Literature Review

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Problems of diagnosis and treatment of aseptic necrosis of the femoral head in contemporary traumatology and orthopedics (literature review)

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Introduction Aseptic necrosis of the femoral head (ANFH) is a severe disease most commonly associated with previous trauma, alcohol intake, administration of corticosteroids or blood diseases. Early diagnosis is difficult, there is no conservative treatment protocol with proven effectiveness, and the organ-preserving surgical treatments which have been used may not always postpone hip arthroplasty. Arthroplasty provides good results in the short and long-term postoperative period, but the prevalence of this disease among young people requires developing new methods of conservative and operative treatment. **Objective** To determine the problems of diagnosis and treatment of aseptic necrosis of the femoral head; to study the experience of current approaches and concepts in the diagnosis and treatment of ANFH; determine the range of the most effective methods for treating this pathology; to establish the relevance of further research on this issue. **Materials and methods** Literature review was conducted of the sources from PubMed and Google Scholar databases. The material was selected that corresponded to the stated purpose of the research topic. For describing some aspects of the aetiology, pathogenesis and development of methods for diagnosing and treating ANFH, earlier publications (2009–2014) were also used. **Results** The main views on the aetiology and pathogenesis of ANFH have been studied. Classical and current diagnostic methods for ANFH were reviewed as well as current operative and conservative approaches to the treatment of this pathology. A review of the main classifications was conducted. **Discussion** Early detection and examination of at-risk patients plays an important role in the diagnosis of ANFH. The results of clinical trials on the use of bisphosphonates seem mixed, as the meta-analysis in five randomized clinical trials (RCTs) in 2016 showed no statistically significant improvement in patients with ANFH. Hyperbaric oxygenation reduces interstitial ischemia by increasing extracellular oxygen concentration and shows encouraging results. Core decompression is recognized as the standard care in the early stages of ANFH. At present, the use of combined treatment with bisphosphonates, core-decompression and mesenchymal stem cells has been investigated. Combined therapy may be effective in slowing the progression of collapse at an early stage of ANFH, but further research is needed to have long-term results. **Conclusion** Aseptic necrosis of the femoral head is a severe polyetiological disease that has not been sufficiently studied. For its diagnosis, it is necessary to take into account the possible risk factors and to ensure an early MRI study. At present, there is no data on a conservative method of treating the early stages of ANFH, which would have high evidence and effectiveness not only in the immediate, but also in the long-term follow-up. It is necessary to conduct additional prospective randomized clinical trials to determine the effectiveness of already known and developed methods of cell therapy in the treatment of ANFH.

Keywords: osteonecrosis of the femoral head; aseptic necrosis of the femoral head (ANFH); avascular necrosis; stem cells; hip arthroplasty

Aseptic necrosis of the femoral head (ANFH) is a severe disease of the musculoskeletal system [1]. The number of patients, according to different authors, ranges from 1.5 to 4.7 % of the total number of patients with orthopedic pathology, and the number of total hip arthroplasties performed for ANFH ranges from 5 to 18 % of those performed annually [2, 3]. Aseptic necrosis of the femoral head is more likely to occur in young people of working age, and namely, men aged 30 to 50 years [4].

Currently, there is no generally accepted protocol for the diagnosis and early detection of ANFH. So, the possibilities of conservative treatment are thus limited [5]. The currently used methods of conservative therapy demonstrate unsatisfactory results. Thus, collapse of the femoral head develops in 75–80 % of patients within a rather short period of time (3-4 years) [1]. The rapid progression of the disease leads to the fact that more than a half of patients undergo total hip arthroplasty in the first three years from its onset. ANFH can be considered the most common cause of total hip replacement at a young age. And although hip arthroplasty is currently an affordable intervention with a proven technique of its performance, available implants, a low risk of postoperative complications and rapid rehabilitation in young patients [6], its implementation in the young age can lead to a number of problems.

There is evidence that ANFH is a serious risk factor for early implant instability after arthroplasty [7]. Repeated surgery is required due to wear of the components of the endoprosthesis or late instability in almost 40 % of patients after 10 years. Installation of endoprostheses with a "ceramic-polyethylene" or "ceramic-ceramic" friction pair may increase the implant survival and delay revision intervention [8]. However, such implants are not included in the compulsory medical insurance program, so their use is limited. In this literature review, we summarize the currently available data and deepen our understanding of the etiology, pathogenesis, diagnostic and treatment options for ANFH.

Purpose: to determine the relevance of the problem of diagnosis and treatment of aseptic necrosis of the femoral head; to study current approaches and concepts in the ANFH diagnosis and treatment; to determine the most effective methods of treating this pathology; to establish the relevance of further research on this issue.

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MATERIAL AND METHODS

A literature review was conducted in October-November 2019 using the PubMed and Google Scholar databases of scientific articles. The search used the following keywords: *avascular necrosis femoral head; avascular necrosis; bone necrosis; cartilage disruption; femoral head; Perthes' disease, stem cells; hip arthroplasty*. From the sources obtained, we chose the ones that corresponded to the stated research topic, with the predominant inclusion of articles published within the period of 2014–2019. Earlier publications (2009–2014) were used for describing some aspects of the etiology, pathogenesis and development of diagnostic and treatment methods in ANFH, given the relevance of the information presented in them.

Aseptic necrosis of the femoral head: general information

ANFH was first described in 1738 by Munro. In 1835, Cruveilhier investigated morphological changes in the femur and concluded that they were associated with impaired blood supply to the femoral head [9]. The term "aseptic necrosis" was proposed by Axhausen in 1907, and in our country the first reports on ANFH in adults were published in 1950 by V.Ya. Fridkin and I.N. Lagunova [10].

ANFH is a severe degenerative disease characterized by an imbalance in the processes of osteogenesis and bone resorption, impaired blood supply to the femoral head, as well as its gradual deformation at the sites of the greatest load. Most often, pathological changes develop in the supralateral segment of the femoral head [11]. The term "avascular necrosis", according to a number of authors, inaccurately reflects the essence of the disease, since the vessels supplying the head of the femur do not disappear, but pathologically change. It leads to disruption of local blood flow. From a terminological point of view in the radiological literature, osteonecrosis of the epiphyseal and articular parts of bones is referred to as avascular necrosis (AVN), and osteonecrosis of the metaphyseal and diaphyseal regions is referred to as bone marrow infarction or metaphyseal infarction (bone marrow necrosis, BMN) [4, 6 8, 11]. ANFH is characterized by apoptosis of osteocytes, bone marrow cells, osteoclasts and osteoblasts what results in bone collapse with subsequent involvement of the articular hyaline cartilage, changes in the configuration of the femoral head surface, and, ultimately, osteoarthritis in adult patients [12]. In children, most of the head cartilage is capable of proliferation; therefore, there remains a possibility to prevent its subsequent degeneration and destruction with restoration of the height and shape of the femoral head [13].

Aetiology

According to the etiological factor, ANFH can be conditionally divided into two groups: associated with the fact of trauma (post-traumatic) and not associated with it (atraumatic or idiopathic) [14]. Trauma-related cases are usually the result of a femoral neck fracture and may manifest in both short and long term. In patients with idiopathic ANFH, a number of predisposing factors have been identified, among which the following have been proven.

Alcohol consumption is the most common etiological factor in adults which is dose-dependent. The risk of the disease increases proportionally with an increase in the amount of alcohol taken (ml per week). Obviously, alcohol disrupts the metabolism of phospholipids and distorts cytokine reactions; however, at the moment, the mechanism of impaired blood supply and the development of ANFH due to alcohol consumption is not completely clear [15]. At the same time, it has been proven that in patients with antiphospholipid syndrome, the risk of developing ANFH is three times higher than in healthy people [16].

Blood diseases such as sickle cell anemia, hereditary thrombophilia, hypofibrinolysis also may lead to ANFH. Thus, it is reported that 50 % of patients develop ANFH after 35 years from the onset of sickle cell anemia [17].

The use of corticosteroids is one of the main etiological factors, also having a dose-dependent impact: the use of more than 20-40 mg per day, especially in long-term treatment, increases the risk of ANFH. There is evidence that autoimmune diseases also increase the risk of ANFH, especially with prolonged use of corticosteroids [18].

It has been proven that the factors listed above are associated with the risk of ANFH, but they do not fully explain the mechanism of impaired blood supply to the femoral head. In children, ANFH is associated with Legg-Calvet-Perthes disease; however, at present, the etiopathogenesis of the disease is also unclear, as well as its role in the development of ANFH [19].

Pathogenesis and the course of ANFH

The pathophysiology of aseptic necrosis in children and adults is similar. A distinctive feature in children is the ability of the epiphyseal cartilage tissue to growth and to restoration of the height of the femoral head, in contrast to adults, in whom a relatively thin epiphyseal cartilage does not have the ability to regenerate. Therefore, progressive pathological changes are usually irreversible [13]. The development of aseptic necrosis can be divided into two successive phases: ischemia and regeneration [20].

The *ischemic phase* begins long before the first clinical manifestations appear. Until now, the primary source of ischemic changes has not been determined. The following is considered: pathology of blood vessels supplying the proximal epimetaphysis of the femur, changes in the blood transported by them or in the subchondral layer, affecting the regeneration of the cartilage tissue matrix [12]. According to Wingstrand et al. [21], ischemia of the femoral head with impaired blood flow does not always lead to the development of pain syndrome which often manifests itself only in the regeneration phase. There are no X-ray signs of the ischemic phase. The first changes appear only in the initial stages of the regeneration phase when revascularization and migration of the cells of osteoblastic differentiation begin and leads to a visible change in the structure of the bone tissue.

Regeneration phase As with any damage to bone tissue, after the onset of ischemia and necrosis,

inflammatory mediators stimulate the appearance of stem cells in the area. This process is ensured by the growth of blood vessels towards the epiphyseal cartilage. Since the beginning of the regeneration phase, two different processes take place in the femoral head. On the one hand, the compact subchondral bone and induced osteoclasts will maintain a negative apposition resorption balance, and on the other hand, the cancellous bone located in the center of the femoral head will have a positive appositional balance due to the activation of osteoblasts. Radiographically, this picture appears as a subchondral radiolucent line. The weakened subchondral bone will no longer be able to support the overlying cartilage, and therefore the articular surface of the femoral head begins to deteriorate. In adults, such changes lead to rapid development of coxarthrosis while in children it is possible to restore the configuration head [12].

Diagnosis of ANFH

A *physical examination* may be helpful in making a diagnosis. Patients suspected of ANFH present with pain in the groin, buttocks, or knee joints. Examination reveals pain in internal rotation of the femur, and significant limitation of internal rotation is a reliable sign of collapse of the femoral head [22].

Radiography becomes the next step in the diagnosis of ANFH. Early manifestations may not be visible in frontal images, but additional views show cystic and / or sclerotic changes in the femoral head. The sign of a sickle (crescent moon) as an area of enlightenment in the subchondral zone of the head indicates a subchondral fracture due to bone necrosis. In the later stages, flattening, collapse, and degenerative changes in the femoral head are visualized [22, 23].

Magnetic resonance imaging (MRI) is the "gold standard" in patients with suspected ANFH and a normal X-ray picture. It has a sensitivity and specificity of 99 %, allowing the detection of ANFH in the early stages. The process is presented as a low-intensity area on T1-weighted images and a high-intensity area on T2-weighted images. Bone marrow edema and intra-articular effusion also confirm the development of ANFH [23].

In the later stages of ANFH, it is better to use radiography and computed tomography (CT) for diagnosis. In some cases, CT can help evaluate a patient with a suspected subchondral fracture, which may not be visible with MRI. Scintigraphy and positron emission tomography are also included in the studies used to diagnose ANFH, but the sensitivity of these methods is not higher than that of MRI [22, 23].

Classification of ANFH

A number of attempts have been taken to create a staged classification of aseptic necrosis in order to assess the results of treatment and prognosis. The earliest classification based on radiographic changes was developed by R.P. Ficat and J. Arlet. In accordance with this classification, *stage 0* is preclinical; *stage 1* – pre-radiological, clinically manifested by joint pain; *stage 2* – X-ray changes with sclerosis, cyst formation and osteopenia but without collapse of the femoral head; *stage 3* – collapse of the femoral head [24].

Classification of M.E. Steinberg/University of Pennsylvania was developed in the 1980s. It is based on the MRI views and changes in the articular surface in ANFH and includes stage 0 (no changes in X-rays and MRI), stage I (clinical signs of the disease, absence of radiographic manifestations, but changes in MRI images or scintigraphy); stage II (progression of osteonecrosis with areas of sclerosis and (or) cysts in the subchondral part of the femoral head but the head remains rounded); stage III (a sign of a crescent moon in X-rays due to an impression fracture of the subchondral bone and formation of a collapse zone); stage IV (flattening of the femoral head, collapse of the subchondral bone and deformation of the articular surface without narrowing of the joint space); stage V (involvement of the acetabulum in the process and narrowing of the joint space); stage VI (disappearance of the joint space, pronounced arthritic changes). The volume of changes in stages I to V is indicated by the letters A, B, and C. A – the volume of the femoral head changes < 15 % of the head; B – the volume of the femoral head changes is 15–30 %; C – the volume of the femoral head changes is > 30 % [25].

The ARCO (Association Research Circulation Osseous) classification also includes four stages, but takes into account the diagnostic findings, localization and extent of osteonecrosis. This classification has been considered difficult to use and is used less in practice than the others. Despite the fact that all of the above classifications have found their application in practice, the most useful is the classification developed by R.P. Ficat and J. Arlet, which is the most accurate in predicting clinical outcome and easier to use. It is most frequently cited in the scientific literature [26].

Conservative treatment

Modification of lifestyle and daily activities, weight loss are often recommended to alleviate the ANFH symptoms. However, these factors do not significantly influence the progression of the disease [27]. Pharmacological and biophysical methods of treatment have been mostly experimental. They include the use of bisphosphonates, anticoagulants, vasodilators, statins and various biophysical factors.

Bisphosphonates reduce the activity of osteoclasts and theoretically may prevent collapse of the femoral head in the early stages of the disease by inhibiting bone remodeling around the necrosis focus [28].

Given that intravascular occlusion is one of the pathophysiological mechanisms, *anticoagulants* and *vasodilators* may theoretically delay or even reverse the progression of the disease, but there is currently insufficient data to confirm the effectiveness of such treatment [28].

One of the potential pathophysiological mechanisms of corticosteroid-induced ANFH is the accumulation of excessive adipose tissue in the bone marrow that leads to an increase in the intraosseous pressure and a decrease in blood flow. It is assumed that *statins* may influence

this mechanism by blocking cholesterol synthesis and lowering lipid levels [29].

In addition to pharmacological treatments, various biophysical factors are applied such as *extracorporeal shock wave therapy* (ESWT), *electrical stimulation*, and *hyperbaric oxygenation*. There is evidence that the use of low-intensity pulsed ultrasound may be a potential method of non-invasive treatment for ANFH [30].

Currently, the possibilities of cell therapy (*platelet-rich plasma* and *stromal stem cells*) for the treatment of ANFH have been much discussed. It is believed that cell therapy may influence bone remodeling in the early stages of the process [31]. At the moment, it is necessary to develop indications for cell therapy, standardize the method of implementation and the method of administration, since the research results differ, depending on the source and population of cells, concomitant therapy.

Currently, conservative treatment for ANFH has a limited use. It is either exclusively experimental, or effective in the early stages of the disease. Most of the presented treatments require additional studies with a high degree of evidence to confirm their effectiveness.

Surgical treatment

Surgical treatment is indicated for patients with late stages of ANFH or if conservative treatment is ineffective in the early stages. Such methods of treatment as arthrodesis of the hip joint, surface replacement arthroplasty and proximal osteotomy of the femur are of limited use, since they are accompanied by complications. Also, they do not sufficiently delay the intervention of total arthroplasty and complicate the subsequent surgical treatment.

Semi-closed percutaneous core decompression of the metaepiphyseal zone of the femoral head is a preserving surgical treatment method performed to reduce intraosseous pressure, improve blood flow in the femoral head, and delay joint arthroplasty [28, 32]. Conventionally, decompression is performed using trephine with a diameter of 8 to 10 mm to remove the focus from the area of the osteonecrotic defect in the femoral head, not penetrating the joint [32, 33, 34]. The use of core decompression leads to satisfactory results for ANFH with signs of pre-collapse and a defect of less than 15 % of the femoral head surface. Decompression is also recommended for severe lesions at risk of collapse [28]. Intraoperative cartilage damage and postoperative subtrochanteric fracture of the femur are its potential complications [32, 34]. Core decompression can be used in combination with additional treatments such *as autologous platelet-rich plasma, mesenchymal stem cells* (MSCs), *various growth factors* and *tantalum rods* [32, 34].

MSCs are introduced to improve osteogenesis by differentiation into osteoblasts and release of growth factors. It might stimulate the restoration of the necrotic focus with further prevention of the femoral head collapse [34]. The introduction of growth factors such as bone morphogenetic proteins (BMPs) and angiogenic *growth factors* may lead to the stimulation of bone tissue regeneration, but further research is needed to determine the ideal route of their administration [35].

The use of *tantalum implants* would theoretically prevent the collapse of the femoral head and stimulate bone repair by providing structural support and due to osteoinductive properties. However, short-term results of treatment and histological examination of the femoral head after this type of arthroplasty did not demonstrate the effect of such treatment [28].

Bone grafting has been developed for the treatment of ANFH since the 1950s and is aimed at prevention of the femoral head collapse. Auto- or allografts have been used that are introduced into the osteonecrosis area according to the Phemister method (core decompression and creating a tract for introducing the graft through the lateral approach), the light-bulb technique (creating a "window" at the border of the neck and head with an access to the necrosis focus) and the trapdoor technique (dislocation of the femoral head, creation of a cortico-cancellous window (trapdoor), removal of the necrosis area followed by grafting) [28, 36]. These treatments are usually used for small to moderate lesions of the femoral head in young patients in order to delay the operation of hip arthroplasty [34].

It was believed that bone autologous plasty on a vascular pedicle would combine the principles of structural support of the femoral head and stimulation of regeneration due to increased blood flow. The bone graft is collected from the patient's fibula, the iliac crest, or a portion of the greater trochanter [37, 38]. The use of a fibular graft on a pedicle is the most studied technique. Anterolateral approach is performed with the exposure of the branch of the lateral circumflex of the femoral artery, treatment of the necrosis zone of the femoral head, collection of the autograft from the fibula, and anastomosis of the peroneal vessels to the branches of the femoral artery. Indications are pre-collapse and collapse of the femoral head in patients aged 20 to 50 years [37].

The implantation of a *beta-tricalcium phosphate bioceramic rod system* into the femoral head has been considered as a treatment option for the early ANFH stages [39]. The system unloads the femoral head and the likelihood of the head collapse decreases. However, in a big area of necrosis, the probability of success decreases but the risk of collapse increases [22].

A technique has been developed with the application of a *cage made of superelastic materials* (nitinol) to provide mechanical support for the necrosis area in the femoral head to prevent collapse. The cage was used in combination with the removal of the necrotic area and bone autoplasty in the early and moderate ANFH stages, but additional research is required for this technique to become widespread [40].

Total hip arthroplasty is indicated for patients with late ANFH stages or after ineffective organ-preserving treatment. Total arthroplasty provides excellent results in the elimination of pain and stability of the result [28, 33]. Early studies demonstrated unsatisfactory

results of joint arthroplasty for ANFH with a high rate of complications. However, with the widespread use of high-molecular-weight cross-linked polyethylene, cementless femoral components, ceramic heads and inserts, the results of arthroplasty for ANFH improved and are close to the results of arthroplasty in osteoarthritis. The timing of surgical intervention and the risk of complications increase in patients that have undergone previous osteotomy or bone grafting but the results have been considered satisfactory [41].

DISCUSSION

Early detection and examination of at-risk patients plays an important role in the diagnosis of ANFH. MRI study of such patients, especially when clinical manifestations appear, is considered justified since early therapy is the key to the success and preservation of the anatomy of the hip joint. Once the femoral head collapses (> 2 mm) or secondary degenerative changes occur, hip-preserving therapies become ineffective, and arthroplasty remains the only treatment option [42]. There are many options for conservative and surgical treatment, but their evidence is limited.

The results of clinical trials on the use of bisphosphonates are ambiguous. A meta-analysis of five randomized clinical trials (RCTs) in 2016 did not reveal significant improvements in patients with ANFH that received bisphosphonate therapy [43, 44]. The meta-analysis in 2018 that included RCTs in animals showed significant improvements in the experiments, but the data have been not confirmed in clinical studies [45]. Considering the side effects of bisphosphonates (pathological fractures of the proximal femur and osteonecrosis of the mandible), additional studies is a need prior to their use in clinical practice.

A prospective study of ANFH associated with coagulopathy has been published that involved patients with pathologies of 30 hip joints. They underwent a course of conservative therapy, including treatment with anticoagulants (enoxaparin 60 mg/day for 3 months). ANFH did not progress beyond stages I and II according to R.P. Ficat and J. Arlet in 53 % of cases with a follow-up period of 4 to 13 years [46]. In an experimental animal model with steroid-induced ANFH, an improvement in blood supply to the femoral head after treatment with enoxaparin and ginkgo biloba extract (as a vasodilator) was revealed, which is comparable to the effect of sildenafil [47, 48]. However, it is currently unknown whether this effect will be reproduced in clinical trials.

Treatment with statins (lovastatin) demonstrates a decrease in adipogenesis, death of bone tissue and bone marrow, as well as leads to increased expression of osteoblast genes. But the results of these studies are ambiguous [49]. Higher-level studies are needed to confirm the effectiveness of statins in clinical practice.

The efficacy of shock wave therapy was investigated in RCTs in patients with ANFH stages I to III (ARCO), compared with core decompression and bone grafting on pedicle. A significant decrease in the severity of pain and a slowdown in the progression of the disease were found [28].

T. Al-Jabri et al evaluated the role of electrical stimulation in the treatment of avascular necrosis of the femoral head in adults. In the early stages, the best responses to treatment with pulsed electromagnetic fields were observed, with improvements in both clinical and radiographic parameters. Pulsed electromagnetic fields may play a role in the treatment of early avascular necrosis. However, a systematic review of the use of electrical stimulation in ANFH has shown unsatisfactory results based on an analysis of ten studies [50].

Hyperbaric oxygenation reduces interstitial ischemia by increasing extracellular oxygen concentration and shows promising results [28, 51].

Core decompression is recognized as the standard care in the early stages of ANFH. However, a 2017 meta-analysis of eleven RCTs showed improved treatment outcome for core decompression combined with autologous plasma and mesenchymal stem cells. The authors emphasize that further studies are needed to compare the combination of core decompression with or without various adjuvant support [52].

N.S. Piuzzi et al demonstrated in a systematic review that only 24.5 % of patients in the cell therapy group experienced progression of ANFH compared with 40 % in the control group. A low complication rate (< 3 %) was also reported with no serious side effects [53].

Platelet-rich plasma contains powerful growth factors that influence osteogenic differentiation of mesenchymal bone marrow stem cells in vitro [54]. However, in in vivo studies on rats with steroid-induced ANFH, the administration of platelet-rich plasma did not have an effect on cell survival and proliferation; therefore, additional studies are required to clarify the effectiveness of its use [55].

Bone autologous plasty on a pedicle has a significantly greater effect on slowing down the progression of ANFH than core decompression. However, it did not lead to a delay in THA at 3-year follow-up [56]. There are studies that do not confirm a higher efficiency of autoplasty using a fibular graft on a pedicle relative to non-vascularized grafting [57].

Currently, the use of combined treatment with bisphosphonates, core-decompression and mesenchymal stem cells has been trialed. Combined therapy may be effective in slowing the progression of collapse at an early ANFH stage, but further research is needed to determine long-term results [58].

Choosing a treatment method for ANFH, one should take into account patient's age, stage of the disease, the location and size of the necrotic lesion, and the Kerboul angle [59]. Conservative treatment is used at an early stage, small lesions in young patients or in patients of any age without clinical manifestations. In elderly patients with a collapse of the femoral head, total arthroplasty is preferable. If conservative treatment is ineffective, organ-preserving surgery should be considered in young patients with a low Kerboul angle

(less than 200°). Ineffective conservative therapy or ineffective organ-preserving surgical treatment, or high values of the Kerboul angle, according to the authors, are indications for THA.

CONCLUSION

Aseptic necrosis of the femoral head is a severe polyetiological disease that has not been sufficiently studied. For establishing this diagnosis, it is necessary to take into account and investigate the alleged risk factors, to ensure an early MRI study of the affected joint, and not only radiography. Timely diagnosis is of particular relevance for identifying reversible stages of ANFH. Currently, there is no data on the conservative methods with high proven evidence for early stages of ANFH with effectiveness not only in the immediate but also in the long-term follow-up. However, operative organ-preserving techniques have been used to delay THA, while the use of stem cells and growth factors during core decompression has been regarded promising. Additional prospective randomized clinical trials to determine the effectiveness of known and developed methods of cell therapy in the treatment of ANFH are a necessity.

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