



## Aseptic Necrosis of the Femoral Head, A Modern View of Treatment and Diagnosis

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**Abstract:** (ANGBC), avascular necrosis (International Classification of Diseases of the 10th revision) is a multifactorial disease affecting mainly young people, leading to the development of secondary severe osteoarthritis of the hip joints with subsequent disability. As an independent disease was first described by E. Bergman in 1927 and E. Freund in 1939. At first, ANGB was compared with Perthes' disease in children, suggesting that adults use the same term, but in children, unlike adults, the disease often ends with the restoration of bone tissue with the preservation of the femoral head. The disease usually develops at the age of 35-55 years (the average age is 38 years).

**Keywords:** aseptic necrosis of the femoral head, osteonecrosis, Leiden factor V, interleukin, cross-linked N-terminal telopeptide, tumor necrosis factor  $\alpha$

The symptoms of ANGB are very diverse and depend on the stage of the disease. At the initial stages, minor attacks of pain may occur for no apparent reason, often with the preservation of a normal volume of movements; pains are noted with internal rotation of the hip. With the progression of the disease, discomfort can be replaced by sudden attacks of severe pain. Such attacks can serve as a signal of the presence of a collapse or fracture of the femoral head, leading to the final stage of degenerative changes. The further development of the disease is typically determined by increasing mechanical symptoms, including a decrease in volume and soreness of movements, the Trendelenburg symptom, crepitation and instability of the femoral head [12].

Clinically, ANGB is characterized by symptoms similar to the manifestations of coxarthrosis:

- 1) pain in the groin area, passing along the anterior and lateral surface of the thigh with irradiation into the knee joint. The pain increases with exertion, radiates to the lumbar region, does not pass at rest and at night;
- 2) restriction of movements in the affected joint, characterized by a violation of self-service;
- 3) lameness on a sore leg when walking;
- 4) rapid development of hip muscle hypotrophy on the affected side;
- 5) shortening of the hip.

According to the Association for the Study of Blood Supply to Bone Tissue (Association Research Circulation Osseous), there are four stages of ANGB:

- Stage I – there are no changes on the radiograph;
- Stage II – demarcation sclerosis of the femoral neck without коллапса;
- Stage III – femoral head collapse: stage IIIA – collapse <3 mm; stage IIIB – collapse >3 mm;

- Stage IV – degenerative changes [16].
- In Russia, the most recognized characteristic of ANGB is in five stages (Fig. 4):
- Stage I – there are no radiological signs. Histologically, necrosis of the spongy substance of the head and its bone marrow is determined. It is clinically manifested by pain and restriction of movements in the joint, muscle hypotrophy; Stage II – impression fractures. There are many microscopic fractures on the background of bone necrosis. Radiologically, the femoral head is homogeneously darkened, its height is reduced, there is no structural pattern, the surface of the head is sometimes in the form of compacted facets, the articular gap is expanded. According to magnetic resonance imaging, a necrotic defect in the head is determined;
- Stage III – “sequestration”. The head flattens and consists of separate structurally isolated fragments of different shapes and sizes, the femoral neck shortens and thickens, the articular gap expands to a greater extent;
- Stage IV – repair. The spongy substance of the femoral head is restored. On the X-ray, sequester-like areas are not visible, the shadow of the head is outlined, rounded cyst-like clearances; Stage V – secondary deforming arthrosis. The bone structure of the femoral head begins to be traced, its shape is significantly changed, the congruence of the articular surfaces is disrupted. It is interesting that the collapse of the femoral head, according to recent data, occurs in a relatively short period of time - 5 months [3].

### ***Diagnostics***

Laser Doppler flowmetry and micro-sensor transducers of intraosseous pressure are used to study the blood circulation of the femoral bone [25]. Histological examination of bone tissue samples taken during endoprosthesis surgery of the affected joint is of great importance. Histological examination makes it possible to diagnose the disease, differentiate it with other pathologies and determine the pathogenetic pathways of the process. With the progression of osteonecrosis, the bone structure changes significantly. Osteoclast activity increases in the subchondral zone and necrosis zone, while osteoblast activity increases in the sclerosis zone (Fig. 5, 6) [39]. During the immunohistochemical examination of bone samples, it was found that the subchondral and necrotic zones are positive for the activator of the NF- $\kappa$ B receptor (RANK) and the RANK ligand (RANKL), sclerotic– by bone morphogenetic protein-2 (BMP2), BMP7, RUNX2 (runt-bound transcription factor-2) and osteoprotegerin (OPG). Osteoblasts (positive for alkaline phosphatase) are detected in a circle of trabeculae in the sclerosis zone with a decrease in their number in the subchondral and necrotic zones in comparison with healthy bone. Osteoclasts (positive for tar-resistant acid phosphatase) they appear around the trabeculae of the subchondral and necrotic regions with a decrease in their number in the sclerotic zone compared to healthy bone (see Fig. 5, 6) [39]. Under microscopy, osteonecrosis is characterized by the formation of empty lacunae with vascular fibrous tissue around in combination with adjacent bone tissue (Fig. 7) [15]. At a higher magnification under a microscope, foci of newly formed bone tissue can be seen next to the empty lacunae (Fig. 8) [33].

In most cases, in ANGB, laboratory parameters, such as prothrombin time, activated partial thromboplastin time, are normal [16]. However, when comparing the indicators of patients with non-traumatic ANGB and healthy volunteers, significant deviations in the concentration of coagulation factors in blood plasma were revealed. Thus, in patients with ANGB, a significant decrease in ghrelin levels, an increase in the levels of Willebrand factor, plasminogen activator-1 (PAI-1) inhibitor, and C-reactive protein were determined in comparison with the control group, which indicates the involvement of these factors in the pathogenesis of the disease [20]. As a diagnostic marker of the development of ANGB, the definition is proposed

the level of interleukin-33 in blood plasma. In a study conducted in 125 patients with ANGB, they showed a significant increase in the level of interleukin-33 (174.33 pg/ml) in comparison with healthy individuals (90.5 pg/ml), regardless of the cause of osteonecrosis [48]. Complex biomarkers for early diagnosis of ANGB are proposed: levels of OPG, RANKL, cross-linked N-terminal telopeptide (NTX), C-terminal procollagen peptide I (PICP), tumor necrosis factor  $\alpha$  and

interleukin-1 $\beta$  for enzyme immunoassay. The examination of patients with ANGBC revealed statistically significant differences in this complex in comparison with healthy individuals [11].

### **Treatment**

It was found that the development of osteonecrosis is associated with a violation of the osteo-gene differentiation of mesenchymal stem cells [13]. This fact has been confirmed both in experimental and clinical studies by the effectiveness of drugs correcting the differentiation of these cells, as well as by the effectiveness of stem cell therapy. Genetic studies can not only confirm the validity of the disease therapy, but also serve as a way to find new, more effective methods of early diagnosis and preventive treatment of osteonecrosis. In this regard, the study of associations of genetic markers with ANGBC is a promising method.

Treatment hip joint surgery does not always provide optimal results for these patients, various procedures are carried out to preserve the joint in the early stages of the disease: central decompression, percutaneous drilling, vascular and non-vascular bone grafting, rotational osteotomy. One assessment of the success of these operations is very variable [19].

Initial treatment in the early stages of ANGBC consists in unloading therapy, which is necessary to prevent damage to the vessels supplying the femoral head with blood and its subsequent collapse. However, this tactic leads to positive results only in 20% of cases. In 80% of cases and more it is necessary to resort to surgical interventions, including total hip replacement (arthroplasty) and other techniques. Among the surgical techniques, a transverse rotational osteotomy of the hip is used, which has been used since 1972 (Fig. 9, 10). However, in 40% of cases, complications are observed in the form of instability of the femoral head [38]. The essence of the operation is to move the necrotized section of the femoral head to the area that is subjected to the least mechanical load.

The ideal surgical tactic for ANGBC is to remove necrotizing bone tissue from the femoral head

Aseptic necrosis of the femoral head is a progressive disease that quickly leads to dysfunction of the hip joint and disability of the patient, therefore, the development of effective methods of treatment of this pathology is an urgent problem of modern surgery. Since two main mechanisms are involved in the pathogenesis of the disease - vascular (circulatory disorders) and tissue (pathology of osteocytes, osteoblasts and osteoclasts), treatment methods are aimed at these links. At the initial stages of osteonecrosis, organ-preserving procedures are performed, including both surgical treatment and the use of various medications and stem cells [18].

Aseptic necrosis most often develops in young and middle-aged people. Since total endoprosthetics

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