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Mineral and bone metabolism in patients with idiopathic scoliosis depending on the magnitude of the deformity

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Abstract
Objective: Analysis of the results of the study of mineral metabolism and bone formation markers in patients with idiopathic scoliosis, depending on the magnitude of the deformity.
Material and methods: Based on the retrospective single-center study in 30 patients diagnosed with scoliosis the preoperative parameters of calcium metabolism (total and ionized calcium, parathyroid hormone, 24-hour urine calcium), phosphorus, bone formation markers (alkaline phosphatase, osteocalcin, P1NP in the blood), deoxypyridinoline in morning urine, blood levels of 25(OH)D have been analyzed. The patients were divided into 3 groups: with a deformity of 25–40 ° (group 1), 40–60 ° (group 2) and 60–80 ° (group 3) (n = 30). The mean age in all groups was 18.5 ± 4.7.
Results: In patients with idiopathic scoliosis, alkaline phosphatase and P1NP significantly exceeded normal values in the first group, which indicated a more high-turnover type of bone remodeling with a deficient level of 25(OH)D. A higher excretion of deoxypyridinoline and a decrease in phosphorus in blood in patients with a deformity of 60–80 ° suggest a violation of the ratio of the processes of synthesis and resorption in bone tissue.
Conclusion: The study of mineral metabolism and all the main markers of bone formation made it possible to obtain a more complete picture of the state of metabolic processes in bone tissue, to obtain reliable data on the effect of some of them on the nature of bone remodeling and the magnitude of spinal deformity.
***Keywords*:** idiopathic scoliosis, calcium metabolism, markers of bone formation
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Минеральный и костный метаболизм у больных идиопатическим сколиозом в зависимости от величины деформации

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Резюме
Цель работы: Анализ результатов изучения минерального обмена и маркеров костеобразования у больных идиопатическим сколиозом в зависимости от величины деформации.
Материал и методы: На основе ретроспективного одноцентрового исследования у 30 больных сколиозом до операции изучали показатели кальциевого обмена (общий и ионизированный кальций, паратгормон, кальций суточной мочи), фосфора, маркеры костеобразования (щелочная фосфатаза, остеокальцин, P1NP в крови), дезоксипиридинолин утренней мочи, уровень в крови 25(OH)D. Все пациенты были разделены на 3 группы: с величиной деформации 25–40° (группа 1), 40–60° (группа 2) и 60–80° (группа 3) (n = 30). Средний возраст во всех группах составил 18,5 ± 4,7 года.
Результаты: У больных идиопатическим сколиозом щелочная фосфатаза и P1NP достоверно превышали нормальные показатели в 1-й группе, что свидетельствовало о более высокооборотном типе костного ремоделирования при дефицитном уровне 25(OH)D. Более высокая экскреция дезоксипиридинолина и снижение показателей фосфора в крови у больных с деформацией 60–80° позволяют предположить нарушение соотношения процессов синтеза и резорбции в костной ткани.

Заключение: Изучение минерального обмена и всех основных маркеров костеобразования позволило создать более полную картину состояния обменных процессов в костной ткани, получить достоверные данные о влиянии некоторых из них на характер костного ремоделирования и величину деформации позвоночника.
***Ключевые слова*:** идиопатический сколиоз, кальциевый обмен, маркеры костеобразования
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Introduction

There is a fairly large number of studies on bone mineral density (BMD) to address the issue of the presence of osteoporosis in patients with idiopathic scoliosis (IS) [1–5]. The presence of osteopenia in patients with IS has been proven, as well as signs of the bone structure infraction, concerning both the quality of trabeculae and architectonics [6–8]. It has been established that with the spinal deformity degree increase in children and adolescents with IS, the frequency of detection of reduced bone mineral density increases [1]. In 2016 B.H.K. Yip et al. found that in patients with IS that have low bone density, progression risk increases depending on the initial magnitude of deformity [3]. Research carried out by X. Sun et al. (2013) showed, that in patients with a deformity angle 32.3 ± 6.6 ° according to the Cobb method, girls with osteopenia with a lower Risser stage were found more often than in a group of patients with a smaller deformity angle (29.1 ± 5.3 °) [9]. In addition, the level of osteoprotegerin (OPG) and osteocalcin (OST), parathyroid hormone (fs-PTH), vitamin D, and the state of mineral metabolism (calcium, phosphorus) have been also studied [4, 5, 10, 11–13]. In 2015 K. Ishida et al. studied bone mineral density and bone metabolism in patients with IS using the markers of bone metabolism – BAP (bone alkaline phosphatase) and TRAP5b (tartrate-resistant acid phosphatase serum band 5). Patients with IS that showed high TRAP5b levels had lower Z-score than patients with normal levels of TRAP5b. The authors attribute a higher rate of bone resorption to low bone density in patients with IS [4].

In 2020 A. Herdea et al. published a conclusion that a positive correlation between vitamin D and calcium along with a negative correlation to Cobb angle is the basis for compulsory study of vitamin D levels in all patients with IS [11]. Data on measuring the correlation of the Cobb angle to the Z-score ($r = -0.39$, $p = 0.02$) were found in the work of L. Cațan et al. [5]. In the conducted studies individual fragments of mineral metabolism and bone formation markers were studied. Not all of them clearly stated the correlation between mineral metabolism disorders or bone mineral density and the degree of spinal deformity which became the basis for this research.

Objective

Analysis of the results of the study of mineral metabolism and bone formation markers in patients with idiopathic scoliosis, depending on the magnitude of the deformity. Mean age in all groups was 18.5 ± 4.7 years.

Material and Methods

A retrospective single-center study has been carried out. In 30 patients with scoliosis, divided into three groups: with a deformity of 25–40 ° (Group 1), 40–60 ° (Group 2) and 60–80 ° (Group 3) (n = 30) calcium metabolism indicators were studied before surgery (total and ionized calcium, parathormone, 24-hour urine calcium), phosphorus, bone formation markers (alkaline phosphatase, osteocalcin, P1NP in the blood), deoxypyridinoline (DPD) in morning urine, blood levels of 25(OH)D. Mean age of patients in all groups was 18.5 ± 4.7. During a separate determination of the mean age in the 1st group a slight difference from the 2nd and 3rd groups appeared (16.1 ± 2.4 years). The patients were examined during preparation for elimination of idiopathic scoliosis surgery in 2018–2020 in a specialized clinic. Criteria for inclusion in the study: patients' age at the time of examination from 14 to 20 years; thoracolumbar spine idiopathic scoliosis; spinal deformity from 25 to 80 ° according to Cobb angle. Exclusion criteria: spine deformity less than 20 ° and more than 80 °, patients' age less than 14 and more than 20, congenital or neuromuscular scoliosis. Biochemical studies were carried out on an automatic analyzer VITROS 5.1FS (Orto Clinical Diagnostics Johnson & Johnson company), hormones study – on automatic analyzers VITROS® ECIQ, mini Vidas, automated system Cobas E 411. To determine the deformity magnitude all patients were examined by radiography and computed tomography. The work was carried out in accordance with the ethical standards of the Declaration of Helsinki of the World Medical Association "Ethical principles for conducting scientific medical research involving humans" as amended in 2013. All patients or their legal representatives signed an informed consent for the publication of data without personal identification. Statistical processing was performed using the AtteStat program (64-bit OS) [9]. The normality check of the quantitative data distribution was performed using the Kolmogorov–Smirnov test. To identify differences between groups in terms of quantitative indicators, Student's t-test with Bonferroni correction was used. Statistical significance level of differences when testing statistical hypotheses equaled $p < 0.05$.

Results

Calcium and phosphorus concentration determination in patients with idiopathic scoliosis is justified by their connection with the exchange of parathyroid hormone, calcitonin, and the active form of vitamin D3.

Mineral metabolism and markers of bone formation indicators study was carried out by us depending on the magnitude of the deformity, since there are studies indicating that a decrease in BMD affects the progression of deformity, and all the mentioned above indicators of calcium metabolism and markers of bone formation affect the state of the bone tissue of the vertebrae [1, 4, 6].

No significant differences were found between groups during the examination of urine calcium, but in the 2nd and 3rd groups its level was slightly below the norm. As for blood calcium, in the 3rd group this indicator was significantly lower than in the first two (figure 1).

Ionized calcium level was also determined as a more informative indicator, in comparison to the examination of total calcium for diagnosis of hypercalcemia conditions. Patients in the 2nd group showed a higher level than in group 1 and 3 (figure 2).

Along with the determination of blood calcium levels, indicators of phosphorus in the blood were studied, since phosphorus concentration depends on the reabsorption of phosphates in renal tubules, the ratio of the synthesis processes and resorption in bone tissue (figure 3).

Bone formation markers study showed that the level of alkaline phosphatase in the 1st group was increased, while in the 2nd and 3rd groups it was within the reference values (figure 4).

One of the bone formation marker indicators – P1NP (procollagen type 1 N-terminal propeptide) significantly decreased as spinal deformity increased. The levels in the 1st group were higher than the norm, which indicated a disturbed ratio of destruction and formation of bone matrix, an increase of the type 1 collagen production, and therefore, of P1NP, which is characteristic for a high-turnover type of bone formation. In the 2nd and 3rd groups its level was within the normal range (figure 5).

In addition, the study of the level of vitamin D (25-OH D3) was carried out to identify secondary hyperparathyroidism, which is accompanied by osteoclastic bone resorption, its density decrease and architectonics change [14]. According to our data, the amount of vitamin D (25-OH D3)

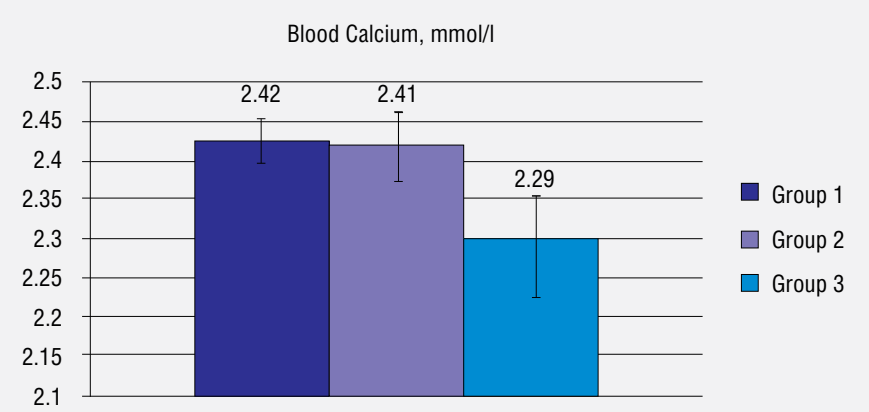

Figure 1. Diagram of the amount of blood calcium in patients with idiopathic scoliosis depending on the magnitude of the deformity

Рисунок 1. Диаграмма содержания кальция крови у больных идиопатическим сколиозом, в зависимости от величины деформации

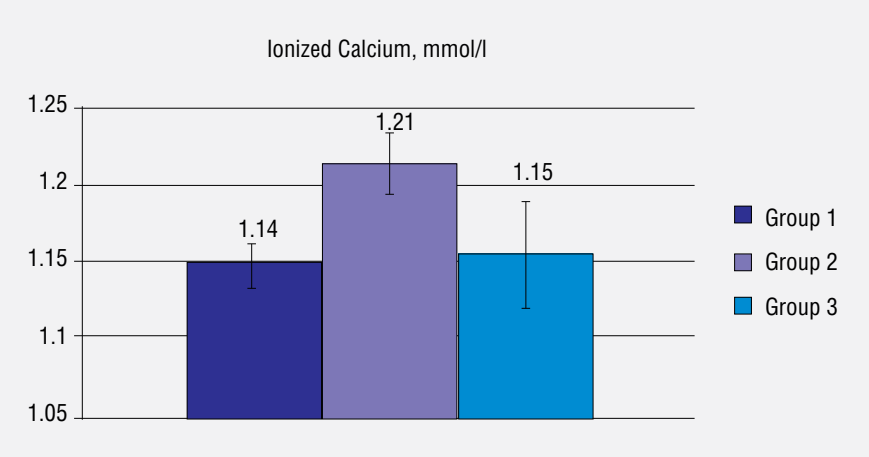

Figure 2. Diagram of the amount of ionized blood calcium in patients with idiopathic scoliosis depending on the magnitude of the deformity

Рисунок 2. Диаграмма содержания ионизированного кальция крови у больных идиопатическим сколиозом, в зависимости от величины деформации

indicated a deficiency in the 1st and 2nd groups (< 20 ng/ml, deficiency), it was unreliably higher, but insufficient in the 3rd group (levels of 25(OH)D from 20 to 30 ng/ml) (figure 6).

The definition of osteocalcin (OC), as the most sensitive marker of bone tissue metabolism was due to the need of identification of the metabolic activity of bone tissue osteoblasts. Osteocalcin is a product of new synthesis, not of the release during the bone resorption. OC is an indicator of the bone metabolism level in general, as well as a possible prognostic indicator of more severe bone disease. In all 3 groups osteocalcin was within the normal range without significant differences (figure 7).

Deoxypyridinoline (DPD) is a product of degradation of bone tissue collagen and is a highly specific marker of bone tissue resorption. It quickly responds to changes in bone remodeling, informs about the process activity, is an early diagnostic criterion. A higher excretion of DPD was revealed in the 3rd group, which indicated a higher rate of bone resorption in patients of this group (figure 8).

The indication of parathyroid hormone was due to the fact that it is one of the main regulators of calcium metabolism in the body. It reduces calcium excretion and increases excretion of phosphorus from the body through the urine, affecting renal tubules. It contributes to the flow of calcium and phosphate from the bones into the blood, inhibiting osteoblasts activity; it helps to increase the pool of osteoclasts by activating osteocytes and osteoclasts. In the examined groups of patients, the PTH level did not differ sufficiently (figure 9).

Discussion

The results of the study showed that in patients with IS alkaline phosphatase and P1NP significantly exceeded normal values in the 1st group, while in the 2nd and the 3rd were within the norm range. This indicates a higher

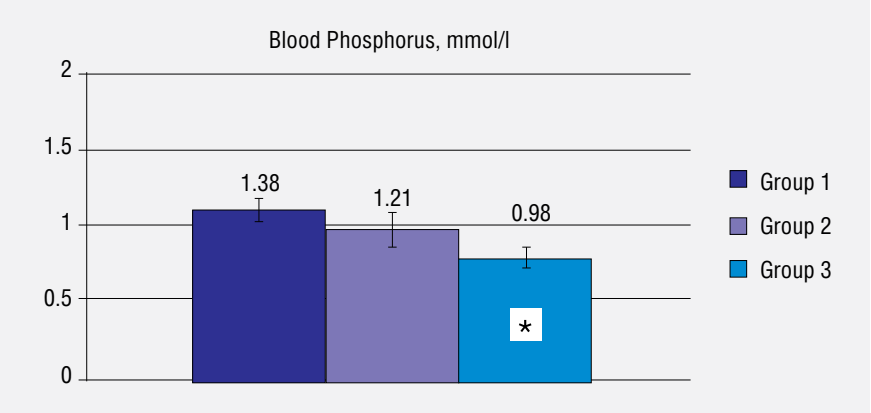

Figure 3. Diagram of the amount of blood phosphorus in patients with idiopathic scoliosis depending on the magnitude of the deformity
Note: (* – p < 0.05)
Рисунок 3. Диаграмма содержания фосфора крови у больных идиопатическим сколиозом, в зависимости от величины деформации
Прим.: (* – p < 0,05)

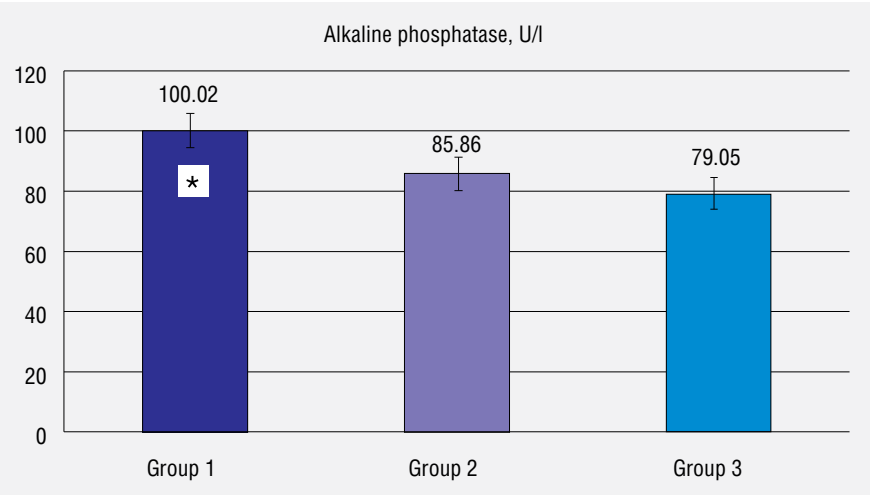

Figure 4. Diagram of alkaline phosphatase indices in patients of three groups
Note: * – significant differences in the first group from the second and third (p < 0.05)
Рисунок 4. Диаграмма показателей щелочной фосфатазы у пациентов трех групп
Прим.: * – достоверные отличия в первой группе от второй и третьей (p < 0,05)

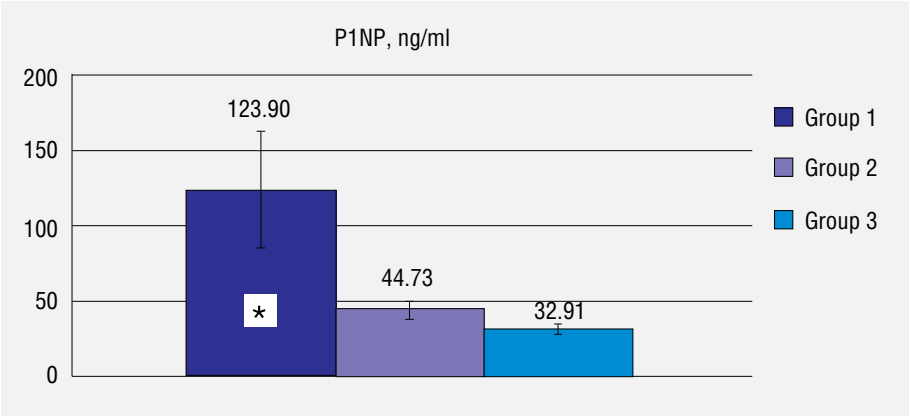

Figure 5. Histogram of P1NP parameters in patients with idiopathic scoliosis depending on the magnitude of the deformity
Note: * – significant differences in the first group from the second and third ($p < 0.05$)
Рисунок 5. Гистограмма показателей P1NP у больных идиопатическим сколиозом, в зависимости от величины деформации
Прим.: * – достоверные отличия в первой группе от второй и третьей ($p < 0,05$)

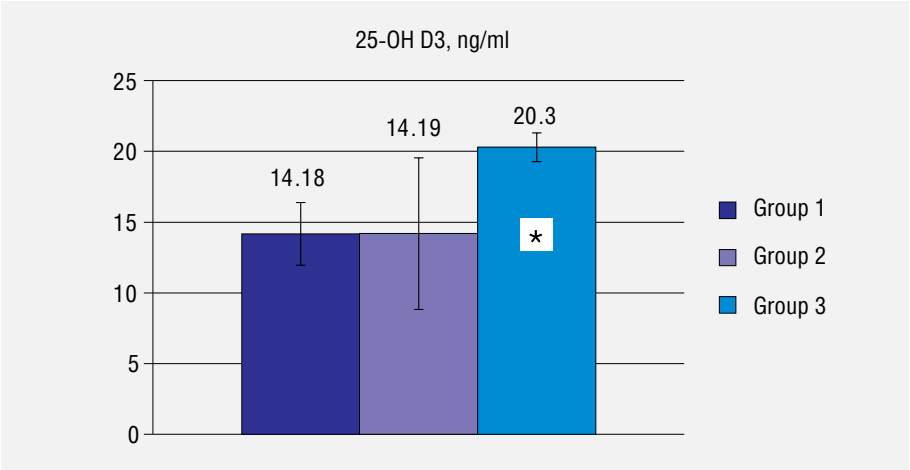

Figure 6. Histogram showing the amount of vitamin D (25-OH D3) in patients with idiopathic scoliosis depending on the magnitude of the scoliotic curve deformity. Groups 1 and 2 – deficiency, group 3 – insufficiency (– $p < 0.05$)*
Рисунок 6. Гистограмма, отражающая содержание витамина D (25-OH D3) у больных идеопатическим сколиозом, в зависимости от величины деформации сколиотической дуги. Группы 1 и 2 – дефицит, группа 3 – недостаточность (– $p < 0,05$)*

turnover in patients of this group and shows the need for additional preoperative examinations, in particular, the study of the mineral density of the vertebrae. It should be mentioned that in the 1st group the mean age was lower than in the 2nd and the 3rd, which could explain the data obtained, since in E.N. Bakhtina et al. (2016) work, it was also stated that in all children with IS the level of 25(OH)D was reduced to a deficiency [14]. Considering the fact that the level of 25(OH)D in the blood was deficient in the 1st group and insufficient in the 2nd and 3rd, secondary hyperparathyroidism can occur in all patients, which could lead to osteoclastic bone resorption, its density decrease and architectonics change. There might be a necessity to correct the amount of vitamin D, but this should be the object of a special study. In the work of A. Herdea et al. (2020), vitamin D and calcium levels were studied in 101 patients with IS (mean age 11.61 ± 2.33). The mean Cobb angle was 26.21 ° ± 12.37 °. Vitamin D level – 24 ng/ml ± 9.64. Calcium levels were in the norm range, average numbers – 9.82 mg/dl ± 0.42. Vitamin D levels in the group of men were lower than in the group of women (19.6 to 25.45 ng/ml) ($p = 0.02$). Vitamin D levels positively correlated with calcium levels ($p = 0.01$, $r = 0.973$), as well as the patients age ($p < 0.001$, $r = 0.158$). Cobb angle negatively correlated with vitamin D level in serum ($p < 0.01$, $r = – 0.472$), which matches our data. The authors believe that the positive correlation between vitamin D levels and calcium, along with the negative correlation with Cobb angle can be further evidence that patients with IS should regularly be examined for vitamin D levels, that could affect the progression of the scoliotic curve [11].

A similar correlation was demonstrated in the work of L. Cațan et al, where it is stated that patients with IS had significantly lower vitamin D levels, calcium and Z-score indicators, than healthy individuals, a significant correlation of the Cobb angle with the Z-score was found

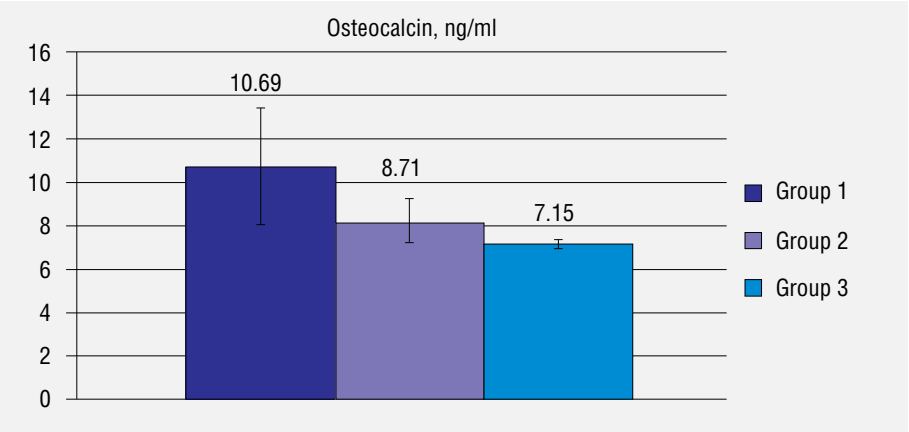

Figure 7. Histogram showing the amount of osteocalcin in patients with idiopathic scoliosis depending on the magnitude of the deformity
Рисунок 7. Гистограмма, отражающая содержание остеокальцина у больных идеопатическим сколиозом, в зависимости от величины деформации

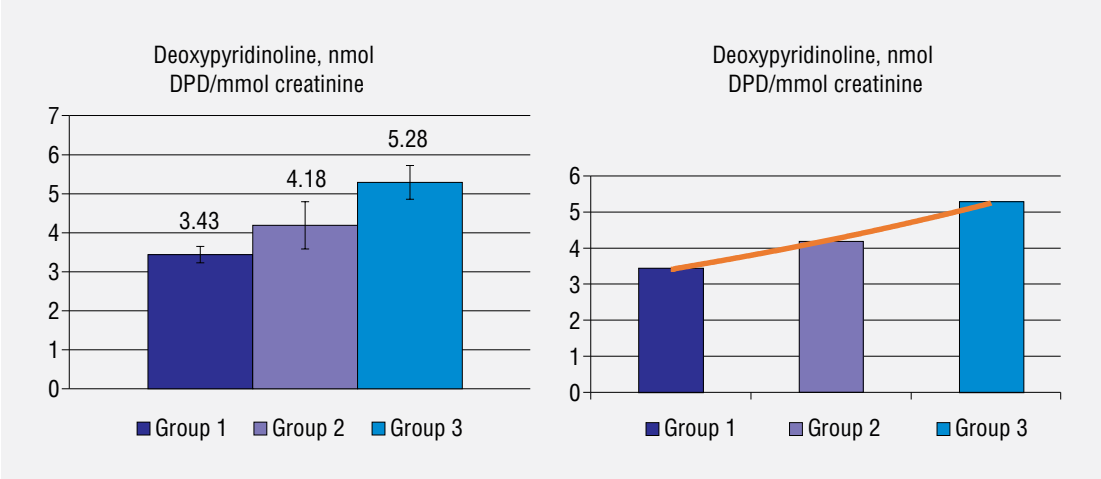

Figure 8. Histogram showing the amount of DPD in patients with idiopathic scoliosis depending on the magnitude of the deformity. The indicators significantly increase in groups 1 and 3, correlating with the severity of scoliosis
Рисунок 8. Гистограмма, отражающая содержание ДПИД у больных идеопатическим сколиозом, в зависимости от величины деформации. Показатели достоверно повышаются в группах 1 и 3, коррелируя с тяжестью сколиоза

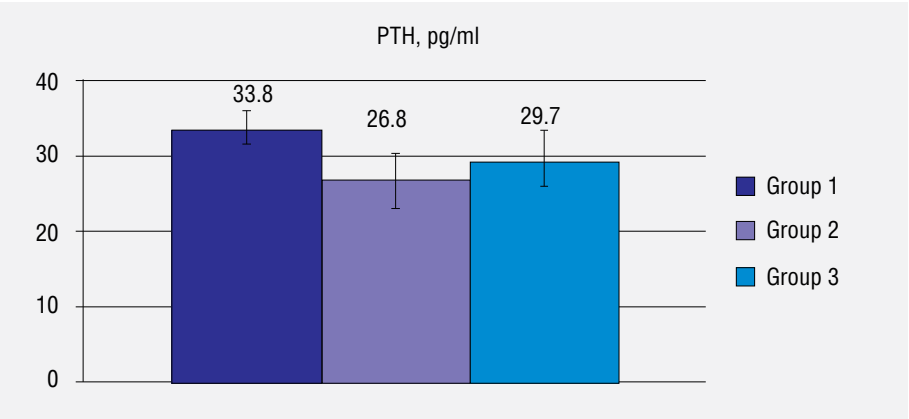

Figure 9. The level of parathyroid hormone in patients with idiopathic scoliosis depending on the magnitude of the deformity
Рисунок 9. Уровень паратиреоидного гормона у больных идиопатическим сколиозом, в зависимости от величины деформации

Table

Indicators of mineral metabolism and some markers of bone metabolism in patients with idiopathic scoliosis depending on the magnitude of the deformity (n = 30)

Таблица

Показатели минерального обмена и некоторых маркеров костного метаболизма у больных идиопатическим сколиозом, в зависимости от величины деформации (n = 30)

Indicator	Magnitude of deformity		
	25–40 °	40–60 °	More than 60 °
Urine calcium	Norm	Below the norm range	
Blood calcium (general)	Norm	Norm	Concentration is significantly higher, than in the 1st and 2nd groups
Ionized calcium	Norm	Concentration is significantly higher, than in the 1st and 2nd groups	Norm
Phosphorus	Norm	Norm	Concentration is significantly lower, than in the 1st and 2nd groups
Alkaline phosphatase	Above the norm range[1]	Norm	Norm
Osteocalcin	Norm	Norm	Norm
P1NP	Above the norm range[2]	Norm	Norm
DPD	Norm	Indicators significantly increase, correlating with the scoliosis severity	
25(OH)D	Deficiency[3]	Insufficient	Insufficient
PTH	Norm	Norm	Norm

[1,2] – significant difference from the norm ($p < 0.01$);

[3] – deficit compared to reference data

[1,2] – достоверные отличия от нормы ($p < 0,01$);

[3] – дефицит в сравнении с референсными данными

($r = – 0.39$, $p = 0.02$) [5]. The study of osteocalcine and receptor activator of nuclear factor-kB ligand (RANKL) in IS patients showed their higher values, than in the control group [15]. A higher excretion of DPD was found in the 3rd group, which indicates a higher rate of bone resorption in patients of this group. Phosphorus levels in the blood were also reduced in the 3rd group, which confirms the ratio disturbance of the processes of synthesis and resorption in bone tissue with severe spinal deformity (60–80 °). The parameters of PTH did not have significant differences with the norm in the groups, which coincides with the opinion of A. Gozdzialska et al (2016) [13].

The study of mineral metabolism and all the main bone formation markers made it possible to obtain a more complete picture of the state of metabolic processes in bone tissue in patients with IS and reliable data on the ways some of them affect the nature of bone remodeling and the magnitude of spinal deformity, which should be taken into consideration during the determination of the scope of diagnostic studies, preoperative preparation and rehabilitation and recovery activities after treatment process. This indicates the practical significance of this work, which shows the necessity of additional preoperative examinations of patients with idiopathic scoliosis, considering the mineral metabolism disorders and bone formation markers change for the amount of vitamin D correction and control of bone mineral density, which is an important predictor for assessing bone quality and prevention of resorptive changes in the implants area.

Conclusions

1. A significant excess of norm values of alkaline phosphatase and P1NP in patients with idiopathic scoliosis in the 1st group indicates a more high-turnover type of bone remodeling and the necessity of additional preoperative examinations, in particular vertebrae mineral density study to prevent complication after the implant insertion.

2. Considering the fact, that the level of 25(OH)D in the blood was deficient in the 1st group and insufficient in the 2nd and 3rd, leading to osteoclastic bone resorption, its density decrease and architectonics change it might be necessary to correct the amount of vitamin D with simultaneous control of parathyroid hormone levels.

3. A higher DPD excretion, along with the decrease of phosphorus in blood in patients of the 3rd group, indicates a ratio disturbance in the processes of synthesis and resorption of bone tissue and should be accompanied by a recommendation to conduct densitometry to determine bone mineral density.

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