтів, остеокальцин — у 33%. У 67% випадків відмічено зниження сироваткового рівня 25(OH)D. У хворих з АВМ встановлено різноспрямовані зміни маркерів метаболізму кісткової тканини. Підвищення рівня β-CTx у I підгрупі та його зниження в II підгрупі пов’язано зі стабілізацією перебігу АВМ та віковими змінами гормонального фону пацієнтів. Між показниками P1NP, β-CTx, остеокальцину та МЩКТ ураженої кінцівки наявні низькі кореляційні взаємозв’язки.

Висновки. У 70% хворих з АВМ нижніх кінцівок виявлено порушення структурного стану кісткової тканини ураженої кінцівки і мінеральної щільності. У хворих з АВМ встановлено різноспрямовані зміни маркерів метаболізму кісткової тканини від меж вікових норм, що вказує на необхідність розробки системи медикаментозної терапії на ранніх кінцевих стадіях захворювання. Ключові слова: артеріовенозна мальформація; мінеральна щільність кісткової тканини; метаболізм кісткової тканини.