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Review

Features of the state of bone tissue in children with cerebral palsy. Part 1. Etiological aspects. A literature review

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ABSTRACT

BACKGROUND: The growth of the human body is the most significant period of development of the bone tissue, because it is during this period that the size, shape, and architectonics of bone are formed against the background of increasing body weight and increasing physical exertion. Considering a number of pathological factors of the underlying disease (alimentary, neurological, hormonal, stress, and physical), bone tissue in children with cerebral palsy grows and develops with deviations from the norm.

AIM: To present up-to-date generalized information about the features of bone tissue in children with cerebral palsy to orthopedic traumatologists, neurologists, and physical therapy specialists.

MATERIALS AND METHODS: Studies on the problem of bone tissue condition in patients with cerebral palsy were analyzed. Data published over the past 20 years were searched in the scientific databases PubMed, Google Scholar, Cochrane Library, Crossref, and eLibrary without language restrictions.

RESULTS: In the last 20 years, the number of studies about pediatric osteoporosis has increased. The gold standard for determining the level of bone mineral density is dual-energy X-ray absorptiometry. However, its use in children has presented some difficulties and limitations. In children, the relationship between bone mineral density values and the risk of fractures has not been well studied, which does not allow us to discuss about osteoporosis based on densitometric bone mineral density data alone. In patients with cerebral palsy, a decrease in bone mineral density and bone mass during growth was found. Previous studies showed that the main factors associated with a decrease in bone mineral density in this group of patients include neuroendocrine causes due to growth retardation against the background of CNS damage, alimentary factors, decreased calcium and vitamin D concentrations, systemic use of glucocorticoids, intake of antiepileptic drugs, decreased motor activity, and low muscle mass. Increasing serum vitamin D concentrations does not have a positive effect on bone mass, although increasing serum calcium concentrations is associated with an increase in bone mineral density.

CONCLUSIONS: Identifying and correcting factors leading to decreased bone mineral density in children with cerebral palsy can improve bone health in this group of patients. The absence of a relationship between bone mineral density values and the risk of fractures in children with cerebral palsy does not allow us to discuss about osteoporosis based only on bone mineral density densitometric data. There may be more factors leading to an increased risk of bone fractures in children with cerebral palsy that require further study.

Keywords: cerebral palsy; bone mineral density; osteoporosis; bone tissue; bone fractures.

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Научный обзор

Особенности состояния костной ткани у детей с детским церебральным параличом. Часть I. Этиологические аспекты. Обзор литературы

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АННОТАЦИЯ

Обоснование. Период роста организма человека наиболее значим для развития костной ткани, так как именно в это время формируются размеры, форма и архитектоника кости на фоне увеличивающегося веса тела и усиливающейся физической нагрузки. На фоне огромного количества патологических факторов основного заболевания (алиментарные, неврологические, гормональные, нагрузочные и физические) костная ткань у детей с церебральным параличом закономерно растет и развивается с отклонениями от нормы.

Цель — представление врачам — травматологам-ортопедам, неврологам и специалистам физической терапии современной обобщенной информации об особенностях состояния костной ткани у детей с церебральным параличом.

Материалы и методы. Проанализирована литература, посвященная проблеме состояния костной ткани у пациентов с детским церебральным параличом. Поиск данных проводили в базах научной литературы PubMed, Google Scholar, Cochrane Library, Crossref, eLibrary без языковых ограничений, преимущественно отбирали работы, опубликованные за последние 20 лет.

Результаты. В последние 20 лет отмечается очевидная тенденция к увеличению количества исследований, посвященных детскому остеопорозу. Золотым стандартом определения минеральной плотности кости считают рентгеновскую двухэнергетическую абсорциометрию, но ее применение ограничено в детском возрасте и вызывает некоторые сложности. У детей связь между значениями минеральной плотности кости и риском переломов недостаточно хорошо изучена, что не позволяет говорить об остеопорозе только на основе денситометрических данных минеральной плотности кости. У пациентов с детским церебральным параличом снижен уровень витамина D и костной массы в процессе роста. Основными факторами, ассоциированными со снижением минеральной плотности кости у данной группы пациентов и выявленными нами в литературных источниках, являются нейроэндокринные причины в связи с задержкой роста на фоне поражения центральной нервной системы, алиментарные факторы, снижение концентрации кальция и витамина D, системное применение глюкокортикоидов, прием противоэпилептических препаратов, уменьшение двигательной активности пациентов, низкий уровень мышечной массы. Увеличение содержания витамина D в сыворотке крови не оказывает положительного влияния на костную массу, при этом увеличение концентрации кальция в сыворотке все же ассоциировано с увеличением минеральной плотности кости.

Заключение. Выявление и коррекция факторов, приводящих к снижению минеральной костной плотности у детей с церебральным параличом, могут улучшить здоровье костей у пациентов данной группы. Отсутствие связи между значениями минеральной плотности кости и риском переломов у детей с церебральным параличом не позволяет говорить об остеопорозе только на основе денситометрических данных минеральной плотности кости. Вероятно, существуют дополнительные факторы, приводящие к увеличению риска переломов костей у детей с церебральным параличом, требующие дальнейшего исследования.

Ключевые слова: детский церебральный паралич; минеральная плотность кости; остеопороз; костная ткань; переломы костей.

Как цитировать

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BACKGROUND

Infantile cerebral palsy (ICP) is the most common cause of motor disorders in childhood. Currently, there are about 17 million patients with ICP in the world [1]. Although ICP is a non-progressive neurological disease, patients may develop secondary orthopedic complications that progress during the child's growth. Such complications include limb joint contractures, joint dislocations, or bone deformities, and may also impair the strength, size, and architecture of the affected bone tissue.

Human growth can be defined as a quantitative increase in the mass of individual organs and the whole body, an increase in the size of the body and its parts, which is associated with a change in the number, properties or size of cells [2]. The growth period is most important for the development of bone tissue, since during this period the size, shape and architecture of the bones are formed in response to the increasing body weight and physical activity. The attention of researchers studying the problem of skeletal health in children is focused on the accumulation of bone mass during human growth and the identification of factors that influence this process. It is well-established that the skeletal system begins to form *in utero*, and at birth, the skeleton is composed of mineralized bone tissue and cartilage elements. As the child grows, the cartilage tissue gradually "ossifies," increasing in size and density. For humans, the peak bone mass is reached at approximately 30 years of age [3]. The normal growth and homeostasis of bone tissue throughout life are ensured by the processes of modeling and remodeling. The functioning of these complex mechanisms influenced by a number of factors, including genetic predisposition, dietary habits, body weight, physical activity, blood levels of calcium and vitamin D, and factors that contribute to bone loss (endocrine, gastrointestinal, autoimmune, and renal diseases). A delay in achieving the peak bone mass during the growth period increases the risk of developing osteoporosis and experiencing bone fractures at a later age [4]. For ICP patients, a multitude of pathological factors associated with the underlying disease (alimentary, neurological, hormonal, stress-related, and physical) contributes to abnormalities in bone tissue growth and development.

We believe that the problem of bone health in ICP patients has been overlooked in the Russian medical literature. A comprehensive understanding of the characteristics of bone tissue and the factors influencing bone mass accumulation in ICP patients is essential for elucidating the etiopathogenesis of secondary osteoporosis in this population and for developing the effective prevention and treatment strategies.

The study aimed to present current, comprehensive data on the characteristics of bone tissue and the factors influencing its development in children with infantile cerebral palsy to orthopedic surgeons, neurologists, and physical therapy specialists.

MATERIALS AND METHODS

The stated aim of the study was achieved by searching for and analyzing scientific literature published primarily over the past 20 years and focused on the problem of bone health in ICP patients. The selection of literature for subsequent review and analysis was based on the criterion of priority given to the studies published in high-impact international journals and those with a high level of evidence. The search was conducted in the scientific databases PubMed, Google Scholar, Cochrane Library, Crossref, and eLibrary with no language restrictions, by keywords "ICP," "bone mineral density," "osteoporosis," and "bone tissue." Given the extensive scope of the problem under investigation and the variety of data presented in the published literature, the approach of narrative review was deemed an appropriate methodology for their analysis and structuring. This approach facilitated the presentation of the key facts in a consistent manner that reflected the authors' view of the problem.

RESULTS AND DISCUSSION

The evaluation of bone mass across different age groups is performed using non-invasive methods for assessment of bone mineralization. A variety of methods are available for the assessment of bone mineral density (BMD). Computed tomography and conventional radiography of bone tissue are used as provisional methods suggestive of a potential decrease in bone density and osteoporosis. Although ultrasound densitometry is considered a promising research method, it has had a limited specificity and may be significantly influenced by the individual patient characteristics. Quantitative computed densitometry is another promising method, which assesses both BMD and microscopic changes in bone architecture.

The current gold standard for bone mineral density measurement is dual-energy X-ray absorptiometry (DEXA), or densitometry. However, this method has certain limitations when used in pediatric practice and is associated with specific challenges [5]. These challenges are attributed to the fact that bone size, shape and density vary with age. However, these parameters are also influenced by other factors, such as gender and ethnicity [6]. Current guidelines recommend that BMD be measured in the spine rather than in the hip. The femur measurements are limited by a lower accuracy, supported by the paucity of reference data available, and associated with the difficulties in identifying bone markers [7]. An age-specific standard deviation (Z-score) is calculated by comparing BMD values with reference data for DEXA

equipment manufactured by the same company. The most exhaustive published reference data are currently available for Hologic [8, 9], GE, Lunar [10, 11] and Norland [12] systems. DEXA densitometer manufacturers emphasize the crucial role of the reference database in ensuring the reliability of imaging results. They highlight that variations in mean values and standard deviations may influence BMD Z-scores. In particular, the failure to use gender-specific reference data may result in an underestimation of BMD in adolescent males, who typically experience the onset of puberty later than females [13].

Chronic or systemic diseases, such as ICP, are frequently associated with delayed bone growth and puberty, which may alter the expected composition of body tissues and thereby complicate the interpretation of DEXA findings. It appears to be a significant challenge to develop a specialized reference database for children with ICP, given the considerable heterogeneity of this neurological disease accompanied by orthopedic complications. It is therefore inadvisable to rely on DEXA bone density scans alone for clinical decision-making in ICP patients.

Despite all the above challenges, DEXA has become the most widely used method to measure BMD due to its speed, accuracy, low radiation exposure, and the availability of pediatric reference data [14–16].

In 2007, the International Society for Clinical Densitometry revised the definition and diagnostic guidelines for osteoporosis in children [17]. These guidelines establish the diagnostic criteria for osteoporosis based on the combination of reduced BMD on DEXA scans and a history of fractures. While older people demonstrate a rather consistent correlation between low BMD values by DEXA and the risk of bone fractures, densitometry results can be used directly to diagnose osteoporosis [4]. However, in the context of pediatric practice, the situation is more complicated. The World Health Organization defines a –2.5 decrease in BMD from the reference value as osteoporosis, which reliably increases the risk of fractures [18]. The correlation between BMD values and the risk of fractures in children remains poorly understood, therefore osteoporosis cannot be definitively diagnosed on the basis of densitometric BMD data alone [7]. In both children and adults, additional factors influence BMD and the risk of fractures. These factors include genetic predisposition, medications, dietary habits, endocrine disorders, lack of mobility, and puberty. However, these factors cannot be used as a diagnostic criterion for the risk of fracture.

Biochemical markers of bone tissue metabolism (such as osteocalcin, bone alkaline phosphatase, and cathepsin K) have been demonstrated to be effective predictors of both the risk of fractures in adults [19] and the response to therapy [20]. Attempts to use these parameters in pediatric practice have proven controversial due to the difficulties associated with interpreting the results [21]. Children have significantly higher levels of bone formation and resorption markers compared to adults. This difference is particularly evident in infancy and early or middle adolescence, when bone growth, modeling, and remodeling are most active [22]. In an exploratory study, the authors investigated the correlation between blood levels of bone markers and the size/density of bone tissue on computed tomography scans. Their findings suggested that there was a negative correlation between bone formation markers and bone density, with no correlation reported for bone size. Moreover, bone resorption markers have been found to be negatively correlated with the size and volume of bone tissue [23]. Similarly to adults, bone marker levels in children vary with time of day and food intake, which further complicates the use of this diagnostic method in pediatric patients. In children, bone marker levels should be additionally adjusted for age, gender, height, and puberty. Furthermore, inter- and intraindividual variability in bone marker values may limit the significance of single measurements and preclude clinical decision making based on them [21]. It is evident that bone markers can be useful in pediatric studies to monitor the bone tissue response to pharmacological treatment. However, the clinical utility of these markers for the assessment of bone quality remains uncertain [4, 22]. Meanwhile, laboratory investigations are a valuable tool for ruling out other forms and causes of osteoporosis.

It has been demonstrated that external factors such as diet, physical and axial loads play a significant role in the child's bone development [24, 25] and remodeling, which is primarily initiated once skeletal growth is completed [26, 27].

Feeding difficulties are a common occurrence, particularly in patients with severe ICP, and are frequently associated with low body weight and malnutrition [28]. Consequently, nutritional disorders represent a significant contributing factor to the deterioration of bone quality in children with infantile cerebral palsy. Nutritional disorders may be attributed to feeding difficulties, including chewing and swallowing disorders (discoordination of the lips, tongue, palate, and pharynx muscles), delayed development due to damage to the brain centers responsible for nutrition and growth (hypothalamic centers). Furthermore, nutritional disorders may result from dental caries/enamel hypoplasia and other dental problems, negative energy balance, and mineral deficiencies induced by chronic use of antiepileptic drugs [29]. Insufficient food intake results in a deficiency of macro- and micronutrients, including those are essential for maintaining the skeletal health. It has been consistently demonstrated that there is a correlation between BMD and adequate nutrition (patient's height, weight, and skinfold thickness) [30].

The beneficial effect of Ca++ and vitamin D on bone mass formation and achievement of peak bone mass and

targeted BMD levels has been extensively documented in scientific literature. It is therefore evident from the vast majority of studies that an increase in dietary calcium intake is associated with a significant enhancement in BMD levels at all skeletal sites. However, the findings of the meta-analysis (2015) on the effect of Ca++ supplementation on bone density [31] state that an increase in dietary calcium intake is associated with a comparable increase in BMD as observed with calcium supplements. Both sources produce a small (1%–2%) non-progressive increase, with no further significant effect at one year. A subgroup analysis of baseline clinical characteristics has demonstrated that an increase in calcium intake is unlikely to result in a clinically significant reduction in the risk of fracture.

The largest number of relevant scientific articles are focused on the effect of vitamin D on bone density. Although the high prevalence of vitamin D deficiency has been well documented in the general population, a definitive assessment of the significance of vitamin D deficiency in ICP patients compared to the general population has yet to be conducted.

The majority of the scientific publications is limited to cross-sectional studies. In 2017, an Indian case-control study [32] documented vitamin D insufficiency in 61% of ICP patients, while 32% were diagnosed with vitamin D deficiency. Seth et al. [33] reported a 60% prevalence of vitamin D deficiency among ICP children. In their study, Toopchizadeh et al. found that 44.6% of ICP children had deficient levels of vitamin D [34]. A Turkish cross-sectional study of 2021 [35] revealed no considerable difference in the prevalence between vitamin D deficiency and insufficiency (28.8% and 22.6%, respectively). In the study by Le Roy et al. [36], different proportions were reported. In the cohort of ICP patients, i.e., almost a half (47.8%) were found to have vitamin D insufficiency, while one third (30.4%) were diagnosed with vitamin D deficiency.

Discrepancies in the prevalence across the studies may be primarily attributed the heterogeneity of the patient population and variabilities in the reference thresholds used to define vitamin D insufficiency and deficiency. E.g., Akpinar [35] defined serum vitamin D deficiency as a level of ⩽12 nmol/L, while the level within the range of 12–20 nmol/L was considered as vitamin D insufficiency. Seth et al. [33] defined an insufficient vitamin D level as 25–50 nmol/L.

The effect of vitamin D on BMD markers also remains inconclusive. A substantial body of research has highlighted a pivotal role of vitamin D in maintaining normal bone tissue and, consequently, in reducing the risk of pathological bone fractures [32–37]. Jekovec-Vrhovsek et al. [38] reported that a 9-month vitamin D and calcium supplementation was found to significantly increase BMD in a group of children with severe (Gross Motor Function Classification System [GMFCS] IV–V) cerebral palsy and epilepsy. However, there was no changes in their physical or ambulatory status. The control group of children who did not receive vitamin D and calcium supplementation continued to lose bone mass.

In addition to these findings, research has shown that osteoanabolic drugs or bone formation supplements (calcium, vitamin D) are ineffective in normalizing BMD in ICP patients [39]. This conclusion has also been corroborated by recent reviews of the literature investigating the effect of vitamin D on BMD. Most studies evaluating the effect of vitamin D, either alone or in combination with calcium, on bone health have yielded inconclusive results. The correlations identified in prospective cohort and case-control studies were weak and rarely supported by the findings from randomized controlled trials. There was also a paucity of evidence to suggest a clear dose-response relationship between vitamin D intake and bone health. Despite the considerable number of recent studies, the currently available evidence too inconclusive support any definitive findings concerning the correlation between serum 25(OH)D levels, vitamin D and calcium supplementation (either alone or in combination), and bone density [40, 41].

Therefore, the available evidence does not support the suggestion that vitamin D has a beneficial effect on BMD in this population. However, the current approach to osteoporosis therapy in pediatric practice is based on the use of vitamin D supplements.

Studies that investigated the relationship between vitamin D and insulin-like growth factor 1 (IGF-1) in ICP patients suggest a promising potential for further research [42]. IGF-1 is a hormone-like peptide synthesized in the liver and muscles in response to the action of somatotropic hormone. IGF-1 has been demonstrated to stimulate osteoblast activity, increase tubular phosphate resorption, and enhance the renal synthesis of the active form of vitamin D [42]. In ICP patients, damage to the central nervous system can contribute to the impaired synthesis of somatotropic hormone and a reduction in IGF-1. In the study by Nazif et al. [42], there was a proportional decrease in both IGF-1 and BMD levels in response to a decline the patient's motor functions. IGF-1 correlated positively with serum vitamin D and BMD. Patients with GMFCS IV–V ICP or those taking anticonvulsants have the highest risk of developing low BMD and IGF-1 levels. In some of these studies, supplementation with higher doses of vitamin D was associated with an increase in IGF-1 and lumbar BMD, but not in proximal femur BMD. In contrast, other studies demonstrated that vitamin D supplementation enhanced proximal femoral bone density [39].

Chronic or long-term drug therapy can have both positive and negative effects on the child's bone health. The previously described calcium or vitamin D supplements and agents that improve the intestinal absorption of essential nutrients have been demonstrated to exert a beneficial effect. However, steroids have been identified as having a negative effect and

resulting in extremely adverse outcomes for BMD in patients of all ages [43]. Systemic glucocorticoids are administered to ICP patients for the treatment of bronchopulmonary dysplasia or specific forms of epilepsy. The long-term use of H^+,K^+-ATPase inhibitors has been associated with malabsorption and an elevated risk of decreased bone density and fractures [44]. A similar effect has been described for aluminum-containing antacids, which bind to phosphorus in the intestine and thereby inhibit its absorption. These pharmaceutical agents are widely used in pediatric patients with cerebral palsy to relieve gastroesophageal reflux disease. However, an analysis of the effect of pharmacotherapy on bone density in individuals with cerebral palsy should be primarily focused on anticonvulsants, given the higher prevalence of epileptiform activity among children with cerebral palsy compared to the general population.

The findings of studies evaluating the effect of antiepileptic drugs on skeletal health in pediatric populations are inconclusive. In 2011, Pack [45] reported that some antiepileptic drugs are associated with adverse effects, attributed to the upregulation of cyp24 (a member of the cytochrome p450 superfamily), which is known to inactivate vitamin D. These findings are corroborated by other researchers who have demonstrated that some anticonvulsants (phenobarbital, phenytoin, and valproic acid) have an adverse impact on vitamin D metabolism [46].

A literature review of relevant studies, including cross-sectional, cohort randomized controlled trials, and case-control studies, has yielded evidence that carbamazepine and valproic acid are associated with lower BMD [47]. Additionally, the same review has indicated that antiepileptic drugs combination therapy has a more significant adverse effect on BMD than monotherapy. However, some studies demonstrate no effect of antiepileptic drugs on bone tissue [46].

Although the plethora of studies have demonstrated a direct correlation between epilepsy, osteoporosis, and an elevated risk of fractures in ICP patients [48], it is not feasible to assess the direct effect of anticonvulsants on the incidence of fractures in isolation from other factors (such as dietary habits, low physical activity, and increased risk of injury), which contribute to the development of osteoporosis and low-energy fractures and are commonly observed in individuals with epilepsy. Linton et al. analyzed population data and concluded that epilepsy in patients with GMFCS IV–V ICP was associated with a 7-fold increase in the incidence of fractures [49], while such a relationship was not revealed in patients with milder forms of ICP [50].

The motor function is a significant factor affecting patient's bone mass. A reduction in physical and axial load in children with cerebral palsy results in significant differences in the shape, length and mass of their bones compared to their healthy peers [51]. Krick et al. have demonstrated the age-dependent progression of growth and weight deficit in ICP patients. Compared to their healthy peers, they were 5% shorter at 2 years of age and more than 10% shorter at 8 years of age [52]. Additionally, the authors revealed a correlation between the patient's motor activity and bone health, whereby the mean length of the measured bones in patients with GMFCS IV–V was found to be 16% shorter than in patients with GMFCS III. In clinical practice, however, the patient's height is of little clinical significance, although it may indirectly suggest an overall reduction in bone mass.

The impaired motor function may be associated with a proportional increase in risks of bone injury, since physical activity has been demonstrated to enhance BMD [53, 54]. However, the contribution of physical activity and minimum references values for ICP patients remains unclear.

In 2002, Henderson et al. reported a mean (±SD) reduction of 1.8 and 3.8 in BMD for patients with GMFCS III and GMFCS IV–V, respectively [55]. The authors concluded that persistent motor impairment may be associated with a reduction in BMD in the distal femur.

In their population study, Linton et al. [49] demonstrated that the incidence and nature of fractures in ambulant ICP patients (GMFCS I–III) did not differ from those in healthy children. This was consistent with the findings of a Danish study [48]. ICP patients with severe motor impairments (GMFCS IV–V) have a higher risk of fractures. In the study by Whitney et al. [56], males with ICP had a 2.9–5.6-fold higher risk of fractures compared to healthy individuals. The published data appears to be quite logical and consistent with the hypothesis that overall physical activity is positively correlated with the patient's level of motor activity. In patients with GMFCS III–V ICP, physical activity is 70%–80% lower compared to their neurologically healthy peers [27, 57].

Muscles play a pivotal role in bone growth. In 1997, Frost [58] suggested that muscle contraction has a greater effect on bone health than axial load. In his mechanostat theory proposed in 1960s, Frost developed the Wolff's law, which postulates that 'mechanical function of bone drives the evolution of its architecture'. Frost described the mechanism by which mechanical load affects bone structure by changing its mass and architecture to provide a structure that can resist typical and regular loads with the minimal and economical amount of energy and structural material. Since changes in the skeleton are driven by the balance between bone growth and bone resorption, the mechanostat uses these processes through effector cells (such as osteocytes, osteoblasts, and osteoclasts) to model the effects on the skeleton. This assumption was corroborated by other scientists [59–61], who demonstrated a positive correlation between the muscle and bone health. Noble et al. reported a positive relationship between thigh muscle volume and femoral strength in ICP patients aged 10 to 23 years. However, no such correlation was identified for the tibia [62].

Obviously, the effect of muscles on bone health is limited to biomechanical processes based on the mechanostat theory. Additionally, hormonal mechanisms play a role, with muscles functioning as an endocrine organ, contributing to the regulation of bone metabolism. This regulation is mediated by cytokines, including IGF-1 and osteonectin [63]. Since ICP patients have a significantly reduced muscle mass and increased fatty infiltration of muscles [64, 65], studies have been conducted to evaluate the effect of adipose tissue on BMD. In previous studies, low levels of circulating vitamin D in the blood have been attributed to obesity and associated cardiometabolic risk factors and pathological conditions, including diabetes mellitus [66–68]. Obesity has been demonstrated to improve BMD in neurologically healthy children and adolescents. However, the authors who have identified this correlation suggest that it is associated with active muscle gain in response to body weight increase [69], although this effect is very unlikely to occur in ICP. The relatively low prevalence of obesity among ICP patients compared to those with other neurological disorders accompanied by orthopedic complications, such as *spina bifida*, and the inconsistency of findings from scientific literature, preclude the clinical utility of this factor.

In addition to the previously mentioned determinants of the bone health, many other factors non-specific for ICP patients may also be relevant, including genetic predisposition, endocrine status (growth hormone deficiency, diabetes mellitus, hyperparathyroidism, and glucocorticoid-induced osteoporosis), gastrointestinal disorders (celiac disease, Crohn's disease, and anorexia nervosa), autoimmune diseases (caused by the overexpression of osteoclastogenic pro-inflammatory factors, such as interleukin 1, interleukin 6, cytokines, tumor necrosis factor 1), renal diseases (in chronic kidney disease, overexpression of fibroblast growth factor 23 suppresses osteoblast differentiation and can result in developing osteoporosis; renal tubular acidosis is associated with hyperchloremic acidosis). Excess of hydrogen ions induces osteoclast activation to compensate for acidosis and calcium mobilization from bone tissue, which also contributes to bone loss.

CONCLUSION

A reduction in bone density is a significant clinical complication in ICP patients. Osteoporosis has been identified as a significant contributor to the progression of bone deformities in a growing child, with the potential to result in low-energy fractures. As a consequence, the patient's ambulance abilities and overall quality of life are significantly impaired. The multifactorial nature of osteoporosis in these population narrows the range of potential prevention strategies to simultaneous and continued correction of all etiological factors. The combined use of osteoanabolic drugs, bone formation supplements (calcium, vitamin D), and bone resorption inhibitors (such as bisphosphonates), ambulance monitoring and regular vertical loading, multilevel single-stage surgery, and the use of specialized osteosynthesis systems, all contribute to a mitigation of the adverse consequences of osteoporosis in ICP patients.

ADDITIONAL INFORMATION

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