BONE MINERAL DENSITY AND BONE METABOLIC MARKERS IN LABORATORY IN MEN WITH MARFANOID HABITUS

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The aim of the research was the study of bone mineral density (BMD) and activity laboratory markers of bone metabolism in juniors with power shortages and marfanoid habitus (MH).

Materials and methods: Twenty 119 males are underweight aged 18 to 25 years old (average age of 20.4 ± 1.5 years). All surveyed was conducted anthropometric, phenotypical, Echocardiography study to identify the mitral valve prolapse (MVP), laboratory examination of the bone forming token (Osteocalcin, alkaline phosphatase), and the dissolution of bone tissue (β-CrossLaps), Dual-energy X-ray densitometry (L1-L4).

Results: Revealed a significant reduction in BMD females with MH as compared to control (Z-criterion –1.23 ± 0.73 and 0.34 ± 0.80, STD, respectively, \( p < 0.00001 \)). BMD significant decrease (–1.5 STD) found a third of individuals with MH and not seen in the control group, \( p = 0.01 \). When assessing young BMD depending on the severity of MVP statistically reliable differences had been received. At the same time that boys with MVP in conjunction with signs MH is characterized by the lowest BMD values. In the analysis of laboratory parameters revealed a significant increase in Osteocalcin and alkaline phosphatase in the Group of persons with MH, indicating bone forming activity in these patients. At the same time, for people with MH is characterized by increasing the level of β-CrossLaps (marker of the dissolution of bone tissue). With the increased activity of the dissolution of bone tissue associated bone such signs as dolyhostenomelia, deformations of thorax and arachnodaktylia.

Conclusion: bone signs dysembriogenesis involved in the diagnostic algorithm MH, contributes to the abnormal formation of bone tissue in these patients. For them is characterized by activation synthesis and dissolution of bone tissue, reducing BMD.

Keywords: bone mineral density; heritable disorders of connective tissue; marfanoid habitus; mitral valve prolapse; signs of bone.
The early development of osteoporosis (OP) is an urgent health problem because the frequency of its complications has increased significantly in recent decades. The formation of a low bone mass peak at a young age is a key factor in OP pathogenesis and associated fractures. Therefore, sentile OP is considered a pediatric disease because its origins can be traced back to childhood (up to 90% of genetically determined bone mass arises during childhood and puberty) [1]. Consequently, in recent years, there has been growing interest in the problem of OP in children and adolescents in Russia.

The introduction of modern survey methods, in particular dual-energy X-ray absorptiometry (hereinafter referred to as densitometry), has enabled us to study the processes of bone mass formation in children and young men. The main determinants of bone mass peak are genetic and environmental factors (intake of calcium, vitamin D, and proteins; adequate physical load; hormonal status; morbidity background; and the effects of smoking and narcotic drugs). Correlations were found between low bone mineral density (BMD) and reduced body weight. This justified the advisability of including persons aged 15–20 years with a low body mass index (BMI) in the survey standards for densitometric BMD determination [8].

Insufficient nutrition is a primary reason for restricting fitness for military service [6, 17]. According to the district military commissions, approximately 25%–30% of conscripts have a body weight deficit [13]. A sufficient number of undernourished individuals experience a reduced BMI due to genetic factors, particularly mutations of the fibrillin genes responsible for the development of Marfan syndrome (MS) and other fibrillinopathies. The most common and studied hereditary connective tissue disorder (HCTD), which is related to the fibrillinopathy group, is called marfanoid habitus (MH) [3]. Today, the algorithm described in the Russian Recommendations [9] is used to recognize MH as a phenotype. In 2017, we clarified the criteria for MH diagnostics by considering the specificity of individual bone signs (BSs). These signs include arachnoidactyly (ARD), dolichostenomelia (DSM), deformity of the chest (DC), and archlike palate [5]. According to our data, MA as a dysplastic phenotype has been identified in 16% of young men and in 9% of girls. We have previously studied the cardiological aspects of MH as a phenotype [16]. Moreover, persons with MH are characterized with supraventricular and ventricular arrhythmias [14], autonomic dysfunction [11, 12], and cardiomyopathies manifested by a decrease in circumferential systolic deformity of the left ventricle at a young age [7].

Bone deformities, OP, and osteopenia all occur in MS [18]. Additionally, laboratory signs of bone formation and activation of osteoresorption are revealed in patients with MS. The laboratory indicators that characterize the processes of bone formation include the level of serum osteocalcin and alkaline phosphatase (AP). Osteocalcin is a protein of non-collagen origin that is synthesized by osteoblasts and reflects their metabolic activity. Persons with MS display increased levels of osteocalcin and AP [10, 19].

The most informative marker of bone resorption is β-CrossLaps, which is a product of collagen type I degradation. This index is elevated in MS, which is a sign of a pathological increase in bone resorption in such patients. Phosphorus-calcium metabolism is regulated by parathyroid hormone (PTH), which is produced by the parathyroid glands. PTH levels increase with hyperphosphatemia, which contributes to the increased intake of calcium in the blood. This is achieved in several ways, primarily by the increased absorption of calcium in the intestine, the increased absorption in the kidneys, and its release from bone tissue. According to the literature, persons with MS have decreased PTH levels and hyperphosphatemia, but their serum calcium levels do not differ from normal values. More detailed data on the relationship between connective tissue hereditary disorders and OP

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are described in a previously published review [2]. Meanwhile, the processes of bone formation and BMD regulation have not yet been studied in a group of individuals with MH. The question of which BSs of dysembryogenesis are most closely related to osteopenia remains unexplored.

This study was conducted to identify the relationship between the state of BMD and individual BSs, including those used for the diagnosis of MH.

**OBJECTIVES**

1. Evaluate the indicators of osteodensitometry in young men with MH.
2. Study BMD in young men with mitral valve prolapse.
3. Determine the activity of the processes of bone formation and bone resorption in persons with MH.

**MATERIALS AND METHODS**

This study included 119 males aged 18 to 25 years (mean age 20.4 ± 1.5 years) recruited from patients who were examined at the State Budgetary Healthcare Institution “City Mariinsky Hospital” (St. Petersburg) with a diagnosis of malnutrition (mean BMI of 16.38 ± 1.1 kg/m²). All subjects underwent anthropometric and phenotypic examinations and an EchoCG study to identify and clarify the degree of prolapse of the mitral valve leaflets (PMV). In 80 young men, bone formation markers (AP and osteocalcin) were determined, and the osteodensitometry of the lumbar spine (L₁–L₄) was assessed. The BMD results of the patients were compared with the reference database comprised in the densitometer software. To evaluate BMD, the Z-criterion was used, which is the number of standard deviations above or below the average for people of a similar age, gender, and ethnicity, taking into account weight and height indices. The densitometry was performed with the use of a Lunar Prodigy apparatus (General Electrics, USA) with ENCORE-2007 software, version 6.80.002. The β-CrossLaps level was determined for 39 young men with malnutrition who underwent a phenotypic examination (the study was conducted in the laboratory service Helix, St. Petersburg).

The MH diagnostics were performed in accordance with the algorithm we clarified [5]. MH was mentioned when at least four BSs with the mandatory presence of ARD (revealing at least one of the symptoms, namely the thumb and the carpal symptoms) and DSM (implementation of at least one of the two coefficients) were identified.

**RESULTS**

BMD was compared among persons with MH signs (17 persons) with a control group (13 young males) and persons having four or more BSs that did not meet the specified MH criteria. The three groups did not differ in body mass index, with values of 16.9 ± 1.5, 17.2 ± 1.3, and 17.4 ± 1.8 kg/m² in the MH group, the four BSs group, and the control group, respectively. The results of the BMD comparison of these groups are presented in Table 1.

As shown in the table, compared to the control group, there was a significant decrease in BMD in groups 1 and 2. The lowest BMD values were found in young males with MH, which was estimated by taking into account the specificity of individual BSs (specified criteria). Simultaneously, a decrease in BMD of less than −1.5 STD was noted in one-third of MH patients but was not detected at all in the control group (p = 0.01). This decrease was found half as frequently in persons with four BSs. A significant decrease in BMD (less than −2.0 STD) was detected in three young males with MH, but a decrease this large did not occur in the other two groups. Notably, although the BMD values were significantly lower in the group of patients with four BSs who did not meet the criteria for MH diagnostics compared to the control group, a marked reduction in mineral density was detected in these patients significantly less frequently than in the MH group.

| Indices of bone mineral density in young men with marfanoid habitu |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| **Indices of osteodensitometry** | **Group 1 with MH (n = 17)** | **Group 2 Four BSs (without MH) (n = 20)** | **Group 3 Control (BS 0–2) (n = 13)** | **Significance of differences** |
| Mean value of BMD in STD (Z-criterion) | −1.23 ± 0.73 | −0.62 ± 0.76 | **0.34 ± 0.80** | 1–3 0.00001 |
| BMD < −1.5 STD | 6 — 35.3 % | 3 — 15.0 % | 0 | 1–3 0.01 (χ² = 5.74) |
| BMD < −2.0 STD | 3 — 17.6 % | 1 — 5.0 % | 0 | 1–3 0.11 (χ² = 2.55) |

Table 1
Further, BMD was assessed in young men, depending on the presence of prolapse of the mitral valve leaflets. PMV signs were identified in half of the examined patients (40 people); primary PMV (deflection of mitral valve leaflets in the left atrial cavity by more than 2 mm) was defined in 12 young males, whereas there was probable PMV (deflection by 1–2 mm) in 28 individuals. In the evaluation of BMD in young males, no statistically significant differences were obtained in different PMV severities (−0.63 ± 0.68 STD in the primary PMV group, −0.96 ± 0.87 STD in the probable PMV group, and −0.65 ± 1.14 STD in persons without PMV (p > 0.05)).

Thus, without considering the signs of MH, it was impossible to evaluate the special aspects of BMD in young men with PMV. Simultaneously, in our opinion, to assess the clinical value of PMV, both the degree of prolapse of the mitral valve leaflets and the combination of PMV with MH signs must be considered [4]. To test this hypothesis, two groups were formed: group 1 consisted of MH young males with any degree of prolapse (11 patients), and the control group consisted of 10 PMV young males having up to two BSs (Table 2).

As shown in the table, when the combination of PMV with the signs of MH were compared with the isolated forms of PMV, significantly lower BMD values were revealed. Simultaneously, one-third of young males with a combination of PMV and MH showed a significant decrease in BMD, whereas no decrease in BMD was detected among young men with isolated forms of PMV.

To establish the correlation between MH and metabolic features of bone tissue, the laboratory markers of bone formation and osteoresorption were analyzed. The results of the analysis of these parameters in young males, depending on the presence of MH signs, are presented in Table 3.

As shown in the table, the selection of a group of individuals with the most significant BSs enables us to detect statistically significant differences in the level of primary markers of bone tissue metabolism. Thus, in MH patients, the levels of osteocalcin and AP were significantly higher, which indicates the activation of bone formation. It is also important that the excess of the threshold values of these indicators was revealed only in young males with MH. There were no significant differences in the concentrations of phosphorus and calcium in the groups formed. Simultaneously, PTH levels were significantly lower in the study group patients, which indicates a disorder of phosphorus-calcium metabolism. Notably, none of the MH subjects had a PTH level beyond the age norm limit.

To determine the activity of bone resorption, the concentration of β-CrossLaps in blood serum was determined in 39 young males with malnutrition. The study group included patients who met the criteria for MH. The control group consisted of young males with single BSs (no more than three). The results are provided in Table 4.
As shown in the table, the level of serum β-CrossLaps was insignificantly higher in the young males of the study group than in those of the control group. However, pathological values (exceeding 0.584 ng/ml) were detected in 84% of the study group patients and in only one-third of the examined persons of the control group (p = 0.002). Thus, for young males with several significant BSs (MA), activation of osteoresorption processes is typical.

The subjects were divided into two groups depending on the serum β-CrossLaps level. The study group consisted of 26 young males with an increased level of this indicator, whereas the control group included 13 people with normal parameter values. The prevalence of BSs was assessed. The results are presented in Table 5.

As shown in the table, young males with an increased level of bone resorption marker (β-CrossLaps) displayed more frequent detection of significant BSs of dysembryogenesis, namely DC, carpal symptom, and DSM, which were assessed according to the recommendations of the Russian Society of Cardiology (implementation of at least one coefficient) [15]. In this case, the prevalence of ARD depends on the diagnostic threshold chosen. Thus, at least one sign (of the thumb or wrist) was determined in the generated groups with the same frequency, and both signs of ARD were detected in 88.5% of the young males of the study group and only in half of the control group (p = 0.01).

Importantly, scoliotic deformity of the spine (SDS), platypodia, and facial dysmorphism were detected in both groups at the same frequency, which again emphasizes their low specificity in the establishment of HCTD. There was an average of nearly one more BS in the group with increased β-CrossLaps levels than in the control (4.5 ± 1.2 and 3.7 ± 1.4 respectively, p = 0.07). MH as a dysplastic phenotype was determined in the vast majority of young males with increased β-CrossLaps levels.

**DISCUSSION**

Thus, the obtained data indicate lower values of BMD in persons with MH estimated according to the clarified algorithm [5]. This was confirmed by the more frequent detection of a significant decrease in BMD in the group of young men with MH, which was not found in individuals with single BSs. Meanwhile, in the group with four BSs, from which MH patients were excluded, BMD values were statistically lower compared to the control group. Cases with a significant decrease in BMD in this group were noted significantly less often than in MH patients.

### Table 4
Concentration of serum β-CrossLaps in young men with marfanoid habitus

| Index                  | Марфаноидная внешность (n = 25) | Контроль (0–3 КП) (n = 14) | Достоверность различий |
|------------------------|--------------------------------|---------------------------|-----------------------|
| β-CrossLaps, ng/ml     | 0.84 ± 0.38                    | 0.76 ± 0.45               | 0.55                  |
| β-CrossLaps > 0.584 ng/ml | 21 — 84.0                     | 5 — 35.7                  | 0.002 (χ² = 9.42)     |

### Table 5
The occurrence of bone signs of dysembryogenesis in young men with different serum β-CrossLaps levels

| Index                        | Increase in β-CrossLaps > 0.584 ng/ml (n = 26) | Normal value of β-CrossLaps (n = 13) | Significance of differences |
|------------------------------|-----------------------------------------------|-------------------------------------|-----------------------------|
| Dolichestostenomelia         | 23 88.5                                       | 7 53.8                              | 0.01 (χ² = 5.85)            |
| Chest deformity              | 21 80.8                                       | 7 53.8                              | 0.07 (χ² = 3.10)            |
| Scoliotic deformity of the spine | 20 76.9                                      | 8 61.5                              | 0.32                        |
| Facial dysmorphism           | 15 57.7                                       | 8 61.5                              | 0.81                        |
| Carpal syndrome             | 24 92.3                                       | 7 53.8                              | 0.005 (χ² = 7.86)           |
| Thumb syndrome               | 24 92.3                                       | 12 92.3                             | 1.0                         |
| Arachnodactyly (one symptom) | 25 96.5                                       | 12 92.3                             | 0.61                        |
| Arachnodactyly (both symptoms) | 23 88.5                                      | 7 53.8                              | 0.01 (χ² = 5.85)            |
| Platypodia                   | 12 46.2                                       | 6 46.2                              | 1.0                         |
| Average number of BSs        | 4.5 ± 1.2                                     | 3.7 ± 1.4                           | 0.07                        |
| Marfanoid habitus            | 21 80.8                                       | 4 30.8                              | 0.002 (χ² = 9.42)           |

**Table 4**

**Table 5**
The absence of differences in the BMI values in the MH groups and the control group indicates that the determining factor in the reduction of BMD is not the level of nutrition, as is commonly believed, but the presence of BSs. It can be asserted with confidence that BSs selected as the most specific for MH diagnostics are associated with a decrease in BMD. These include ARD, DC, archlike palate, and DSM coefficients. Moreover, BSs such as SDS, platypodia, and facial dysmorphism do not obviously contribute to the value of BMD.

The determination of BMD in PMV patients without regard to the degree of involvement of the bone system does not enable us to detect significant differences compared to the control group. The severity of prolapse also does not affect the frequency of BMD reduction since it was comparable in individuals with primary and probable PMV and did not differ in the control group. Meanwhile, in addition to signs of MA, the lowest BMD values were found in young males with PMV. A significant decrease in BMD was demonstrated in more than one-third of patients with a combination of PMV and MH.

Significant changes in biochemical parameters were also revealed that characterize bone metabolism in young people, depending on the presence of MH signs. An increase in the levels of osteocalcin and AP, which are the main laboratory markers for bone tissue formation, is intrinsic to such young males. The increase in bone formation in such patients is accompanied by an increase in the demand for calcium in bone tissue. This is usually implemented through the activation of PTH, which contributes to the increased calcium reabsorption in the renal tubules and its more active absorption in the intestine. Meanwhile, we detected a significant decrease in PTH levels in young people with MH, which apparently determines the reduction of BMD in young males with MH. However, we detected no difference in the concentrations of calcium and phosphorus in the blood serum.

Studies have shown that activation of the processes of bone formation in MH patients is combined with an increase in the reverse processes, namely bone resorption. This is evidenced by a significant increase in collagen degradation products, specifically \( \beta \)-CrossLaps, in the blood serum of young males. The analysis of the incidence of BSs in individuals revealed that signs such as DSM, ARD, and DC are detected significantly more frequently in patients with increased \( \beta \)-CrossLaps levels. Using the proposed algorithm, MH is identified 2.5 times more frequently in individuals with increased \( \beta \)-CrossLaps levels than in individuals with normal values of this index.

The data obtained show a close relationship between the BSs of dysembryogenesis and the activity of metabolic processes in bone tissue.

**CONCLUSIONS**

1. For young males with MH and the presence of specific BSs, a marked decrease in BMD is characteristic. The decrease in mineral density is closely related to BSs such as ARD, DSM, chest deformities, and archlike palate.

2. In persons with mitral valve prolapse, the presence and degree of osteopenia are not associated with the severity of the leaflets prolapse but are associated with the symptoms of MH.

3. For young men with MH, the increased activity of serum markers of bone formation (AP and osteocalcin) and bone tissue degradation (\( \beta \)-CrossLaps) is characterized by the decrease in PTH levels, which causes the deficiency of bone tissue in such patients.

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