Genij Ortopedii. 2022. Vol. 28, no. 2. P. 274-281.

Review article

https://doi.org/10.18019/1028-4427-2022-28-2-274-281

Conservative treatment of avascular necrosis of the femoral head (literature review)

M.A. Panin[1], A.V. Boiko[1]✉, M. Dzh. Abakirov[1], A.S. Petrosyan[2], D.A. Ananin[1], M.M. Awad[1]

[1] Peoples' Friendship University of Russia, Moscow, Russian Federation
[2] City Clinical Hospital № 17, Moscow, Russian Federation

Corresponding author: Andrey V. Boyko, boiko120393@gmail.ru

Abstract

Introduction Avascular necrosis of the femoral head is a debilitating disease affecting people of working age and having an important medical and social role. Total hip arthroplasty is the only effective treatment for late stages of necrosis. Various joint-preserving operations and non-surgical methods can be successfully used for less severe types. There is no unequivocal opinion on the effectiveness of various conservative treatments offered for avascular necrosis of the femoral head. **The aim** was to summarize data on the role of medications and physiotherapy in treatment of avascular necrosis of the femoral head through the analysis of the modern world literature. **Material and methods** The original literature search was conducted on key resources including elibrary, PubMed and ResearchGate. **Results** Outcomes of avascular necrosis of the femoral head treated conservatively were overviewed. The effectiveness of various treatments using bisphosphonates, anticoagulants, statins, prostacyclin derivatives was evaluated. Physiotherapy with shock wave therapy, pulsating electromagnetic fields, and hyperbaric oxygenation was also reviewed. Conservative treatment is reported to be effective only for early (pre-collapse) stages of avascular necrosis of the femoral head. **Conclusions** A conservative treatment used as a monotherapy for AVN cannot be assessed as a standalone procedure because various combinations of comprehensive treatment are used for the majority of patients. There are no studies in the literature comparing the effectiveness of conservative therapies using iloprost and statins, bisphosphonates and anticoagulants, shockwave and hyperbaric oxygen therapy in homogeneous patient samples. A deeper study of the underlying pathogenesis of avascular necrosis of the femoral head is required to develop personalized treatment strategies.

Keywords: avascular necrosis, osteonecrosis, conservative treatment, pre-collapse stages, bisphosphonates, anticoagulants, statins, prostacyclin derivatives, shock waves, pulsed electromagnetic fields, hyperbaric oxygen therapy

For citation: Panin M.A., Boiko A.V., Abakirov M. Dzh., Petrosian A.S., Ananin D.A., Avad M.M. Conservative treatment of avascular necrosis of the femoral head (literature review). *Genij Ortopedii*, 2022, vol. 28, no 2, pp. 274-281. https://doi.org/10.18019/1028-4427-2022-28-2-274-281

INTRODUCTION

The treatment of avascular necrosis (AVN) of the femoral head remains an unresolved problem, in early stages of the disease, in particular, when the treatment is aimed at relieving pain, reducing the volume of the lesion and preventing progression [1]. Clinical practice guidelines developed by expert clinicians of our country suggest that conservative treatment of AVN is indicated for patients with early stages of the disease (stages 1, 2), but is ineffective for subchondral fracture of the femoral head (stages 3, 4) [2]. A variety of conservative treatments described in the literature ranges from recommendations for weight loss, use of drugs to biophysical therapy. This review presents current information on the effectiveness of conservative treatment of AVN of the femoral head.

The aim was to summarize data on the role of medications and physiotherapy in treatment of avascular necrosis of the femoral head through the analysis of the modern world literature.

MATERIAL AND METHODS

The original literature search was conducted on key resources including elibrary, PubMed and ResearchGate. The following terms were used as search keywords: aseptic/avascular necrosis / osteonecrosis / AVN, femoral head, conservative treatment; anticoagulants / bisphosphonates / statins / iloprost / extracorporeal shock waves / pulsed electromagnetic fields / hyperbaric oxygen therapy. We reviewed publications of any type regardless of the language and the year of the publication (preference was given to publications of the last decade). We placed no restrictions on study design: randomized or non-randomized clinical trials, cohort studies, case-control studies. We explored the references of the articles reviewed to additionally search for contributions on the topic.

RESULTS AND DISCUSSION

Weight loss Weight loss is traditionally considered as an important component of conservative treatment of AVN with the effectiveness being debatable. A meta-analysis of 21 studies concerning the conservative treatment of AVN (819 patients, long-term results at 2.8 years) performed by M. Mont et al. showed that progression of the disease was detected radiographically in 74 % of the cases and 78 % of patients underwent surgical treatment of AVN. The authors reported no significant differences in patients with substantial, moderate weight loss and in patients without weight loss [3]. M. Mont et al. analyzed the effectiveness of weight loss (as the only method of therapy) after 7 years in 819 patients with asymptomatic AVN. The authors reported progression to symptoms or femoral head collapse in 59 % of patients [4]. Progression of the disease was rather dependent on the initial size of the necrotic area than the extent of weight loss in the course of conservative treatment: AVN progressed in 32 % of cases with small lesions versus 84 % with large necrosis areas. The authors suggested that AVN was more "aggressive" in patients with sickle cell anemia (femoral head collapse in 74 %) than in patients with systemic lupus erythematosus (femoral head collapse in 17 %). Progression of AVN was not dependent on the extent of weight loss but was associated with etiological factors and lesion size [5]. An experimental study reported by Okazaki S. et al. showed no effect of axial load on the hip joint in the rat models with steroid-induced necrosis on disease progression [6]. However, necrosis of the femoral head was likely to develop in different ways in tetrapods and biped animals due to different load distribution. Thus, weight loss in an AVN patient resulting from the standalone therapy should be recognized as ineffective in preventing disease progression but the method can be recommended in combination with medication therapy and surgical treatment [7].

Medication therapy

Bisphosphonates Bisphosphonates are effective treatments for osteoporosis reducing osteoclast activity and increasing bone density. Hypothetically, the use of bisphosphonates reducing osteoclast activity in the early stages of AVN may help prevent subchondral collapse of the femoral head. J. Cardoso et al. suggested that the use of bisphosphonates in AVN patients could provide favorable results in relieving pain, improving mobility and reducing the incidence of articular collapse [8]. S. Agarwala et al. explored long-term results of treatment with bisphosphonates in 395 patients at a mean follow-up of 4 years. Patients were treated with oral alendronate for three years at a dose of 10 mg per day. Disease progression to the stage of femoral head collapse was detected in 12.6 % of patients with stage 1 AVN and in 55.8 % with stage 2 [9]. Then the authors performed a 10-year follow-up study of 53 patients stages 1, 2, 3 AVN who were treated with alendronate 70 mg/week for 3 years. Only 13 % of stage 3 AVN cases required total hip arthroplasty and more than 70 % of controls who received no alendronate had to undergo arthroplastic procedure [10]. On the contrary, H. Yuan et al. conducted a meta-analysis (5 randomized and controlled trials) and reported no statistically significant differences in the progression of AVN and the frequency of total hip arthroplasty (with the exception of stage 1 AVN) in patients taking and not taking alendronate. The authors suggested that the effectiveness of bisphosphonates in the treatment of AVN was not obvious, and further research required. Long-term use of bisphosphonates is associated with a risk of osteonecrosis of the mandible and atypical hip fractures, and their use should be discussed with patients about adverse side effects [11].

There is a controversy in the results reported in a prospective randomized multicenter study performed for 110 patients with unilateral grades 1-2 AVN of the femoral head and neglected cases of small (less than 30 %) areas of necrosis. The patients were randomly divided into 2 equal groups with those who received 5 mg of zolendronate intravenously once a year for 2 years (n = 55) and controls who received no drug. The collapse of the femoral head that required arthroplasty was detected in 19 out of 55 patients in the study group and in 20 out of 55 controls with the differences being not statistically significant. The authors concluded that ineffective use of zolendronate in the cohort of patients could be associated with medium-sized and large lesions of the femoral head [12]. Despite the fact that the effective treatment of early stages of AVN with bisphosphonates is recognized, there are still no clear recommendations regarding doses and duration of use. Treatment with bisphosphonates can be ineffective with significant lesions of the femoral head even in precollapse stages.

Russian researchers reported efficient use of Forsteo (teriparatide) in the treatment of early stages of AVN of the femoral head. Teriparatide is a derivative of

parathyroid hormone to stimulate bone formation by increasing the activity of osteoblasts in comparison with the activity of osteoclasts. The effectiveness of conservative treatment of precollapse stages of AVN of the femoral head can be enhanced with daily subcutaneous injections of teriparatide (12 months) following intra-articular administration of perftoran and demixid into the affected hip joint [13]. There is evidence of the successful use of teriparatide in patients with AVN of the femoral head with the ineffective use of bisphosphonates, non-steroidal anti-inflammatory drugs, hyperbaric oxygenation [14].

Anticoagulants Anticoagulants are widely used for patients with impaired hemostasis [15]. Effective use of anticoagulants can be achieved in early stages of AVN. C. Glueck et al. prospectively studied (level of evidence 2) 25 patients (35 femoral heads, AVN stages 1–2) with AVN and thrombophilia or hypofibrinolysis. who were anticoagulated for 3 months with 6000 units of enoxaparin daily. The results of treatment were assessed at 3 years. The authors reported no progression of AVN in 95 % cases of primary osteonecrosis that was observed only in 20 % of patients with corticosteroid-associated secondary osteonecrosis [16]. The authors concluded that enoxaparin may prevent progression of primary hip osteonecrosis, decreasing the incidence of total hip replacement.

T. Chotanaphuti et al. retrospectively studied 36 patients (49 femoral heads) who had stage I-II AVN. In the study group, 18 patients (26 hips) received 6,000 units of Enoxaparin daily for 3 months. In the control group, 18 patients (23 hips) received no Enoxaparin. All patients were given radiographic evaluations every three months for a minimum of 24 months. Long-term results evaluated at 2 years showed progression of AVN to the collapse of the femoral head in 43 % of cases in the experimental group and 78.3 % in the control group ($p = 0.042$). The authors concluded that low molecular weight heparins can slow down progression of idiopathic AVN of the femoral head [17].

In 2017, P. Guo et al. conducted a meta-analysis to explore the effectiveness of anticoagulants based on the results of the treatment of a total of 218 femoral heads with stage I-II AVN. The authors reported 95 % of patients showing no progression of necrosis for 2 years due to enoxaparin therapy. The positive effect was noted in patients with primary AVN of the femoral head and anticoagulants were ineffective in secondary steroid induced necrosis [18]. Anticoagulants were shown to be effective in early stages of AVN in patients with hereditary and acquired thrombophilia and coagulopathy but the effectiveness of anticoagulants was not reported for other etiological factors in the development of AVN.

Statins. AVN is characterized by fatty infiltration of bone tissue and statins can be used for the correction of hyper- and dyslipoproteinemia, for secondary corticosteroid associated AVN [19, 20]. Many authors reported the positive effect of statins on the production of bone morphogenetic protein 2 in osteoblasts and the improvement of bone formation by reducing the activity of osteoclasts that inhibit bone resorption [21, 22, 23].

J. Pritchett et al. retrospectively reviewed the records of 284 patients who were taking statin drugs at the time they were started on high dose steroids. Magnetic resonance imaging scans were used to verify the osteonecrosis at 5–11 years and only 1 % from the group had osteonecrosis develop. The data presented demonstrated the effectiveness of statins in the prevention of corticosteroid related AVN [24]. The 1 % incidence was much less than the 3 % to 20 % incidence usually reported for patients receiving high-dose steroids [25]. H. Yin retrospectively analyzed 36 AVN patients (58 hips) who were treated with core decompression of the affected femoral head. Some patients underwent surgical treatment (32 femoral heads) combined with simvastatin treatment and the rest of the patients underwent surgical treatment alone. Successful clinical results were achieved in 84 % in the simvastatin group compared with 58 % of patients not taking statins [26]. The authors reported no correlation between the effectiveness of statin use and the etiology of AVN (idiopathic, steroid-, alcohol-induced).

A controversial opinion publication was brought out by M. Ajmal et al. who retrospectively identified 2 881 patients receiving high doses of corticosteroids after renal transplantation. Of the 2881 patients, 338 received statins. At 7.5 years, osteonecrosis of the femoral head was reported in 4.4 % of patients treated with corticosteroids + statins versus 7 % in patients not taking statins with differences being not statistically significant. The authors considered the role of statins in the prevention of "corticosteroid AVN" being questionable [27]. Most authors believe that the use of statins is justified in steroid- and alcohol-induced AVN considering the pathogenesis and the mechanism of the drug action. However, the opinion is not generally accepted.

Vasodilators (derivatives of prostacyclin) Prostacyclin derivatives inhibit platelet aggregation, adhesion and activation, cause dilatation of arterioles

and venules, reduce vascular permeability, activate fibrinolysis, inhibit adhesion and migration of leukocytes after endothelial injury, reduce the formation of free oxygen radicals which can promote bone regeneration at the cellular level. Vasodilators such as iloprost (a derivative of prostacyclin) were shown to be effective in the treatment of patients with vasculitis, systemic lupus erythematosus, Raynaud's syndrome, sickle cell anemia [28, 29, 30]. A. Disch et al. reported a prospective comparative study of 16 patients with bone marrow edema of the femoral head and 17 patients with early-stage AVN; patients received iloprost in both groups. Patients showed a significant improvement in pain and physical activity in both groups [31]. T. Claßen et al. explored the effectiveness of iloprost treatment in 108 patients with AVN grades 1–4. The need for total hip arthroplasty was assessed at 4 years. The authors reported the high efficiency of iloprost in precollapse stages. However, 4 % of the treated joints with grade 1, 20 % with grade 2, 71 % with grade 3 and 100 % with grade 4 underwent subsequent total joint replacement [32]. I. Pountos and P.V. Giannoudis, analytical reviewers, reported promising results of iloprost treatment in early stages of AVN but further data on its safety, dosage and efficiency through randomized multicenter studies were desirable in order to reach final conclusions [33].

Traditional Chinese medicine The possibilities with traditional Chinese medicine in the treatment of AVN are reported in the literature. Q-S. Wei et al. reported the use of herbal medicine (capsule Huo Xue Tong Luo) with a pro-angiogenic pharmacological effect in patients with idiopathic necrosis. The HXTL capsule contained Kayan leaf, Chinese angelica sinensis, red peony root and others. The study included 59 patients with early stages of AVN (54 asymptomatic, 5 symptomatic) and the effectiveness of treatment was assessed at 6–16 years with very encouraging results obtained. The collapse of the femoral head (pronounced progression of the disease) was observed in 3.4 % at 4 years, 16.5 % at 6 years and 39.8 % at 9 years [34]. Chinese experts offered the HUO-GU formula for the treatment of steroid-induced necrosis of the femoral head. The drug was aimed at suppressing adipogenic differentiation in bone marrow stromal cells and improving osteogenesis [35, 36]. The herbal medicine was prescribed to 45 patients (86 femoral heads) with steroid-induced AVN grade 1–2. The results were followed up for 14 years: total arthroplasty was performed in 5 patients only [37]. The study was conducted only on the Asian population. However, the high efficiency of herbal medicine attracted the attention of researchers. E.E. Volkov and V.B. Simonenko reported the experience with traditional Chinese medicine in the treatment of AVN that allowed them to avoid collapse in more than 80 % of patients [38].

Physiotherapeutic methods of treatment

Extracorporeal shock wave therapy Extracorporeal shock wave therapy (ESWT) induces the expression of angiogenic growth factors that stimulate neoangiogenesis [39]. The physiotherapy can be effective in AVN. C. Wang et al. suggested that ESWT appeared to be more effective than core decompression and nonvascularized fibular grafting in 57 hips with AVN involved in a randomized controlled trial [40]. M. Vulpiani et al. reported the effectiveness of ESWT in reducing pain and in slowing down the progression of bone damage evaluated in 36 patients with unilateral AVN grades I, II and III at 2 years in a prospective study. Patients from stage I group and stage II group achieved significantly better results than patients from stage III group at follow-up time points ($p < 0.005$). Moreover, 66 % of patients with stage 3 AVN required total hip arthroplasty [41]. The authors of a meta-analysis conducted in 2018 also reported the effectiveness of ESWT in the treatment of patients with early-stage AVN (4 articles, 230 patients). There were patients who received a course of ESWT (study group) and those who did not (control group). The authors established a significant improvement in the Harris Hip Score in the study group compared to the controls with no differences in the intensity of pain identified in the study and control groups [42]. ESWT was shown to improve the hip joint in the early-stage AVN and to be ineffective in the collapsed femoral head. However, there have been no guideline issued for the use of the method in clinical practice.

Pulsed electromagnetic field Pulsed electromagnetic field (PEF) and ESWT can be used in the treatment of AVN stimulating osteogenesis and angiogenesis [43, 44]. L. Massari et al. conducted a retrospective study of 76 patients with AVN stages 1-2-3 who underwent PEF for 5 months, 8 hours a day. Long-term results were assessed at 2 years: total hip replacement was required for only 6 % of patients with AVN stages 1–2 and 80 % of cases with AVN stage 3 [45]. Most of publications on the use of electromagnetic fields in the treatment of AVN date back to 1980–2010, and several fundamental studies published in the last few years reported a positive effect of a PEF electromagnetic field on osteoblast proliferation and the clinical course of osteoporosis [46, 47]. This suggests a positive therapeutic effect of a PEF for AVN. There have been no clear clinical recommendations for

the treatment of AVN using PEF considering the paucity of publications to date.

Hyperbaric oxygen therapy Hyperbaric oxygen therapy (HOT) induces vasoconstriction reducing cellular edema with decreased level of cell adhesion and microcirculation restored due to decreased intercellular pressure [48]. The use of HOT in AVN can be effective. N. Reis et al. reported effective HOT in the treatment of 16 hips in stage 1 AVN. All patients received 100 % oxygen at a pressure of 2–2.5 atm for 90 minutes a day for 100 consecutive days. Overall, 81 % of patients who received HBO therapy showed a return to normal on MRI [49]. E. Camporesi et al. reported a double-blind study of 20 femoral heads with stage 2 AVN with long-term results followed up for 7 years. Ten hips were treated with HOT and 10 with hyperbaric aeration (30 treatments over 6 weeks). The authors found that patients receiving HOT showed improved pain after 20 procedures and none of the patients required total hip arthroplasty for 2 years [50].

Chinese scientists performed a meta-analysis in 2017 to systematically evaluate the clinical effect of HOT in the treatment of femoral head necrosis. Nine cohort studies involving 318 HBO cases were included. The outcomes of the patients were divided into two subgroups (Asians and non-Asians). All patients received sessions of HOT. Evaluating the effect of treatment the authors obtained outstanding results. The inclusion of HOT in the treatment of AVN led to an improved clinical effect in the subgroup of Asian patients and more than 7 times in the subgroup of non-Asian patients compared with the cohort of patients who did not receive HOT [51]. G. Uzun and co-authors also reported a positive effect of HOT indicating the absence of disease progression with "survival of the head" seen in 90 % of cases of a meta-analysis. However, the authors indicated small samples, nonhomogeneous comparison groups and inability to rule out other factors that would affect the outcome [52]. We trust that randomized trials of larger cohorts of patients are needed in order to obtain adequate clinical recommendations for the use of HOT in the treatment of AVN.

Untreated AVN is known to result in a fracture of the femoral head within 2 years [53]. Most patients with unilateral AVN are likely to develop bilateral involvement within 2 years [54, 55]. F. Castro and R. Barrack suggested that conservative treatment of non-traumatic AVN can reduce the intensity of pain and is effective for preventing progression through improved function of the joint [7]. Conservative treatment can be produced in early stages of AVN. Many authors appreciate the effectiveness of conservative treatment at precollapse stages of AVN being comparable to the surgical methods of core decompression [56, 57].

CONCLUSION

A conservative treatment used as a monotherapy for AVN cannot be assessed as a standalone procedure because various combinations of comprehensive treatment are used for the majority of patients. There are no studies in the literature comparing the effectiveness of conservative therapies using iloprost and statins, bisphosphonates and anticoagulants, shockwave and hyperbaric oxygen therapy in homogeneous patient samples. No clear recommendations for the use of drugs and physiotherapy in the early stages of AVN are available for practitioners or available clinical recommendations are reduced to listing medications and methods of physiotherapy. The lack of generally accepted treatment protocols is largely due to an incomplete understanding of the etiology and pathogenesis of various forms of AVN. If the use of statins is pathogenetically justified in steroid- and alcohol-induced osteonecrosis, then presciptions for so-called idiopathic necrosis are produced ex juvantibus without a clear understanding of the pathogenesis of the disease. A deeper study of the underlying pathogenesis of avascular necrosis of the femoral head including genetic predisposition is required to develop personalized treatment strategies.

REFERENCES

1. Odarchenko D.I., Dzyuba G.G., Erofeev S.A., Kuznetsov N.K. Problemy diagnostiki i lecheniia asepticheskogo nekroza golovki bedrennoi kosti v sovremennoi travmatologii i ortopedii (obzor literatury) [Problems of diagnosis and treatment of aseptic necrosis of the femoral head in contemporary traumatology and orthopedics (literature review)]. *Genij Ortopedii*, 2021, vol. 27, no. 2, pp. 270-276. DOI: 10.18019/1028-4427-2021-27-2-270-276.
2. Torgashin A.N., Rodionova S.S., Shumskii A.A., Makarov M.A., Torgashina A.V., Akhtyamov I.F., Kovalenko A.N., Zagorodnii N.V., Mironov S.P. Lechenie asepticheskogo nekroza golovki bedrennoi kosti. Klinicheskie rekomendatsii [Treatment of aseptic necrosis of the femoral head. Clinical guidelines]. *Nauchno-prakticheskaia Revmatologiia*, 2020, vol. 58, no. 6, pp. 637-645. (in Russian) Available at: https://doi.org/10.47360/1995-4484-2020-637-645 (accessed 15.12.2020).

3. Mont M.A., Carbone J.J., Fairebank A.C. Core decompression versus nonoperative management for osteonecrosis of the hip. *Clin. Orthop. Relat. Res*., 1996, no. 324, pp. 169-178. DOI: 10.1097/00003086-199603000-00020.
4. Mont M.A., Zywiel M.G., Marker D.R., McGrath M.S., Delanois R.E. The natural history of untreated asymptomatic osteonecrosis of the femoral head: a systematic literature review. *J. Bone Joint Surg. Am*., 2010, vol. 92, no. 12, pp. 2165-2170. DOI: 10.2106/JBJS.I.00575.
5. Hernigou P., Poignard A., Nogier A., Manicom O. Fate of very small asymptomatic stage-I osteonecrotic lesions of the hip. *J. Bone Joint Surg. Am.*, 2004, vol. 86, no. 12, pp. 2589-2593. DOI: 10.2106/00004623-200412000-00001.
6. Okazaki S., Nagoya S., Tateda K., Katada R., Mizuo K., Watanabe S., Yamashita T., Matsumoto H. Weight bearing does not contribute to the development of osteonecrosis of the femoral head. *Int. J. Exp. Pathol*., 2012, vol. 93, no. 6, pp. 458-462. DOI: 10.1111/j.1365-2613.2012.00836.x.
7. Castro F.P. Jr., Barrack R.L. Core decompression and conservative treatment for avascular necrosis of the femoral head: a meta-analysis. *Am. J. Orthop*. (Belle Mead NJ), 2000, vol. 29, no. 3, pp. 187-194.
8. Cardoso J.B., Andrade D.M., Santiago M.B. The use of bisphosphonate in the treatment of avascular necrosis: a systematic review. *Clin. Rheumatol*., 2008, vol. 27, no. 6, pp. 685-688. DOI: 10.1007/s10067-008-0861-9.
9. Agarwala S., Shah S., Joshi V.R. The use of alendronate in the treatment of avascular necrosis of the femoral head: follow-up to eight years. *J. Bone Joint Surg. Br*., 2009, vol. 91, no. 8, pp. 1013-1018. DOI: 10.1302/0301-620X.91B8.21518.
10. Agarwala S., Shah S. Ten-year follow-up of avascular necrosis of femoral head treated with alendronate for three years. *J. Arthroplasty*, 2011, vol. 26, no. 7, pp. 1128-1134. DOI: 10.1016/j.arth.2010.11.010.
11. Yuan H.F., Guo C.A., Yan Z.Q. The use of bisphosphonate in the treatment of osteonecrosis of the femoral head: a meta-analysis of randomized controlled trials. *Osteoporos. Int*., 2016, vol. 27, no. 1, pp. 295-299. DOI: 10.1007/s00198-015-3317-5.
12. Lee Y.K., Ha Y.C., Cho Y.J., Suh K.T., Kim S.Y., Won Y.Y., Min B.W., Yoon T.R., Kim H.J., Koo K.H. Does Zoledronate Prevent Femoral Head Collapse from Osteonecrosis? A Prospective, Randomized, Open-Label, Multicenter Study. *J. Bone Joint Surg. Am*., 2015, vol. 97, no. 14, pp. 1142-1148. DOI: 10.2106/JBJS.N.01157.
13. Shusharin A.G., Polovinka M.P. Opyt primeneniia preparata Forsteo pri lechenii patsientov s asepticheskim nekrozom golovki bedrennoi kosti [Experience with the use of Forsteo preparation in the treatment of patients with aseptic necrosis of the femoral head]. *Osteoporoz i Osteopatii*, 2016, vol. 19, no. 2, pp. 110-111. (in Russian)
14. Galluccio F., Matucci-Cerinic M. Efficacy of Short-term Teriparatide for Hip Osteonecrosis. *J. Rheumatol*., 2016, vol. 43, no. 11, pp. 2084-2085. DOI: 10.3899/jrheum.160190.
15. Glueck C.J., Freiberg R.A., Wissman R., Wang P. Long term anticoagulation (4-16 years) stops progression of idiopathic hip osteonecrosis associated with familial thrombophilia. *Adv. Orthop*., 2015, vol. 2015, 138382. DOI: 10.1155/2015/138382.
16. Glueck C.J., Freiberg R.A., Sieve L., Wang P. Enoxaparin prevents progression of stages I and II osteonecrosis of the hip. *Clin. Orthop. Relat. Res*., 2005, no. 435, pp. 164-170. DOI: 10.1097/01.blo.0000157539.67567.03.
17. Chotanaphuti T., Thongprasert S., Laoruengthana A. Low molecular weight heparin prevents the progression of precollapse osteonecrosis of the hip. *J. Med. Assoc. Thai*., 2013, vol. 96, no. 10, P. 1326-1330.
18. Guo P., Gao F., Wang Y., Zhang Z., Sun W., Jiang B., Wang B., Li Z. The use of anticoagulants for prevention and treatment of osteonecrosis of the femoral head: A systematic review. *Medicine* (Baltimore), 2017, vol. 96, no. 16, pp. e6646. DOI: 10.1097/MD.0000000000006646.
19. Jones J.P. Jr. Fat embolism and osteonecrosis. *Orthop. Clin. North Am*., 1985, vol. 16, no. 4, pp. 595-633.
20. Chang C., Greenspan A., Gershwin M.E. The pathogenesis, diagnosis and clinical manifestations of steroid-induced osteonecrosis. *J. Autoimmun*., 2020, vol. 110, 102460. DOI: 10.1016/j.jaut.2020.102460.
21. Mundy G., Garrett R., Harris S., Chan J., Chen D., Rossini G., Boyce B., Zhao M., Gutierrez G. Stimulation of bone formation in vitro and in rodents by statins. *Science*, 1999, vol. 286, no. 5446, pp. 1946-1949. DOI: 10.1126/science.286.5446.1946.
22. Sugiyama M., Kodama T., Konishi K., Abe K., Asami S., Oikawa S. Compactin and simvastatin, but not pravastatin, induce bone morphogenetic protein-2 in human osteosarcoma cells. *Biochem. Biophys. Res. Commun*., 2000, vol. 271, no. 3, pp. 688-692. DOI: 10.1006/bbrc.2000.2697.
23. Ahn K.S., Sethi G., Chaturvedi M.M., Aggarwal B.B. Simvastatin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, suppresses osteoclastogenesis induced by receptor activator of nuclear factor-kappaB ligand through modulation of NF-kappaB pathway. *Int. J. Cancer*, 2008, vol. 123, no. 8, pp. 1733-1740. DOI: 10.1002/ijc.23745.
24. Pritchett J.W. Statin therapy decreases the risk of osteonecrosis in patients receiving steroids. *Clin. Orthop. Relat. Res*., 2001, no. 386, pp. 173-178. DOI: 10.1097/00003086-200105000-00022.
25. Mont M.A., Pivec R., Banerjee S., Issa K., Elmallah R.K., Jones L.C. High-Dose Corticosteroid Use and Risk of Hip Osteonecrosis: Meta-Analysis and Systematic Literature Review. *J. Arthroplasty*, 2015, vol. 30, no. 9, pp. 1506-1512.e5. DOI: 10.1016/j.arth.2015.03.036.
26. Yin H., Yuan Z., Wang D. Multiple drilling combined with simvastatin versus multiple drilling alone for the treatment of avascular osteonecrosis of the femoral head: 3-year follow-up study. *BMC Musculoskelet. Disord*., 2016, vol. 17, no. 1, pp. 344. DOI: 10.1186/s12891-016-1199-0.
27. Ajmal M., Matas A.J., Kuskowski M., Cheng E.Y. Does statin usage reduce the risk of corticosteroid-related osteonecrosis in renal transplant population? *Orthop. Clin. North Am*., 2009, vol. 40, no. 2, pp. 235-239. DOI: 10.1016/j.ocl.2009.01.004.
28. Disch A.C., Matziolis G., Reinke P., Perka C. Intravenous iloprost treatment for severe bone pain caused by sickle cell crisis. *Thromb. Haemost*., 2004, vol. 91, no. 5, pp. 1047-1049. DOI: 10.1055/s-0037-1614202.
29. Marasini B., Massarotti M., Bottasso B., Coppola R., Del Papa N., Maglione W., Comina D.P., Maioli C. Comparison between iloprost and alprostadil in the treatment of Reynaud's phenomenon. *Scand. J. Rheumatol*., 2004, vol. 33, no. 4, pp. 253-256. DOI: 10.1080/03009740310004711.
30. Mathieu A., Sanna G., Mameli A., Pinna C., Vacca A., Cauli A., Passiu G., Piga M. Sustained normalization of cerebral blood-

flow after iloprost therapy in a patient with neuropsychiatric systemic lupus erythematosus. *Lupus*, 2002, vol. 11, no. 1, pp. 52-56. DOI: 10.1191/09611203302lu137cr.
31. Disch A.C., Matziolis G., Perka C. The management of necrosis-associated and idiopathic bone-marrow oedema of the proximal femur by intravenous iloprost. *J. Bone Joint Surg. Br*., 2005, vol. 87, no. 4, pp. 560-564. DOI: 10.1302/0301-620X.87B4.15658.
32. Claßen T., Becker A., Landgraeber S., Haversath M., Li X., Zilkens C., Krauspe R., Jäger M. Long-term Clinical Results after Iloprost Treatment for Bone Marrow Edema and Avascular Necrosis. *Orthop. Rev*. (Pavia), 2016, vol. 8, no. 1, pp. 6150. DOI: 10.4081/or.2016.6150.
33. Pountos I., Giannoudis P.V. The role of iloprost on bone edema and osteonecrosis: Safety and clinical results. *Expert. Opin. Drug Saf*., 2018, vol. 17, no. 3, pp. 225-233. DOI: 10.1080/14740338.2018.1424828.
34. Wei Q.S., Hong G.J., Yuan Y.J., Chen Z.Q., Zhang Q.W., He W. Huo Xue Tong Luo capsule, a vasoactive herbal formula prevents progression of asymptomatic osteonecrosis of femoral head: A prospective study. *J. Orthop. Translat*., 2018, vol. 18, pp. 65-73. DOI: 10.1016/j.jot.2018.11.002.
35. Kong X., Li X., Zhang C., Zhu L., Liu C., Qin Q., Liu C., Wang Q., Zhu J., Wu X., Wan H., Chen W., Lin N. Ethyl acetate fraction of Huogu formula inhibits adipogenic differentiation of bone marrow stromal cells via the BMP and Wnt signaling pathways. *Int. J. Biol. Sci*., 2017, vol. 13, no. 4, pp. 480-491. DOI: 10.7150/ijbs.18430.
36. Kong X., Li X., Zhang C., Zhu L., Wan H., Zhu J., Liu C., Su H., Qin Q., Chen W., Lin N. Aqueous Fraction of Huogu Formula Promotes Osteogenic Differentiation of Bone Marrow Stromal Cells Through the BMP and Wnt Signaling Pathways. *Rejuvenation Res*., 2016, vol. 19, no. 6, pp. 509-520. DOI: 10.1089/rej.2015.1795.
37. Huang Z., Fu F., Ye H., Gao H., Tan B., Wang R., Lin N., Qin L., Chen W. Chinese herbal Huo-Gu formula for the treatment of steroid-associated osteonecrosis of femoral head: A 14-year follow-up of convalescent SARS patients. *J. Orthop. Translat*., 2020, vol. 23, pp. 122-131. DOI: 10.1016/j.jot.2020.03.014.
38. Volkov E.E., Simonenko V.B. Bezoperatsionnoe lechenie asepticheskogo nekroza golovki bedrennoi kosti [Non-surgical treatment of aseptic necrosis of the femoral head]. *Zemskii Vrach*, 2012, no. 3, pp. 17-19. (in Russian)
39. Alves E.M., Angrisani A.T., Santiago M.B. The use of extracorporeal shock waves in the treatment of osteonecrosis of the femoral head: a systematic review. *Clin. Rheumatol*., 2009, vol. 28, no. 11, pp. 1247-1251. DOI: 10.1007/s10067-009-1231-y.
40. Wang C.J., Wang F.S., Huang C.C., Yang K.D., Weng L.H., Huang H.Y. Treatment for osteonecrosis of the femoral head: comparison of extracorporeal shock waves with core decompression and bone-grafting. *J. Bone Joint Surg. Am*., 2005, vol. 87, no. 11, pp. 2380-2387. DOI: 10.2106/JBJS.E.00174.
41. Vulpiani M.C., Vetrano M., Trischitta D., Scarcello L., Chizzi F., Argento G., Saraceni V.M., Maffulli N., Ferretti A. Extracorporeal shock wave therapy in early osteonecrosis of the femoral head: prospective clinical study with long-term follow-up. *Arch. Orthop. Trauma Surg*., 2012, vol. 132, no. 4, pp. 499-508. DOI: 10.1007/s00402-011-1444-9.
42. Hao Y., Guo H., Xu Z., Qi H., Wang Y., Lu C., Liu J., Yuan P. Meta-analysis of the potential role of extracorporeal shockwave therapy in osteonecrosis of the femoral head. *J. Orthop. Surg. Res*., 2018, vol. 13, no. 1, pp. 166. DOI: 10.1186/s13018-018-0861-7.
43. Yen-Patton G.P., Patton W.F., Beer D.M., Jacobson B.S. Endothelial cell response to pulsed electromagnetic fields: stimulation of growth rate and angiogenesis in vitro. *J. Cell Physiol*., 1988, vol. 134, no. 1, pp. 37-46. DOI: 10.1002/jcp.1041340105.
44. Canè V., Botti P., Soana S. Pulsed magnetic fields improve osteoblast activity during the repair of an experimental osseous defect. *J. Orthop. Res*., 1993, vol. 11, no. 5, pp. 664-670. DOI: 10.1002/jor.1100110508.
45. Massari L., Fini M., Cadossi R., Setti S., Traina G.C. Biophysical stimulation with pulsed electromagnetic fields in osteonecrosis of the femoral head. *J. Bone Joint Surg. Am*., 2006, vol. 88, no. Suppl. 3, pp. 56-60. DOI: 10.2106/JBJS.F.00536.
46. Zhang B., Xie Y., Ni Z., Chen L. Effects and Mechanisms of Exogenous Electromagnetic Field on Bone Cells: A Review. *Bioelectromagnetics*, 2020, vol. 41, no. 4, pp. 263-278. DOI: 10.1002/bem.22258.
47. Wang T., Yang L., Jiang J., Liu Y., Fan Z., Zhong C., He C. Pulsed electromagnetic fields: promising treatment for osteoporosis. *Osteoporos. Int*., 2019, vol. 30, no. 2, pp. 267-276. DOI: 10.1007/s00198-018-04822-6.
48. Banerjee S., Issa K., Pivec R., Kapadia B.H., Khanuja H.S., Mont M.A. Osteonecrosis of the hip: treatment options and outcomes. *Orthop. Clin. North Am*., 2013, vol. 44, no. 4, pp. 463-476. DOI: 10.1016/j.ocl.2013.07.004.
49. Reis N.D., Schwartz O., Militianu D., Ramon Y., Levin D., Norman D., Melamed Y., Shupak A., Goldsher D., Zinman C. Hyperbaric oxygen therapy as a treatment for stage-I avascular necrosis of the femoral head. *J. Bone Joint Surg. Br*., 2003, vol. 85, no. 3, pp. 371-375. DOI: 10.1302/0301-620x.85b3.13237.
50. Camporesi E.M., Vezzani G., Bosco G., Mangar D., Bernasek T.L. Hyperbaric oxygen therapy in femoral head necrosis. *J. Arthroplasty*, 2010, vol. 25, no. 6 Suppl., pp. 118-123. DOI: 10.1016/j.arth.2010.05.005.
51. Li W., Ye Z., Wang W., Wang K., Li L., Zhao D. Clinical effect of hyperbaric oxygen therapy in the treatment of femoral head necrosis: A systematic review and meta-analysis. *Orthopade*, 2017, vol. 46, no. 5, pp. 440-446. (in English) DOI: 10.1007/s00132-016-3360-8.
52. Uzun G., Mutluoglu M., Ersen O., Yildiz S. Hyperbaric oxygen therapy in the treatment of osteonecrosis of the femoral head: a review of the current literature. *Undersea Hyperb. Med*., 2016, vol. 43, no. 3, pp. 189-199.
53. Beckmann J., Roth A., Niethard C., Mauch F., Best R., Maus U. Knochenmarködem und atraumatische Femurkopfnekrose : Therapie [Bone marrow edema and atraumatic necrosis of the femoral head: Therapy]. *Orthopade*, 2015, vol. 44, no. 9, pp. 662-671. (in German) DOI: 10.1007/s00132-015-3146-4.
54. Hofmann S., Mazières B. Osteonekrose: Natürlicher Verlauf und konservative Therapie [Osteonecrosis: natural course and conservative therapy]. *Orthopade*, 2000, vol. 29, no. 5, pp. 403-410. (in German) DOI: 10.1007/s001320050461.
55. Stulberg B.N., Davis A.W., Bauer T.W., Levine M., Easley K. Osteonecrosis of the femoral head. A prospective randomized treatment protocol. *Clin. Orthop. Relat. Res*., 1991, no. 268, pp. 140-151.
56. Mont M.A., Cherian J.J., Sierra R.J., Jones L.C., Lieberman J.R. Nontraumatic Osteonecrosis of the Femoral Head: Where Do We Stand Today? A Ten-Year Update. *J. Bone Joint Surg. Am*., 2015, vol. 97, no. 19, pp. 1604-1627. DOI: 10.2106/JBJS.O.00071.

57. Maus U., Flechtenmacher J., Peters K.M. Konservative Therapie der atraumatischen Hüftkopfnekrose [Conservative treatment of atraumatic femoral head necrosis]. *Orthopade*, 2018, vol. 47, no. 9, pp. 735-744. (in German) DOI: 10.1007/s00132-018-3616-6.
58. Panin M.A., Zagorodnii N.V., Samokhodskaia L.M., Boiko A.V. Znachenie polimorfizmov gena metilentetragidrofolatreduktazy (MTHFR) v patogeneze netravmaticheskogo asepticheskogo nekroza golovki bedrennoi kosti [Significance of methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms in the pathogenesis of non-traumatic aseptic necrosis of the femoral head]. *Vestnik Travmatologii i Ortopedii im. N.N. Priorova*, 2020, vol. 27, no. 2, pp. 19-23. (in Russian) DOI: 10.17816/vto202027219-23.
59. Panin M.A., Zagorodnii N.V., Samokhodskaia L.M., Boiko A.V. Znachenie polimorfizmov genov trombotsitarnykh integrinov (ITGα2/ITGβ3) v patogeneze netravmaticheskogo asepticheskogo nekroza golovki bedrennoi kosti [Significance of platelet integrin (ITGα2/ITGβ3) gene polymorphisms in the pathogenesis of non-traumatic aseptic necrosis of the femoral head]. *Meditsinskii Vestnik Severnogo Kavkaza*, 2020, vol. 15, no. 1, pp. 84-86. (in Russian) DOI: 10.14300/mnnc.2020.15019.

The article was submitted 15.02.2021; approved after reviewing 16.03.2021; accepted for publication 26.01.2022.

Information about the authors:

1. Mikhail A. Panin – Candidate of Medical Sciences, panin-mihail@yandex.ru, SPIN-код: 5834-3500;
2. Andrey V. Boyko – boiko120393@gmail.ru;
3. Medetbek Dzh. Abakirov – Doctor of Medical Sciences, Professor, medetbek@mail.ru
4. Armenak S. Petrosyan – Candidate of Medical Sciences, armenak.p@gmail.com;
5. Danila A. Ananin – Candidate of Medical Sciences, Ananuins@list.ru, https://orcid.org/0000-0003-0032-4710, SPIN-код: 1446-8368;
6. Morad M. Awad – M.D., moradawadov@gmail.com.

The authors declare that there is no conflict of interest.

The authors received no specific funding for this work.