



BONE METABOLISM BIOMARKERS IN WALKING CHILDREN WITH CEREBRAL PALSY

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Background. Osteoporosis is an important factor in the pathogenesis of orthopedic manifestations in children with cerebral palsy. It was previously demonstrated that children with cerebral palsy have specific changes in bone metabolism, which can cause changes in laboratory parameters compared with other orthopedic patients without neurological backgrounds.

Aim. The aim of this study was to assess bone metabolism biomarkers in children with cerebral palsy, identifying distinguishing characteristic patterns in comparison with patients with orthopedic pathology without neurological backgrounds.

Materials and methods. This study evaluated the concentrations of calcium, phosphorus, β -cross laps, osteocalcin, vitamin D, CICP, and alkaline phosphatase in the blood serum of 50 children with cerebral palsy aged between 6 to 12 years with GMFCS levels I–III. The control group consisted of 50 patients with plano-valgus deformities of the feet.

Results. The alkaline phosphatase activity in the group of children with cerebral palsy was 170.25 ± 59.35 u/L, while in the control group it was 145.58 ± 46.29 u/L; the CICP concentration in the study group was higher than in the control group (324.01 ± 174.10 and 269.68 ± 240.98 , respectively). The concentration of β -cross laps, osteocalcin, calcium, and vitamin D in the study group was lower than in children with flat feet.

Conclusions. This study demonstrated multidirectional changes in the biomarkers of bone metabolism that are characteristic of walking children with cerebral palsy. These changes are characterized by a corresponding increase in the activity of osteoresorption and osteoreparation. This makes it possible to justify the combined use of metabolites and metabolic activators (calcium and vitamin D) and drugs that suppress osteoresorption (bisphosphonates) for the prevention and treatment of osteoporosis in children with cerebral palsy.

Keywords: bone metabolism; biomarkers; cerebral palsy.

БИОМАРКЕРЫ МЕТАБОЛИЗМА КОСТНОЙ ТКАНИ У ДЕТЕЙ С ЦЕРЕБРАЛЬНЫМ ПАРАЛИЧОМ, СПОСОБНЫХ К ПЕРЕДВИЖЕНИЮ

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Обоснование. Системному остеопорозу придают большое значение в патогенезе ортопедических нарушений у пациентов с детским церебральным параличом. Мы предположили, что у детей с детским церебральным параличом, способных к ходьбе, существуют особенности костного метаболизма, которые могут проявляться изменениями лабораторных параметров по сравнению с пациентами с ортопедическими заболеваниями без неврологического фона.

Цель — выявление особенностей метаболизма костной ткани на основании определения его биомаркеров у больных детским церебральным параличом, способных к ходьбе, по сравнению с пациентами с ортопедической патологией без неврологического фона.

Материалы и методы. Мы оценивали концентрацию кальция, фосфора, маркера костной резорбции β -crossLaps, остеокальцина, витамина D, C-концевого пропептида коллагена I типа и активность щелочной фосфатазы в сыворотке крови 50 пациентов с детским церебральным параличом в возрасте от 6 до 12 лет с уровнями моторных функций по шкале GMFCS I–III. Контрольную группу составили 50 пациентов с плановальгусными деформациями стоп.

Результаты. Активность щелочной фосфатазы в группе детей с детским церебральным параличом составила $170,25 \pm 59,35$ ЕД/л, а в контрольной — $145,58 \pm 46,29$ ЕД/л; концентрация C-концевого пропептида коллагена I типа в группе пациентов с ДЦП была выше, чем в контрольной ($324,01 \pm 174,10$ и $269,68 \pm 240,98$ соответственно). Концентрация β -crossLaps, остеокальцина, кальция и витамин D в основной группе была ниже, чем у детей с плоскостопием без общего неврологического фона.

Заключение. Изменения биомаркеров обмена костной ткани у детей с церебральным параличом, способных к самостоятельному передвижению, характеризуются параллельным повышением активности процессов остеорезорбции и остеорепарации, что позволяет обосновать возможность комбинированного применения препаратов, активизирующих костный анаболизм или являющихся его субстратом (кальций, витамин D), и препаратов, подавляющих остеорезорбцию (в частности, бисфосфонатов) для профилактики и лечения остеопороза у детей с церебральным параличом.

Ключевые слова: метаболизм костной ткани; биомаркеры; детский церебральный паралич.

In recent decades, interest in the study of osteoporosis in children has increased significantly [1, 2]. A number of factors can adversely affect the process of increasing bone mass in childhood and adolescence, which can result in an increased risk of fractures [3]. The mechanical strength of the bone is determined by its size, geometry, quality, and bone tissue weight and depends on a combination of genetic and hormonal factors, physical activity, and nutrition [4].

Diagnosis of osteoporosis in children is more complicated than in adults, due to physiological age-related changes in bone mineral density [5]. In 2007, the International Society of Clinical Densitometry published guidelines and definitions for the diagnosis of osteoporosis in children, which established diagnostic criteria for osteoporosis, namely a combination of low bone mineral mass according to densitometry (dual-energy X-ray absorptiometry) and a history of fractures [6]. Dual-energy X-ray absorptiometry is most often used to assess the mineral density of bone tissue [7], but its use in pediatric patients is associated with certain methodological limitations [8]. In addition, it does not provide an idea of the pathogenesis of a decrease in bone mineralization, namely an increase in catabolism or a decrease in anabolism.

Changes in bone tissue, which are signs of systemic osteoporosis, are of great importance in the pathogenesis of orthopedic disorders in pediatric patients with neuro-orthopedic diseases, including cerebral palsy (CP) [9]. The high risk of bone fractures in patients with neuromuscular diseases is discussed widely in the literature [10]. Risk factors

for osteoporosis in CP patients include decreased motor activity, axial load, and immobilization after surgical treatment, anticonvulsant therapy, nutritional disorders, and low growth rates [11, 12]. However, despite the apparent evidence of causal relationships, the orthopedic pathology and pathogenesis in CP has not been sufficiently studied.

To date, the diagnosis of osteoporosis in pediatric patients with severe multisystem diseases, including those with CP, is very difficult [13]. Densitometry in CP patients can be hindered by difficulty in positioning the child (contracture, asymmetry of the posture, implants as a result of previous surgeries) [14]. Nevertheless, determining the state of bone tissue in CP patients remains relevant to assessing the risk of secondary disorders, as well as the progression of deformities and bone fractures [15].

A number of studies in recent years have shown a direct relationship between the level of global motor functions according to the GMFCS classification (Gross Motor Function Classification System) and bone mineral density, namely the worse the general motility of a CP patient, the lower the bone mineral density [16]. The authors associated this pattern with motor activity. However, the differences in total motor activity between GMFCS levels I and II, as well as between levels IV and V, are not so significant as to explain fully the pronounced differences in absorptiometry. In addition, in patients with hemiplegia and GMFCS level I, the density of mineral bone tissue was different on the paresis side and on the intact side, despite minimal differences in load [17]. The authors suggested

that not only the nature of the load but also more significant factors associated with the main neurological disease, determine the change in bone mineral density in pediatric patients with CP.

As a hypothesis, we suggested that in CP patients who are able to walk, there are features of bone metabolism, which can be manifested by changes in laboratory parameters compared with patients with orthopedic diseases without a neurological aspect. To test this hypothesis, we decided to examine a group of CP patients, capable of walking and with deformities of the musculoskeletal system, which may occur among patients with orthopedic pathology who do not have a neurological disease as the predominant diagnosis. As such a deformity, we adopted planovalgus deformity of the feet. Deformities of the feet are the most common orthopedic manifestation of CP and one of the main indications for surgical treatment for this disease. Planovalgus deformity of the feet, in turn, is the most common variant of foot deformity in CP. In this regard, we found it possible to compare the indicators of bone metabolism in CP patients with foot deformities and capable of walking (I–III levels according to the GMFCS scale), with the corresponding indicators in patients with severe platypodia.

In recent years, the so-called biomarkers of osteoporosis have been used to diagnose and monitor osteopenic conditions. This term implies a group of laboratory indicators that reflects, directly or indirectly, the intensity of the osteogenic and osteoresorption processes and allows monitoring of the course of the disease and efficacy of treatment. Osteocalcin, alkaline phosphatase, C-terminal propeptide, and carboxyterminal telopeptide of type I collagen are the most studied among them. An analysis of the available literature revealed that recent publications provide no data on the nature of absolute and relative (compared with other categories of patients with orthopedic pathology) values of these biomarkers in CP patients.

Osteocalcin is a hydroxyapatite-binding protein synthesized only by osteoblasts and odontoblasts, as well as chondrocytes in the process of hypertrophy. Osteocalcin is a late marker of osteoblastic activity, so it is used as an indicator of bone anabolism activity.

Alkaline phosphatase is a membrane-bound enzyme located on the cytoplasmic membrane

of osteoblasts. It plays an important role in the formation and mineralization of osteoids and serves as an indicator of osteoblastic activity.

C-terminal propeptide of type I collagen (CICP) is a product of post-translational modification of the corresponding protein, which is formed mainly in proliferating osteoblasts and fibroblasts and is an indicator of osteoblastic activity.

Carboxyterminal telopeptide of type I collagen (also known as CrossLaps) is a degradation product of the corresponding protein and exists in two forms (alpha and beta isomers). An increase in the serum concentration of the beta form (β -CrossLaps) may indicate an intensity of osteoresorption.

This study aimed to identify special aspects of bone tissue metabolism based on determination of its biomarkers in CP patients with the ability to walk, compared with patients with orthopedic pathology without a neurological background.

Materials and methods

The main group consisted of 50 CP patients aged 6 to 12 years (mean age was 9.4 years). All patients could walk in accordance with the severity of the underlying disease (GMFCS levels: I — 8; II — 17; III — 25 patients, respectively). The control group consisted of 50 pediatric patients aged 5–13 years (mean age was 8.3 years) with plano-valgus deformities of the feet (hypermobile platypodia with shortening of the Achilles tendon in 22 patients; tarsal coalitions in 12; congenital malformations in 7; secondary and post-traumatic deformities in 9 patients). The criterion for exclusion from the study included orthopedic surgeries during the previous 2 years, as well as concomitant neurological and somatic diseases requiring constant medical treatment (including epilepsy).

In order to determine biomarkers of bone tissue metabolism upon admission to the start of surgical treatment, the patients within an overall examination underwent an additional sampling of 3 ml of venous blood. Patients' parents were informed of an additional examination, and relevant informed consent was obtained from them.

Laboratory analysis methods. The concentration of total calcium, phosphorus, and alkaline phosphatase activity in blood serum was determined by using a colorimetric photometric test with an AU 480 analyzer. The standard values of total calcium

in pediatric patients aged 2–12 years old were 2.2–2.7 mmol/l. Values of phosphorus in pediatric patients of preschool age were 1.45–2.1 mmol/l, and those in school age children were 1.45–1.78 mmol/l. Alkaline phosphatase activity in children aged 1–14 years old was 60–400 U/L.

The concentrations of β -CrossLaps, osteocalcin, vitamin D, and CICP were determined by using an electrochemiluminescent immunoassay. Reference values for these indicators were calculated for pediatric patients of different ages [18].

Statistical data analysis was performed using the software package IBM SPSS Statistics v. 23. The distribution normality was checked based on the calculation of the Kolmogorov–Smirnov criterion. The data obtained were characterized by a normal distribution in all groups. Descriptive statistics are presented as $M \pm S$, where M is the mean and S is the standard deviation. The distribution width was 95% of the confidence interval. The parameters in the study groups were evaluated using the t -test for independent samples, while the Levene test indicated equal variances, which enabled use of the t -test. Significant differences were considered at $p \leq 0.05$.

Results

The results of a comparative analysis of the data from two groups of patients are presented in the table.

As can be seen from the table, mineral metabolism in CP patients was characterized by multidirectional changes compared with patients in the control group (pediatric patients with platypodia). These changes are represented by both an increase in the processes of osteoresorption and activation of osteoreparation. So, the activity of alkaline phosphatase in the group of CP patients was 170.25 ± 59.35 U/l, and 145.58 ± 46.29 9 U/l in the control; the concentration of CICP in the group of CP patients was higher than in the control group (324.01 ± 174.10 and 269.68 ± 240.98 , respectively), but the last indicator did not reach a statistically significant difference in our study. On the contrary, the concentration of β -CrossLaps, osteocalcin, calcium, and vitamin D in the main group was lower than in pediatric patients with platypodia without a general neurological aspect (except for the last indicator, the differences were statistically significant).

Indicators of bone metabolism in CP patients and platypodia

Parameter	Diagnosis	Value	<i>t</i> -Criterion for equality of means	
			<i>t</i>	two-tailed significance
Alkaline phosphatase, U/L	CP	170.25 ± 59.35	2.086	0.042*
	Platypodia	145.58 ± 46.29		
Phosphorus, mmol/l	CP	1.51 ± 0.16	0.282	0.779
	Platypodia	1.50 ± 0.24		
Calcium, mmol/l	CP	2.50 ± 0.09	2.069	0.043*
	Platypodia	2.56 ± 0.05		
Vitamin D, ng/ml	CP	38.98 ± 15.34	1.785	0.080
	Platypodia	50.26 ± 24.40		
β -CrossLaps, ng/ml	CP	1.37 ± 0.59	2.023	0.048*
	Platypodia	1.78 ± 0.74		
Osteocalcin, ng/ml	CP	65.01 ± 25.98	1.444	0.047*
	Platypodia	76.47 ± 36.92		
CICP, ng/ml	CP	324.01 ± 174.10	0.519	0.606
	Platypodia	269.68 ± 240.98		

Note. CP — cerebral palsy, CICP — C-terminal propeptide of type I collagen. **t*-test less than 0.05.

Discussion

Disorders of mineral metabolism that can lead to secondary changes in the musculoskeletal system are described in many orthopedic diseases that are not directly related to the primary pathology of metabolism. The pathogenesis of these disorders is not fully understood. The mechanical factor associated with load characteristics (reduction of total intensity, limitation of high-intensity activities, in particular, sports, mechanical overload of certain structures of the musculoskeletal system associated with deformities) is most often discussed as a likely pathogenetic mechanism. In pediatric patients with neuro-orthopedic diseases, the most possible factor leading to impaired bone mineralization is considered to be a decrease of overall motor activity, or so-called osteopenia due to inactivity, characterized by a decrease in bone anabolism. Nevertheless, studies have shown that the use of drugs that activate bone anabolism or are substrates of bone formation (calcium, vitamin D) does not normalize bone mineral density in CP patients. For this reason, in recent years, much attention has been paid to the use of drugs that inhibit osteoresorption, including bisphosphonates, for the treatment of osteopenic conditions, including in CP patients. One of the theoretical counterarguments for the use of bisphosphonates is a possible decrease in the activity of bone anabolism, which may lead to their inefficiency. In addition, a decrease in the mechanical load on the bone can also hypothetically lead to the absence of a positive effect of antiresorptive therapy.

This study is characterized by the comparison of groups of independently moving patients with foot deformities dominating the orthopedic status.

As a result of the study, we identified a general tendency to change the main indicators, which affect, among other things, the mechanical properties of the bone in CP patients, namely the activation of both osteoresorption and osteoreparation. In particular, an increase in activity of alkaline phosphatase (170.25 ± 59.35 U/L in the main and 145.58 ± 46.29 U/L in the control group), CACP concentrations (324.01 ± 174.10 and 269.68 ± 240.98 , respectively) indicates an increase in osteoblastic activity in CP patients of the group under study, and the concentration of osteocalcin, which also serves as an indicator of

bone anabolism activity, and vitamin D, which is its regulator, were, on the contrary, higher in pediatric patients with platypodia without a neurological aspect. The concentration of β -CrossLaps, which characterizes osteoresorption, was lower in the main group than in pediatric patients with platypodia without a general neurological aspect.

Therefore, the biological processes that reflect the studied biomarkers of bone metabolism cannot be reduced to a simple formula for enhancing the processes of catabolism or weakening the anabolism processes. In this regard, a probable strategy for influencing bone metabolism in CP patients should be a combination of bone anabolism stimulation and suppression of catabolism through the combined use of appropriate pharmacological agents.

Some of the factors that may have hindered the interpretation of our data are the relatively small sample and limited nature of the main group (pediatric patients with level I–III disabilities according to GMFCS and capable of movement). As a result, we did not compare the anthropometric parameters of the patients of the main and control groups, although this could affect the results to some extent.

The reference values of biomarkers are determined for pediatric patients of different ages; however, their rather wide scatter found in the literature and the lack of clear population standards should be noted. In the framework of this study, we did not set the aim of determining the standards of the biomarkers described above. The main result was a comparative analysis of indicators in the group of CP patients and patients with a similar orthopedic pathology, but without a neurological aspect. Since the study was performed within the framework of one laboratory, we considered the absence of our own reference population base an unimportant factor.

Nevertheless, the general tendency revealed in this study indicates quite definitely that metabolic disorders that can negatively affect the mineral density of bone tissue and lead to deterioration in its mechanical properties are registered in most pediatric patients with orthopedic diseases, primarily neuro-orthopedic pathologies.

Changes in the mechanical load typical for patients with both primary orthopedic pathology and orthopedic manifestations of CP do not explain the whole complex of changes occurring. Further

studies using more specific and sensitive indicators of bone metabolism, as well as taking into account more detailed groups of patients, are likely to establish the specific contribution of orthopedic and neurological factors in the change in bone metabolism and the pathogenesis of osteoporosis in CP patients.

Conclusion

The condition of the child's bone tissue, including its strength characteristics, depends both on the initial properties of bone tissue, determined by the characteristics of its metabolism and on external mechanical factors acting on the growing bone. Special aspects of neuro-orthopedic diseases are disorders that develop in both fundamental components of this system. We have demonstrated multidirectional changes in the biomarkers of bone tissue metabolism, characteristic of pediatric patients with CP, capable of independent movement. The changes revealed consist of a parallel increase in activity of the osteoresorption and osteoreparation processes. This enables us to substantiate the possibility of the combined use of drugs that activate bone anabolism or serve as its substrate (calcium, vitamin D), as well as drugs that suppress osteoresorption (in particular, bisphosphonates) for the prevention and treatment of osteoporosis in CP patients.

Additional information

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Conflict of interest. The authors declare no obvious or potential conflicts of interest related to the publication of this article.

Ethical considerations. The study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association as amended by the Ministry of Health of Russia, approved by the ethics committee of the Turner Scientific Research Institute for Children's Orthopedics (protocol No. 7 of 22.08.2013).

The legal representatives of the patients gave their consent for processing of personal data and their publication.

Contribution of authors

V.M. Kenis created the concept and design of the study, data collection and processing, wrote the article.

S.L. Bogdanova conducted laboratory research, wrote the corresponding section of the article.

T.N. Prokopenko was involved in selection and clinical examination of the patients and data processing.

A.V. Sapogovsky performed statistical processing of the material, wrote the corresponding section of the article.

T.I. Kiseleva performed selection and clinical examination of the patients.

All authors made a significant contribution to the research and preparation of the article, read and approved the final version before publication.

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