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Review

Legg–Calvé–Perthes disease presenting with osteoarthritis: Mechanisms of the development and prospects of conservative therapy using bisphosphonates

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ABSTRACT

BACKGROUND: Aseptic necrosis of the femoral head in children remains a subject of great interest among specialists, despite its long history of study. The Legg–Calvé–Perthes disease is the most common form of aseptic necrosis of the femoral head in children. The necrotic lesion in the femoral head results from the blockage of the arterial blood supply to the epiphysis, leading to its infarction. Some children experience a more aggressive disease course, with signs of osteoarthritis, which can result in the early development of coxarthrosis. Numerous publications have demonstrated the successful use of bisphosphonates in adult patients with aseptic necrosis of the femoral head.

AIM: To generalize data on the use of bisphosphonates in children with the Legg–Calvé–Perthes disease presenting with signs of osteoarthritis through the analysis of contemporary global literature.

MATERIALS AND METHODS: A literature search was conducted in the open databases of PubMed, Science Direct, and Google Scholar, and the analysis depth spanned 20 years. The search terms used included "Legg–Calvé–Perthes disease," "aseptic (avascular) necrosis of the femoral head," and "bisphosphonates." The review encompassed the literature on bisphosphonates, their biological action, effectiveness of their use in patients with aseptic necrosis of the femoral head, and results of our research.

RESULTS: Studies on the efficacy of bisphosphonates in children with Legg–Calvé–Perthes disease are limited. Currently, the effect of bisphosphonates on disease course and outcome is unknown. Despite this, mechanisms of chronic inflammation are increasingly mentioned in the literature, which may directly or indirectly influence the clinical course and outcome of the disease. The key is the hyperactivity of osteoclasts in osteonecrosis. The experience of using bisphosphonates in adult patients with aseptic necrosis of the femoral head had positive results in preventing the progression of the deformity of femoral head deformity.

CONCLUSIONS: Bisphosphonates are specific inhibitors of osteoclast activity, which has been used in many diseases. The results and inferences of using bisphosphonates in children with Legg–Calvé–Perthes disease will lead to the formulation of a new treatment algorithm.

Keywords: avascular necrosis of the femoral head; Legg-Calve-Perthes disease; synovitis; osteoarthritis; bisphosphonates.

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Научный обзор

Болезнь Легга – Кальве – Пертеса, протекающая с признаками остеоартрита: механизмы возникновения и перспективы консервативной терапии с применением бисфосфонатов

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АННОТАЦИЯ

Обоснование. Асептический некроз головки бедренной кости у детей остается предметом пристального внимания специалистов, несмотря на многолетнюю историю его изучения. Наиболее частая разновидность асептического некроза головки бедренной кости у детей — болезнь Легга – Кальве – Пертеса. Хорошо известно, что очаг некроза в головке бедренной кости формируется вследствие блокирования артериального притока к эпифизу, то есть его инфаркта. У части детей отмечают более агрессивный вариант течения заболевания — с признаками остеоартрита, который приводит к раннему развитию коксартроза. В многочисленных публикациях продемонстрировано успешное применение бисфосфонатов у взрослых пациентов с асептическим некрозом головки бедренной кости.

Цель — путем анализа современной мировой литературы обобщить данные относительно перспективности применения бисфосфонатов у детей с болезнью Легга – Кальве – Пертеса с признаками остеоартрита.

Материалы и методы. Проведен поиск литературы в открытых информационных базах PubMed, Science Direct, Google Scholar с глубиной анализа 20 лет. В качестве поисковых ключевых слов использовали «болезнь Легга – Кальве – Пертеса», «асептический (аваскулярный) некроз головки бедренной кости» и «бисфосфонаты». Обзор дополнен литературными данными о бисфосфонатах, их биологическом действии, эффективности применения у пациентов с асептическим некрозом головки бедренной кости, а также результатами собственных наблюдений.

Результаты. Работы по изучению эффективности применения бисфосфонатов у детей с болезнью Легга – Кальве – Пертеса немногочисленны. В настоящее время не известен характер влияния бисфосфонатов на течение и исход заболевания. Несмотря на это, в литературных источниках все чаще упоминаются механизмы хронического воспаления, которые могут напрямую или косвенно влиять на клиническое течение и исход болезни. Ключевой из них — гиперактивность остеокластов в очаге остеонекроза головки бедренной кости. Опыт применения бисфосфонатов у взрослых пациентов с асептическим некрозом головки бедренной кости показал положительные результаты в предотвращении прогрессирования деформации головки бедренной кости.

Заключение. Бисфосфонаты — высокоэффективные ингибиторы остеокластов, применяемые при многих тяжелых заболеваниях. Изучение и последующее обобщение результатов использования бисфосфонатов помогут выработать новый алгоритм лечения детей с болезнью Легга – Кальве – Пертеса с признаками остеоартрита.

Ключевые слова: асептический некроз головки бедренной кости; болезнь Легга – Кальве – Пертеса; синовит; остеоартрит; бисфосфонаты.

Как цитировать
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BACKGROUND

Aseptic necrosis of the femoral head (ANFH) has been known for a long time. The incidence of ANFH ranges from 0.4 to 29 cases per 100,000 children across diverse ethnic groups. Typically, ANFH occurs in stages, with the lesion in most cases being unilateral (85–90%). Legg–Calvé–Perthes disease (LCPD) is the most common type of ANFH in pediatric patients [1]. The underlying mechanism of formation of a focus of necrosis in LCPD is avascular, leading to infarction of the epiphysis. The factors causing this condition are not fully understood [2]. During the initial phase of development of femoral head necrosis, as a rule, a transient inflammatory reaction of the joint is noted, often resembling the course of arthritis [3]. At the stage of an impression fracture, typical radiological signs are registered, particularly the line of a subchondral fracture in the epiphysis, which makes it possible to identify the disease. The process of new bone tissue formation begins during the destructive disintegration of the epiphysis into fragments. The disease outcome is more favorable with timely, comprehensive treatment [4]. However, despite receiving appropriate therapy, up to a quarter of pediatric patients are susceptible to a more aggressive version of the disease, marked by osteoarthritis symptoms. Factors contributing to the development of osteoarthritis in LCPD have not yet been fully determined. Several studies have noted that this disease course is characterized by an increase in the area and longer persistence of the necrosis focus, accompanied by an aggressive form of chronic synovitis. This combination leads to severe deformity of the femoral head and early development of coxarthrosis [5]. Traditional pathogenetic conservative therapy for LCPD turned out to be ineffective. However, according to the literature, conservative treatment with bisphosphonates significantly reduced the disease manifestations in adult patients with ANFH. This fact makes the administration of bisphosphonates to pediatric patients with LCPD with signs of osteoarthritis very promising [6, 7].

The work aimed to summarize data on the prospects of using bisphosphonates in pediatric patients with LCPD disease with signs of osteoarthritis by analyzing modern world literature.

MATERIALS AND METHODS

We searched the PubMed, Science Direct, and Google Scholar databases for articles published between 2003 and 2023 using the keywords "Legg–Calvé–Perthes disease," "aseptic (avascular) necrosis of the femoral head," and "bisphosphonates." We considered any publications regardless of their language of publication. The article is supplemented with literature materials focusing on the study of the pathogenesis mechanisms and osteoarthritis implementation in patients with ANFH. Based on the literature data and the results of our research, information about bisphosphonates, their biological action, and efficiency in ANFH patients is presented.

RESULTS AND DISCUSSION

The database search identified 370 publications, focusing on bisphosphonates used in animal models or meta-analyses. In this regard, the search was supplemented with an age characteristic of 0–18 years. Following this, only 27 articles were selected for further analysis. Among these, four of the selected publications contained descriptions of clinical cases, and four publications presented meta-analysis or thematic literature review. Additionally, four publications dealt with issues of pathophysiology or systemic effect of bisphosphonates in pediatric patients, and two publications presented treatment of osteonecrosis of the femoral head in the presence of hemoblastosis. Furthermore, four publications contained materials on using bisphosphonates in pediatric patients with posttraumatic avascular necrosis. Two publications presented information on technetium-99m-methylene diphosphonate (99mTc-MDP) in the diagnosis of avascular necrosis, while five articles were appropriate to the subject of the request regarding the use of bisphosphonates in idiopathic avascular necrosis. In addition, two articles were related to bisphosphonate therapy in pediatric patients with systemic lupus erythematosus and sickle cell anemia. During the first decade (2003–2013), there were no randomized clinical trials related to the issue of the effectiveness of bisphosphonates in pediatric patients or their effect on the X-ray anatomical presentation. In the second decade (2013–2023), only five randomized clinical trials were presented. However, analysis of publications showed that four articles described patients over 18 years of age and concerned the pediatric population only indirectly. Thus, only one full-fledged study that analyzed the effectiveness of zoledronic acid in pediatric patients with LCPD has been identified [49].

Idiopathic ANFH

ANFH has been known for a long time and has been studied thoroughly. However, several mechanisms are still not clarified, including the cause of the formation of a focus on avascular necrosis. Despite the noninflammatory nature of the disease, recent literature has been increasingly discussing some mechanisms of chronic inflammation, which can directly or indirectly affect the course and outcome of the disease. This fact somewhat modifies the classical ideas about aseptic necrosis [9]. Currently, ANFH is considered a multifactorial disease, and the inflammatory process can be regarded as one of the factors of aggression [10]. ANFH is registered in pediatric

patients with rheumatic diseases, congenital blood diseases (hemophilia, thrombophilia, sickle cell anemia, and α-thalassemia), hemoblastosis, hyperhomocysteinemia, and less often with other pathologies.

The structural changes in idiopathic ANFH are based on vascular disorders that are directly related to inflammatory processes in the endothelium of the vascular wall, changes in the shape of erythrocytes or blood rheology toward increased viscosity, and processes of occlusion or obliteration of small vessels. In some cases, ANFH may be immune-mediated or even be caused by molecular genetic aspects [11]. While studying ANFH in pediatric patients with rheumatic diseases, in which the vector of the blood coagulation system changes toward hypercoagulation or vasculitis is registered, it turned out that the disease prevalence is low [12]. In pediatric patients with rheumatological pathology, avascular necrosis was most common in the group of patients with systemic lupus erythematosus (5.4–8.4%, up to 15% of cases, according to some studies) and less often in patients with juvenile arthritis and dermatomyositis [13]. At the same time, the hormone-dependent theory regarding the origin of ANFH has not consistently been supported. When explaining the cause of the development of infarction of the femoral head epiphysis, experts most often leaned toward the concepts of chronic inflammation, hypercoagulation, and vasculopathy [14]. For example, among the various forms of juvenile arthritis, the systemic variant (the most severe form of the disease) accounted for the largest number of cases of avascular necrosis. At the same time, the timing of the deformity formation coincided with the peak of high laboratory and clinical activity of the disease. For articular forms of juvenile arthritis, cases of avascular necrosis during childhood were quite rare.

Clinical cases of avascular necrosis in adulthood in patients with certain variants of rheumatoid arthritis in which the disease onset occurred during childhood are relatively few in the literature [15]. Among deficiency conditions, researchers have predominantly focused on vitamin D and its metabolites. Several studies have indicated a correlation between severe vitamin D deficiency (less than 15 ng/ml) and the risk of avascular necrosis in pediatric patients [16, 17]. From an inflammatory perspective, this is probably due to the ability of the active metabolite of vitamin D (cholecalciferol) to intertwine with the innate immune system, regulating the synthesis and cellular secretion of major proinflammatory cytokines (interleukin-6, tumor necrosis factor-α and interferon α) [18]. Additionally, there are suggestions in some sources regarding the involvement of molecular genetic mechanisms in the pathogenesis of ANFH. Several candidate genes have been discovered, and single nucleotide polymorphisms, according to scientists, may play a role in bone metabolism and potentiate the risks of developing ANFH. Among them are the *Klotho (KL)*, *BMP6*, and *ANXA2* genes [19]. Over the past few years, a relationship between a heterozygous mutation in the *COL2A1* gene and ANFH has been established. In the cases described, the course of avascular necrosis in this category of patients has a familial aggregation and is characterized by bilateral lesions, even in cases where onset occurs during childhood. However, many researchers attribute this form of ANFH more to type 2 collagenopathy with the development of osteonecrosis [20]. In LCPD in pediatric patients, according to numerous molecular genetic studies, no candidate genes have been identified that increase the risk of the disease [21].

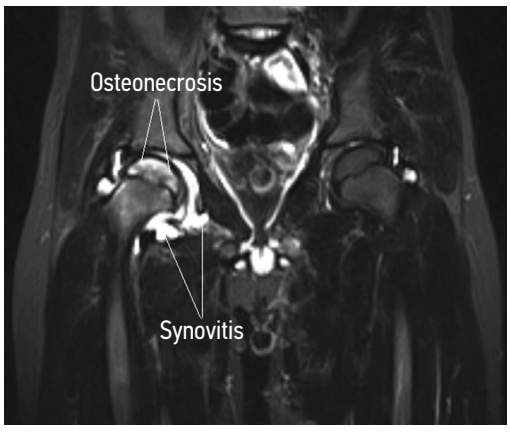

Fig. 1. Magnetic resonance imaging shows the initial stage of ANFH (from the author's archive). A magnetic resonance imaging scan reveals osteonecrosis of the femoral head on the right, massive trabecular edema, as well as pronounced symptoms of synovitis with overstretching of the joint capsule

ANFH and osteoarthritis

Currently, very ambiguous ideas have been formed about osteoarthritis in pediatric patients in the structure of ANFH. The mechanisms of the formation of chronic inflammation against avascular necrosis have yet to be thoroughly established. There are several theories, among which uncontrolled hyperactivity of osteoclasts, the syndrome of an exaggerated inflammatory response with overexpression of the main proinflammatory cytokines (interleukin-6 and tumor necrosis factor alpha), or the model of antiphospholipid syndrome are most consistent with ideas about the course of chronic inflammation [22, 23]. In the early stages of the disease, pediatric patients with ANFH have increased levels of the main proinflammatory cytokines in the synovial environment [24]. The role of osteoclast hyperactivity in the formation of osteonecrosis lesion has been well-established over many years of research (Fig. 1). Recent studies using immunochromatographic analysis have demonstrated overexpression of the receptor activator of nuclear transcription factor NF-κB (RANK) in the site of aseptic necrosis of bone tissue in the early stages of the disease [25]. RANK is a type I transmembrane protein belonging to the tumor necrosis

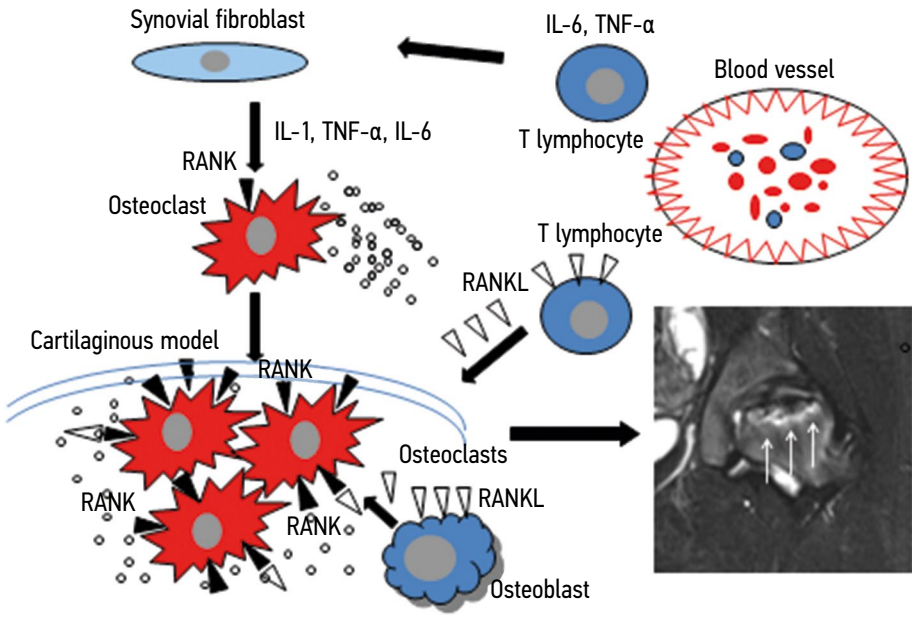

Fig. 2. Scheme of osteoclast activation in the focus of osteonecrosis (from the author's archive). Explanation is presented in the text. RANK, cellular receptor activator; RANKL, receptor ligand; IL-6, interleukin-6; IL-1, interleukin-1, TNF-α, tumor necrosis factor alpha

factor receptor superfamily (TNFRSF). Its ligand, the type II transmembrane protein RANKL, is expressed on the surface of activated T cells, bone marrow stromal cells, and osteoblasts [26]. When the RANK receptor binds to its ligand RANKL on the cell surface, osteoclastogenesis from progenitor cells is triggered or mature osteoclasts are activated (Fig. 2) [27]. A natural antagonist of RANKL, osteoprotegerin (OPG), a so-called "decoy receptor," functioning as a soluble homologue of RANK that blocks its interaction with RANKL. Overexpression of the OPG protein was found in the late stages of avascular necrosis in areas of active bone sclerosis [28]. Most researchers have observed the presence of concomitant synovitis in the early stages of the disease in the presence of a focus on necrosis. In contrast, synovitis was not registered in the later stages of the disease. The findings suggest osteoarthritis secondary to avascular necrosis (LCPD) may be associated with osteoclast hyperactivity. However, the lack of widespread incidence of synovitis in pediatric patients with a focus on necrosis indicates hidden molecular genetic mechanisms involved in the implementation of chronic inflammation, one of which may be the phenomenon of an exaggerated immune response [29].

Currently, the treatment of osteoarthritis in the presence of LCPD represents an unsolved problem in pediatric rheumatic orthopedics. Most pediatric rheumatologists interpret the inflammatory process against aseptic necrosis as synovitis of a secondary nature, the absence of factors of autoimmune aggression, which excludes the possibility of using antirheumatic drugs [30]. Moreover, despite the seemingly chronic nature of the course, synovitis, combined with aseptic necrosis, does not fit into any of the criteria for rheumatic disease. This predetermines the impossibility of using immunosuppressive therapy in this category of patients. In this case, the inflammatory process in the joint persisting for at least 6 weeks in a child with avascular necrosis cannot but be associated with the course of the disease. This form of inflammation, emanating from the focus of necrosis, leading to the onset and progression of femoral head deformity, and affecting the cartilaginous model, should be interpreted as osteoarthritis [31]. Undoubtedly, suppression of this inflammatory process is required (Fig. 3). Therapy with nonsteroidal anti-inflammatory drugs is often insufficient and does not help to subside the inflammatory changes. That is why it is necessary to strengthen anti-inflammatory therapy using immunosuppressive drugs. However, using algorithms and

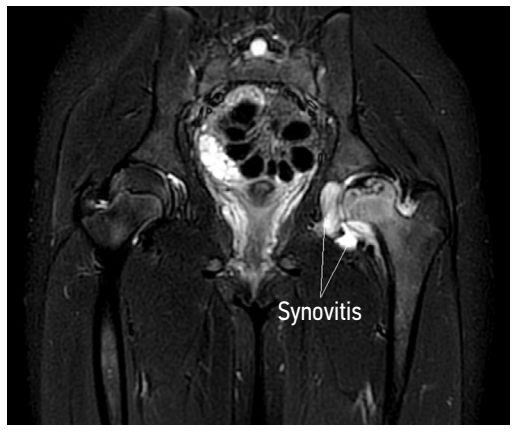

Fig. 3. Magnetic resonance imaging shows stage 2 of osteochondropathy of the femoral head on the left with signs of osteoarthritis (from the author's archive). Magnetic resonance imaging in T2 STIR modes reveals an extensive area of femoral head destruction, signs of trabecular edema, and chronic synovitis

regimens of immunosuppressive therapy with the inclusion of antirheumatic disease-modifying drugs is not the responsibility of the orthopedic physician. In addition, the orthopedist needs the necessary skills to assess the efficiency and safety of immunosuppressive therapy in pediatric patients. This clearly demonstrates the unresolved problem of treating chronic synovitis in pediatric patients with LCPD and necessitates involving a rheumatologist. At the same time, despite the disease's multifactorial nature, several pathogenetic mechanisms still have clearly described aspects. Numerous studies have shown the leading role of uncontrolled activation of osteoclasts in the formation of ANFH, accompanied by overproduction of proinflammatory cytokines and the development of chronic synovitis [32]. Such a reaction of the synovial membrane is not unfounded and can be associated with hidden mechanisms of autoaggression. Therefore, a selective model for the treatment of chronic synovitis in pediatric patients with LCPD may not have a direct immunosuppressive effect on inflammation but an indirect one by blocking osteoclast hyperactivity [33].

Bisphosphonates and their use in patients with ANFH

It is well-known that bisphosphonates have been used in pediatric rheumatology for a long time. Their use extends beyond conditions like osteogenesis imperfecta and systemic idiopathic osteoporosis. This type of therapy is directly indicated for several rheumatological diseases, including nonbacterial osteomyelitis, juvenile dermatomyositis, and ankylosing spondylitis [34]. Bisphosphonates in pediatric patients with rheumatic diseases can deactivate osteoclasts and directly influence the cellular components of immunity, including synovitis, by inhibiting the hyperactivity of inflammatory cells [35]. However, for many years, the immunosuppressive and anti-inflammatory effects of bisphosphonates have been relatively understudied. Bisphosphonates are inorganic analogs of pyrophosphate with different mechanisms of action. Their physicochemical properties stem from their high affinity for apatite crystals, which inhibits the formation and slows down the dissolution of calcium phosphate crystals. Bisphosphonates can be classified according to the presence or absence of a nitrogen atom in the R2 chain, namely, amino (sodium alendronate, pamidronate, risedronate, ibandronate, and zoledronate) and nonaminobisphosphonates (clodronate, tiludronate, and etidronate). While osteoclasts are the main target of bisphosphonates, studies show that monocytes, macrophages, lymphocytes, and synoviocytes may also be affected [36]. Bisphosphonates have a high affinity for calcium ions and therefore penetrate well into bone tissue, where they concentrate around osteoclasts, creating a high concentration within resorption lacunae.

The molecular mechanism of action of bisphosphonates on osteoclasts involves inhibiting key enzymes of the mevalonate pathway, necessary for the synthesis of cholesterol and isoprenoid lipids (farnesyl and geranylgeranyl diphosphate synthases). These are necessary for the prenylation of signaling G proteins that regulate cellular vital processes. Blocking these enzymes in cells initiates the process of cellular apoptosis. Aminobisphosphonates are significantly superior in antiresorptive activity to drugs without amino groups [37]. The effect of bisphosphonates on monocytes and macrophages is heterogeneous. The immediate effect of bisphosphonates is associated with the hyperproduction of proinflammatory cytokines by macrophages and monocytes during the first 3 days after the drug administration. With prolonged therapy with bisphosphonates, the anti-inflammatory effect is achieved by inhibiting the subtype of gamma/delta T cells (γδ T cells), which play an important role in the adaptive immunity of the child and triggering of the immune response in the body tissues of an adult, that is, a mild immunosuppressive effect is achieved [38].

Using bisphosphonates to prevent the progression of femoral head deformity and reduce symptoms of osteonecrosis is a relatively new approach. Interim studies suggest that in adults with osteonecrosis of the femoral head, bisphosphonates may reduce pain, improve hip function, prevent further progression of the femoral head deformity, and delay joint replacement [39]. This effect has been demonstrated in both animal models and clinical studies in adults [40, 41]. According to a meta-analysis conducted by a group of scientists led by Dr. Donghai Li in 2018, numerous studies show the efficiency of bisphosphonates in treating ANFH. However, it's worth noting that some experts are somewhat critical of the findings. Additionally, the effectiveness of bisphosphonates in preventing femoral head deformity may vary [42]. In clinical trials, a team led by Dr. Young-Kyun Lee (South Korea) in 2015 used zoledronate to treat patients with early-stage ANFH and moderate to large volumes of necrosis. It was established that zoledronic acid does not prevent femoral head collapse and is not able to reduce the need for total hip arthroplasty. In addition, in 2012, Dr. Meng Fan et al. (China) demonstrated in experimental studies that zoledronic acid can inhibit neovascularization in the focus of osteonecrosis, negatively affecting bone tissue restoration [43]. The data are more optimistic regarding ibandronic acid. Compared in the course of trials, ibandronic acid resulted in better bone volume maintenance after induction of ischemic osteonecrosis. In addition, in clinical practice, sodium ibandronate helps to increase the mineral content in the trabecular part of the bone, thereby significantly improving the nanomechanical properties of the anatomical structure. The authors of the publication concluded that ibandronic acid is better suited for adult patients with femoral head osteonecrosis [44].

Use of bisphosphonates in pediatric patients with Legg–Calvé–Perthes disease

Studies examining the efficiency of bisphosphonates in pediatric patients with ANFH are scarce. Clinical data supporting the use of bisphosphonates in juvenile forms of osteonecrosis are limited and should be critically evaluated [45]. A database search revealed a need for more information on the effectiveness of bisphosphonates in pediatric patients with ANFH, including LCPD. We examined proposed solutions to optimize therapy for osteoarthritis in pediatric patients with LCPD. An analysis of a series of patients treated at H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery indicated that in LCPD with signs of a pronounced inflammatory process in the early stages of the disease, the volume of the necrosis focus often increased, and extrusion subluxation developed in the affected joint. Additionally, synovitis hindered timely conservative and surgical treatment. Without proper treatment, this disease variant inevitably ended in the formation of gross deformity of the articular components (Fig. 4). Similar conclusions regarding the negative impact of chronic synovitis on the disease course were made in English-language studies [46]. Currently, in the treatment of pediatric patients with LCPD, previously developed schemes are traditionally used in the form of conservative measures using abduction orthoses and plaster casts, as well as surgical interventions, namely, triple pelvic osteotomy, Salter pelvic osteotomy, varus femoral osteotomy. The listed treatment methods, included in the concept of containment therapy, are based on the complete "immersion" of the femoral head into the acetabulum, which is necessary to prevent the head deformity progression and improve its shape, as well as restore the congruence of the articular surfaces. However, this treatment option cannot positively affect the hyperactivity of osteoclasts in the area of necrosis, including the course of osteoarthritis [47, 48]. Consequently, numerous studies have been aimed at finding a drug therapy model that would reduce inflammation and osteoclast activity, preventing the progression of head deformity, and restoring its sphericity [49].

Based on the materials studied, we proposed a new concept of conservative pathogenetic therapy in pediatric patients with LCPD with signs of osteoarthritis. The treatment model used for adult patients was applied and consists of the short-term use of bisphosphonates [50]. The treatment protocol represents a series of infusions of ibandronate sodium in pediatric patients with LCPD with signs of osteoarthritis at the stages of impression fracture and fragmentation. The dose, duration, and safety monitoring of bisphosphonates follow the clinical guidelines of the European Society of Rheumatology for treating nonbacterial osteomyelitis in pediatric patients (CARRA, 2017, 2019) [51]. According to international registers, the efficiency of this bisphosphonate therapy regimen in pediatric patients reaches 75% [52]. Thus, adding a course of

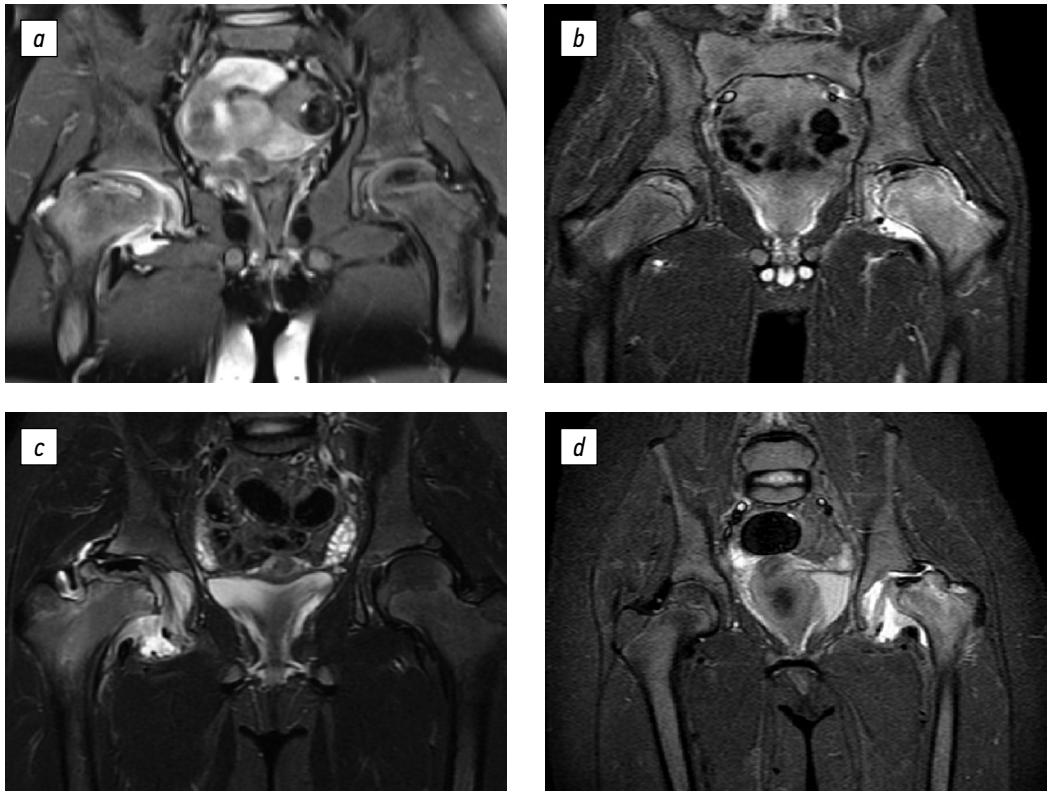

Fig. 4. A series of magnetic resonance imaging in pediatric patients with LCPD with signs of osteoarthritis: (*a, b*) without subluxation in the affected joint; (*c, d*) with subluxation of the femoral head (from the author's archive)

bisphosphonates to conservative therapy in pediatric patients with LCPD with signs of osteoarthritis is very promising. It is possible that in the near future, this may solve the problem of treating inflammation in pediatric patients with ANFH.

CONCLUSION

Currently, the number of pediatric patients with LCPD and children with an aggressive form of the disease is not decreasing, including osteoarthritis. There are few studies on the efficiency of bisphosphonates in pediatric patients with LCPD; the nature of the effect of bisphosphonates on the course and outcome of the disease has yet to be discovered. This problem needs to be studied more. The study and subsequent generalization of the results will help develop a new algorithm for treating pediatric patients with LCPD with signs of osteoarthritis. In the future, this will likely delay, and in some cases prevent, the hip replacement.

ADDITIONAL INFORMATION

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Ethical considerations. The protocol for examination and treatment of pediatric patients was approved by the local ethics committee of H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery of the Ministry of Health of Russia (minutes of meeting No. 3 of October 28, 2009).

Author contributions. *A.N. Kozhevnikov* created the concept and design of the study and wrote the text; *D.B. Barsukov* collected and processed the material, performed staged editing of the text; *A.R. Gubaeva* performed analysis of the data obtained and staged editing of the text.

All authors made significant contributions to the study and preparation of the article; they read and approved the final version before its publication.

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