Genij Ortopedii. 2023;29(1)110-116.

Review article

https://doi.org/10.18019/1028-4427-2023-29-1-110-116

Experimental animal models of osteonecrosis

Anastasia V. Sertakova✉, Vladimir Yu. Ulyanov, Elmira A. Magomedrasulova

V.I. Razumovsky Saratov State Medical University, Saratov, Russian Federation

Corresponding author: Anastasia V. Sertakova, anastasiya-sertakova@yandex.ru

Abstract

The objective was to analyze experimental animal models of osteonecrosis (ON) using the femoral head, show advantages and disadvantages, capacity to translate the findings for adult and pediatric orthopaedics, potential model modifications for orthopaedic and rheumatology research. **Material and methods** The original literature search was conducted on key resources including PubMed, Web of Science, Cochrane Library, E-library, and the Springer databank. Literature searches included Russian, English, and Italian studies. The research covered studies of 1980 to 2021 and included important landmarks of laboratory experiments with animal models. **Results and discussion** Although there was no ON model with ideal conditions found for it, the choice of a model could be based on the researcher's goal reproducing ON as a type of "osteochondropathy" to explore the results applicable to pediatric orthopaedics or classical ON in adults. Animals with long-term open growth plates, intensive blood circulation in the bone and rapid regeneration being characteristic of juvenile models of rats, rabbits and pigs could be appropriate for the experiment. Dogs, sheep, pigs and emus, in particular, were practical for reproducing ON in adults. Non-traumatic models of ON in adults were reversible and consistent with early stages of the condition. **Conclusion** The need for ON simulation increased due to progressing orthobiological techniques (PRP-therapy, BMCs technologies, etc.) in the treatment of ON. Application of orthobiological treatment resulted in heterogeneous, scattered outcomes being statistically unreliable and necessitating the search for optimal animal models and assessment of treatment methods for ON in modern orthopaedics.

Keywords: femoral head osteonecrosis, osteochondropathy, animal model, experiment, orthobiologics

For citation: Sertakova AV, Ulyanov VYu, Magomedrasulova EA. Experimental animal models of osteonecrosis. *Genij Ortopedii*. 2023;29(1):110-116. doi: 10.18019/1028-4427-2023-29-1-110-116

INTRODUCTION

Osteonecrosis (ON) is a group of pathological conditions of unknown etiology and is characterized by impaired metabolism of bone, cartilage and microcirculation in the nidus, development of secondary osteoarthritis of the adjacent joint [1-4]. ON commonly affects the head and condyles of the femur, epicondyle of the tibia, the head of the shoulder and the talus [5]. ON of childhood and adolescence is classified as a group of so-called "osteochondropathy" with a frequency of 0.4-20.9:100,000 in Legg-Calve-Perthes disease (LCPD) [6]. Important manifestation of ON include: early onset (5-14 years and 30-45 years, 3♂ : 1♀); lack of treatment in the early stages that leads to deformity of the articular surfaces in 80 % of cases; the risk of high instability of total joint replacement as a method of treatment – up to 40 % of cases in the first 10-15 years; early disability and limited mobility [6-9]. Etiopathogenetic causes of ON development include idiopathic (possibly hormonal overload) spasm of microvasculature and transition to ischemic stasis and local bone infarction due to increased cellular hypoxia [6, 10]. Most methods of treating ON in clinical practice are reduced to eliminating the mechanical collapse of the bone tissue in the affected area (rotational osteotomies, auto- and alloplasty with bone grafts, tunnel decompression) and the methods show obscure results at a long term [4, 5]. There is a need of new treatment protocols that can be developed and tested at preclinical trials [11]. Early and late stages of ON are perfectly reproduced on the animal model, which must meet the following criteria: it should reflect the whole of the etiological factors of the process; reflect all stages of development of the osteonecrotic process, including repair [5]. The objective was to analyze experimental animal models of osteonecrosis (ON) using the femoral head, show advantages and disadvantages, capacity to translate the findings for adult and pediatric orthopaedics, potential model modifications for orthopaedic and rheumatology research.

MATERIAL AND METHODS

The original literature search was conducted on key resources including PubMed, Web of Science, Cochrane Library, E-library, and the Springer databank using keywords: osteonecrosis, experimental model, in vivo/in vitro experiments, laboratory animals. Literature searches included Russian, English, and Italian studies. The research covered studies of 1980 to 2021 and included important landmarks of laboratory experiments with animal models. The inclusion criteria included: review articles, multicentre studies, controlled cohort studies, uncontrolled cohort studies, case-control studies in animals with reproducible ON.

RESULTS AND DISCUSSION

The set of experimental models is presented in Figure 1 with the description, advantages and disadvantages to be presented in our review.

Animal model of ON caused by trauma

Traumatically induced ON can be divided into three large groups according to the mechanism of reproduction: 1) ON caused by surgical vascular deprivation; 2) ON caused by physical factors; 3) ON caused by chemical factors. Physically and chemically induced ON can cause changes similar to bone infarction and potentially lead to subchondral bone collapse. The model of ON caused by vascular deprivation can capacitate study of microcirculatory disorders in detail as a link in the pathogenesis of multifactorial pathology. In Russia, Prof. G.S. Kilchevsky offered a method for modeling avascular necrosis of the femoral head in 1963 [12]. The method suggested an intracapsular circular section of the synovial membrane performed at the base of the neck and ligation of the round ligament of the femoral head. M. Nishino et al. [13] explored the model in adult dogs reproducing ON by dislocating the femoral head and ligating the medial and lateral circumferential arteries and veins. MRI showed extensive areas of subchondral necrosis of the femoral head in 80 % of the animals at 2 and 4 weeks, however, the animals were not followed up.

J.G. Hofstaetter et al. [14] reproduced ON in adult rabbit models. They created a model by complex surgical removal of the joint capsule, catheterization and sealing of the periosteal vessels, ligation of the round ligament of the femoral head, and destruction of the bone marrow through a narrow channel along the posterior wall of the femoral head to interrupt intramedullary blood flow. CT and histological examination indicated to ON in 2 out of 15 (13.3 %) animals at 6 and 12 months, and zones of osteolysis and subchondral fractures were seen in the remaining rabbits. This might be due to the reversibility of ON, in four-legged animals, in particular, as well as the long period of observation in the rabbit model, which had an increased blood flow even in adulthood.

Many studies [15-20] reported simulated ON in rat models, where the condition was reproduced by dislocation of the femoral head, transection of the round ligament, double dissection of the capsule and periosteum. Some researchers recorded ON, bone neoformation without collapse (decrease in head height) at 42 days [15-17]. The predominance of osteoporosis and osteoarthritis over ON was reported [19-20]. The piglet model was another popular model of ON with vascular deprivation [21–24] and used ligation of the femoral head and transection of the ligamentum teres. J.G. Hofstaetter et al. [24] reported gross radiological and morphological necrotic changes similar to the initial stage of LCPD with delayed epiphyseal growth at 4 weeks and severe flattening of the head at 8 weeks. M.F. Swiontkowski et al. [25] demonstrated a different model of ON in a piglet using an iatrogenic fracture of the femoral neck and internal fixation of the head with a metal construct. Histological examination showed ON foci in all animals with disoriented trabeculae and mechanical collapse of the subchondral zones at 8 weeks and similar results were recorded by J.G. Seiler et al. [26] on 12-week-old piglets, reproducing the protocol of the Swiontkowski experiment. In 2004, a team of authors together with Prof. I.V. Kirgizova offered a method for creating a model of osteochondropathy of the femoral head in the experiment. Changes in the bone structure characteristic of ON were achieved by increasing the intraosseous pressure. The study was conducted on 10 outbred dogs aged 4-6 months. A sterile stainless metal clamp was placed around the femur and tightened for periosteal compression [27]. The authors reported the method as reliable and received histological evidence of ON at 4-6 weeks.

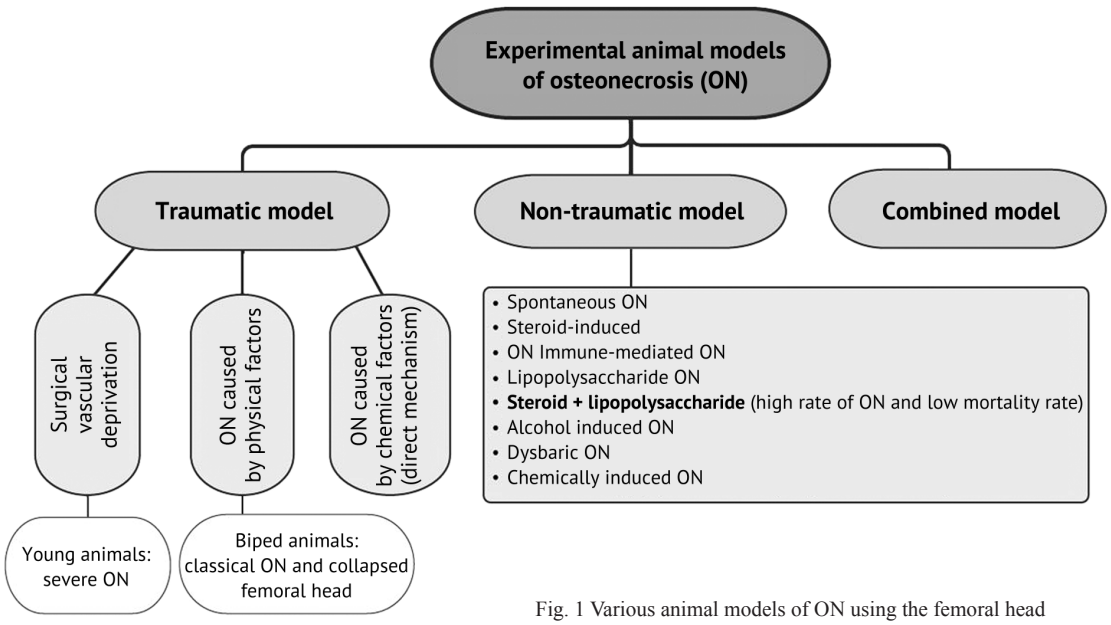

Fig. 1 Various animal models of ON using the femoral head

Animal model of ON caused by physical factors

Cryogenic and thermal physical factors are successfully used to provoke the development of ON. Despite the fact that the ON caused by the factors is not of a natural nature, the staging of the process corresponds to classical changes [28-30]. The cryodestruction causes cellular and vascular destruction. Local hyperthermia at 43-45°C with a constant effect on paraarticular tissues for a certain period indirectly induces cell apoptosis due to overheating of the cell fluid and cytostructures including DNA [31]. V.A. Filippenko et al. offered a method for modeling the ON of the femoral head using direct exposure to liquid nitrogen on the upper pole of the experimental femur of an animal (rabbit/dog) twice with a cryoprobe at a temperature of -100 °C at the border of the cartilaginous cover of the head for 5 minutes with an interval of 4 weeks. The authors reported the positive results with the method reported [32]. Other authors simulated ON in horses by deep freezing with a cryoprobe and exfoliation of the periosteum from the neck and intertrochanteric zone, but the result was poor: an incomplete defect of the femoral head was obtained without signs of collapse, and the staging of the process did not correspond to the classical grading [33]. M.G. Conzemius et al. [34] modeled ON on emu ostriches by local injection of liquid nitrogen on the femoral head near the transition to the neck and additional ligature ligation of the vessels. This experiment showed very good results with the changes reflecting stages of necrosis. Gait disturbance in the form of lameness was noted in 16 of 19 birds, cartilage fragmentation and loss of the shape of the articular end noted in 13 of 19 birds and a subcapital fracture seen in 4 birds [34]. Other authors reported a similar model of ON in sheep, having obtained histological verification of the process at 6-12 weeks with no decrease in the height of the femoral head [35]. There is a well-known model of ON in rabbits, caused by microwave heat with a temperature effect on the femoral head at 55 °C for 10 minutes [30]. The authors reported large areas of damage thin a short period of time (up to 4 weeks) with symptoms of osteoporosis, degenerative cysts, and spontaneous ON repair at 6-8 weeks, and 69 % of the animals lost their normal configuration of the femoral head due to collapse at 12 weeks. There are works describing simulated ON using X-ray focus therapy [36–39], however, the experiments were accompanied by technical difficulties and suffering of animals, and the results of most of them were rated as poor with no staging and collapse in ON.

Animal model of ON caused by chemical factors

J. Manggold et al. [40] induced ON in sheep by intraosseous administration of ethanol obtaining histologically verified partial necrosis in the animals at 12 weeks. One animal died at the time of injection and a subcapital fracture was seen in another animal at 6 weeks. Some authors suggested blowing talc into the joint cavity and injecting the coal tar preparation subperiosteally (in dogs). The method was supplemented by alcoholization of the sacral plexus with 96° alcohol. The authors reported grade 1 AVN at 2 months, grade II AVN at 3 months, and grade III AVN at 4.5 months [41], however, access to the joint was required for the experiment which could result in inflammatory complications. In 2006 A.S. Boyko published a dissertation study and described a method for ON modeling with a thrombovar introduced into the subepiphyseal zone of the femur of an experimental animal (dog). The syndrome of local hypercoagulation with impaired venous outflow from the proximal femoral epimetaphysis was shown to be one of the main links in the pathogenesis of AVN of the femoral head based on the experimental model [42].

Animal model of ON caused by non-traumatic factors

Non-traumatic ON can be divided into three major groups according to the mechanism of reproduction: 1) steroid-induced, 2) lipopolysaccharide-induced, and 3) mediated chemically-induced (horse serum, alcohol, baric factor, etc.). Some authors reported the so-called spontaneous ON in laboratory animals with negligible results [43, 44].

Steroid-induced OB in an animal model

The targeted intake of corticosetroids is one of the proven and direct factors in the development of ON in humans [45]. There are many reports in the literature describing an experimental model of steroid-induced ON, however, the interpretation of the results is important for orthopaedic surgeon treating the adult population, with few cases of steroid-induced ON in the pediatric population. Many studies describe the formation of an ON model in rabbits by the schematic administration of methylprednisolone intramuscularly [46, 47]. In one study, rabbits were injected intramuscularly with metipred at a rate of 20 mg/kg once, and signs of necrosis were recorded in 83 % of the animals; the diagnosis was histologically verified 3 weeks after injection [48]. Other authors, using similar models, obtained 70 % of ON with histological verification of the diagnosis after 4 weeks with 20 % mortality from injection [49] or a preclinical stage of bone marrow edema without transition to ON [50]. X Zhang et al. [51] described steroid-induced ON in rats with the administration of metipred at a rate of 21 mg/kg/daily/4 weeks in 80 % of animals with osteochondropathy (i.e., with preservation of trabecular osteoblasts). Other authors [52] published the results of an experiment on a chicken model with intramuscular administration of metipred 3 mg/kg/during a week, and received ON

with repair in 4 out of 12 chickens at 24 weeks with 48 % of the birds died. A. Xavier et al. [53] performed a systematic review of works published between 2011 and 2021, studied 284 full-text studies and statistically analyzed 53 protocols for creating a model of ON and osteoporosis using steroids. The authors obtained the following results: 1) the most popular animal models were rats (66 % of works) and mice (32 %), rabbits and sheep accounted for no more than 1 %, piglets/horses/dogs, etc. were used in 1 % of works; 2) dexamethasone was used in 49 % of studies, prednisolone in 22 %, and metipred in 14 % of cases intramuscularly and in 22 % of cases and 14 % orally; 3) dosages of prednisolone for rats ranged from 0.1 mg/kg/daily/60 days or 25 mg/kg/2 times a week/6 weeks; for mice, prednisolone was administered at 0.8 mg/kg/daily/3 weeks or 4 mg/kg/daily/3 weeks; rabbits and sheep were given dexamethasone 3 mg/kg/twice a week/12 weeks and prednisolone 0.6 mg/kg/5 times a week/7 months. Unfortunately, direct comparison between studies on model efficacy has been difficult due to heterogeneity of information regarding dose, route of administration, duration, and type of bioavailability in animals.

Lipopolysaccharide-induced ON

There are a number of studies devoted to the study of ON obtained by this method. A group of authors [54] reported ON obtained on a rabbit model by a single intravenous injection of lipopolysaccharide (10ų/kg) and fixed in 77 % of cases in a multifocal form at 4 weeks (4 out of 35 rabbits died after the administration of the drug). ON developed similarly to the Schwartzman reaction due to the organization of microthrombi in the microvasculature of the subchondral bone; necrosis in the epiphysis was achieved only in 9 % of the animals. A. Sakaguchi et al. [55] reported daily administration of lipopolysaccharide to male rats (n = 5) resulted in histologically verified ON in all animals at 4 week despite the parallel administration of bisphosphonates.

Mediated chemically induced OH
(horse serum, alcohol, baric factor, etc.)

ON can be caused by the introduction of various immune preparations. Some authors [56] simulated the process in rabbits by intravenously injecting sterile inactivated horse serum 10 ml/kg twice for 3 weeks and obtained signs of an early stage of necrosis in 64 % of the animals by the third week of the experiment without subchondral collapse. There are numerous works reporting modeling of ON by a combined administration of steroids and lipopolysaccharides [57-59] or horse serum [60], however, the results cannot be interpreted due to the small number of animals, the absence of severe stages of ON and the high mortality of animals.

The model of alcohol-associated ON is popular in Asian countries, in China, in particular [45]. A protocol for modeling ON in mice was developed with alcohol (20 ml/kg, 46 % ethanol solution) being injected into the stomach and ON with decreased height of the femoral head and epiphysis developed at 6 months [61]. C. Jaffre et al. [62] analyzed a number of studies investigating the association of daily alcohol intake in rats/rabbits for 4-6 weeks with the onset of ON and concluded that the results are difficult to interpret based on the current understanding of the effects of alcohol on bone metabolism, and there are problems related to protocol including dose, duration, and possible alcohol withdrawal in animals. Some authors demonstrated the simulation of ON by pressure. For example, C.E. Lehner et al. [63] reported dysbaric ON in adult sheep 12-13 and 24 hours after exposure to compressed air (2.6-2.9 atmospheres) for 2 months, however, only small areas of osteolysis were histologically obtained.

There is an interest in creating a biological model of ON with etiopathogenetic considerations and pathophysiological stages of the process. The technique is essential due to the widespread introduction of minimally invasive orthobiological techniques in the treatment of orthopaedic pathology [64, 65]. We came to the conclusion that a model with ideal conditions for it does not exist, however, given the initial goals and desired results, the choice is still possible. The cost of acquisition and care, availability, tolerance to captivity and ease of maintenance, adaptability in the group, low operating costs, resistance to infections and diseases, uniformity of animals, similarity to humans in biological characteristics, tolerability of surgical interventions are the main factors in the choice of animals. The lifespan of the species should be appropriate for the duration of the study [66]. Rats, rabbits and dogs are optimal models. Despite the fact that many authors [67, 68] have studied the differences in the composition, density, and quality of bones in different species (humans, dogs, sheep, pigs, cows, chickens) and have come to the conclusion that the bone tissue of dogs and pigs is more similar to human, this may not be a fundamental point for modeling ON, since the bone tissue is of the same type in terms of anatomical and pathomorphological nature. The type of animal does not matter, since there is a pathogenetic effect on bone tissue in the methods proposed [69]. The division is due to the researcher's goal of reproducing ON by the type of "osteochondropathy" to study the results applicable to pediatric orthopaedics or classical ON of an adult. Animals with long-term open growth plates, intensive blood circulation in the bone and rapid regeneration are practical for osteochondropathy, which are characteristic to the rat, rabbit and pig models [64]. With the multifactorial nature of ON in children and the minimality of the traumatic agent, it is preferable to use non-traumatic models of ON (Fig. 1) with minimal

surgical or chemical exposure to foreign substances, i.e., a combination of steroid-induced ON with low vascular deprivation [12-27]. The pathophysiological model offered by I.I. Kuzhelevsky et al. [70], who developed a model using paraarticular norepinephrine in combination with exercise can be more promising. Reproducing ON in adults, preference is given to dogs, sheep, pigs and emus, in particular. Bipedal emus demonstrated excellent results of ON staging, taking into account clinical manifestations [34]. The disadvantage with the model is slow growth and costly maintenance. Traumatic models of pathology with the advantage of focal necrosis of the femoral head, staging up to the complete collapse of the head and a decrease in the height are excellent for an adult ON. Non-traumatic models of ON in adults showed less remarkable data with necrosis being often reversible or consistent with early stages.

CONCLUSION

There is a need to search for animal models to reproduce avascular necrosis as a common pathological process in orthopaedics with catastrophic consequences for the individual. The need for ON modeling has increased due to the progress of orthobiological techniques (PRP-therapy, BMCs-technologies, etc.) in the treatment of early stages of the disease with diagnosis being available in clinical practice. However, the results of the treatment methods are heterogeneous, scattered, statistically relative and are subject of discussion. The search for optimal animal models and assessment of methods for the treatment of ON in modern orthopaedics is a necessity.

REFERENCES

1. Torgashin AN, Rodionova SS, Shumsky AA, Makarov MA, Torgashina AV, Akhtyamov IF, Kovalenko AN, Zagorodniy NV, Mironov SP. [Treatment of aseptic necrosis of the femoral head. Clinical guidelines]. *Nauchno-prakticheskaia Revmatologiia*. 2020;58(6):637-645. (In Russ.) doi: 10.47360/1995-4484-2020-637-645
2. Matveev R.P., Bragina S.V. [Avascular necrosis of the femoral head (Review of the literature)]. *Ekologiia Cheloveka*. 2018;25(3):58-64. (In Russ.)
3. Hines JT, Jo WL, Cui Q, Mont MA, Koo KH, Cheng EY, Goodman SB, Ha YC, Hernigou P, Jones LC, Kim SY, Sakai T, Sugano N, Yamamoto T, Lee MS, Zhao D, Drescher W, Kim TY, Lee YK, Yoon BH, Baek SH, Ando W, Kim HS, Park JW. Osteonecrosis of the Femoral Head: an Updated Review of ARCO on Pathogenesis, Staging and Treatment. *J Korean Med Sci*. 2021 Jun 21;36(24):e177. doi: 10.3346/jkms.2021.36.e177
4. Holtmann H, Lommen J, Kübler NR, Sproll C, Rana M, Karschuck P, Depprich R. Pathogenesis of medication-related osteonecrosis of the jaw: a comparative study of in vivo and in vitro trials. *J Int Med Res*. 2018 Oct;46(10):4277-4296. doi: 10.1177/0300060518788987
5. Fan M, Peng J, Qin L, Lu S. Experimental animal models of osteonecrosis. Rheumatol Int. 2011 Aug;31(8):983-994. doi: 10.1007/s00296-011-1819-9
6. Rubashkin SA, Sertakova AV, Dohov MM, Timaev MH. Degenerative hip disorders in children. *Pediatric Traumatology, Orthopaedics and Reconstructive Surgery*. 2018;6(3):78-86. doi: 10.17816/PTORS6378-86
7. Kozhevnikov OV, Lysikov VA, Ivanov AV. [Legg-Calve-Perthes disease: etiology, pathogenesis, diagnosis and treatment]. *Vestnik Travmatologii i Ortopedii im N.N. Priorova*. 2017;24(1):77-87. (In Russ.) doi: 10.17816/vto201724177-87
8. Petek D, Hannouche D, Suva D. Osteonecrosis of the femoral head: pathophysiology and current concepts of treatment. *EFORT Open Rev*. 2019 Mar 15;4(3):85-97. doi: 10.1302/2058-5241.4.180036
9. Lespasio MJ, Sodhi N, Mont MA. Osteonecrosis of the Hip: A Primer. *Perm J*. 2019;23:18-100. doi: 10.7812/TPP/18-100
10. Teplenkii MP, Chepeleva MV, Kuznetsova EI. [Perthes disease: immunological aspects]. *Klinicheskaia Laboratornaia Diagnostika*. 2020;65(4):239-243. (In Russ.) doi: 10.18821/0869-2084-2020-65-4-239-243
11. Chereshnev VA, Shilov YuI, Chereshneva MV, Samodelkin EI, Gavrilova TV, Gusev EYu, Gulyaev IL. *Experimental models in pathology: textbook*. Perm: Perm State University. un-t, 2011. 266 p. (In Russ.)
12. Kilchevskiy GS. [Avascular necrosis of the femoral head under experiment]. *Ortopediia, Travmatologiia i Protezirovanie*. 1963;(7):30-34. (In Russ.)
13. Nishino M, Matsumoto T, Nakamura T, Tomita K. Pathological and hemodynamic study in a new model of femoral head necrosis following traumatic dislocation. *Arch Orthop Trauma Surg*. 1997;116(5):259-262. doi: 10.1007/BF00390048
14. Hofstaetter JG, Wang J, Yan J, Glimcher MJ. The effects of alendronate in the treatment of experimental osteonecrosis of the hip in adult rabbits. *Osteoarthritis Cartilage*. 2009 Mar;17(3):362-370. doi: 10.1016/j.joca.2008.07.013
15. Peled E, Bejar J, Zinman C, Boss JH. Vasculature deprivation-induced osteonecrosis of rats' femoral heads associated with the formation of deep surface depressions. *Arch Orthop Trauma Surg*. 2007 Jul;127(5):369-374. doi: 10.1007/s00402-006-0258-7
16. Vadasz Z, Misselevich I, Norman D, Peled E, Boss JH. Localization of vascular endothelial growth factor during the early reparative phase of the rats' vessels deprivation-induced osteonecrosis of the femoral heads. *Exp Mol Pathol*. 2004 Oct;77(2):145-148. doi: 10.1016/j.yexmp.2004.06.002
17. Levin D, Norman D, Zinman C, Misselevich I, Reis DN, Boss JH. Osteoarthritis-like disorder in rats with vascular deprivation-induced necrosis of the femoral head. *Pathol Res Pract*. 1999;195(9):637-647. doi: 10.1016/S0344-0338(99)80129-0
18. Norman D, Reis D, Zinman C, Misselevich I, Boss JH. Vascular deprivation-induced necrosis of the femoral head of the rat. An experimental model of avascular osteonecrosis in the skeletally immature individual or Legg-Perthes disease. *Int J Exp Pathol*. 1998 Jun;79(3):173-181. doi: 10.1046/j.1365-2613.1998.00063.x
19. Peskin B, Shupak A, Misselevich I, Zinman C, Levin D, Jacob Z, Reis DN, Boss JH. Transphyseal osseous bridges in experimental osteonecrosis of the femoral head of the rat. Histologic study of the bony bridges connecting the epiphyseal with the metaphyseal bony trabeculae through gaps in the physeal cartilage. *J Pediatr Orthop B*. 2001 Jul;10(3):214-8.
20. Peled E, Bejar J, Zinman C, Boss JH, Reis DN, Norman D. Prevention of distortion of vascular deprivation-induced osteonecrosis of the rat femoral head by treatment with alendronate. *Arch Orthop Trauma Surg*. 2009 Feb;129(2):275-279. doi: 10.1007/s00402-008-0656-0
21. Kim HK, Su PH, Qiu YS. Histopathologic changes in growth-plate cartilage following ischemic necrosis of the capital femoral epiphysis. An experimental investigation in immature pigs. *J Bone Joint Surg Am*. 2001 May;83(5):688-697. doi: 10.2106/00004623-200105000-00007
22. Koob TJ, Pringle D, Gedbaw E, Meredith J, Berrios R, Kim HK. Biomechanical properties of bone and cartilage in growing femoral head following ischemic osteonecrosis. *J Orthop Res*. 2007 Jun;25(6):750-757. doi: 10.1002/jor.20350
23. Kim HK, Sanders M, Athavale S, Bian H, Bauss F. Local bioavailability and distribution of systemically (parenterally) administered ibandronate in the infarcted femoral head. *Bone*. 2006 Jul;39(1):205-212. doi: 10.1016/j.bone.2005.12.019
24. Hofstaetter JG, Roschger P, Klaushofer K, Kim HK. Increased matrix mineralization in the immature femoral head following ischemic osteonecrosis. *Bone*. 2010 Feb;46(2):379-385. doi: 10.1016/j.bone.2009.10.006
25. Swiontkowski MF, Tepic S, Rahn BA, Cordey J, Perren SM. The effect of fracture on femoral head blood flow. Osteonecrosis and revascularization studied in miniature swine. *Acta Orthop Scand*. 1993 Apr;64(2):196-202. doi: 10.3109/17453679308994570

26. Seiler JG 3rd, Kregor PJ, Conrad EU 3rd, Swiontkowski MF. Posttraumatic osteonecrosis in a swine model. Correlation of blood cell flux, MRI and histology. *Acta Orthop Scand*. 1996 Jun;67(3):249-254. doi: 10.3109/17453679608994682
27. Kirgizov IV, Gorbunov NS, Kirpichev SV, Dudarev VA. *Sposob sozdaniia modeli osteokhondropatii golovki bedrennoi kosti* [The way of creating a model of osteochondropathy of the femoral head]. Patent RF no. 2229167, G098B 23/28, 2004. (In Russ.)
28. Reed KL, Brown TD, Conzemius MG. Focal cryogen insults for inducing segmental osteonecrosis: computational and experimental assessments of thermal fields. *J Biomech*. 2003 Sep;36(9):1317-1326. doi: 10.1016/s0021-9290(03)00154-4
29. Mont MA, Einhorn TA, Sponseller PD, Hungerford DS. The trapdoor procedure using autogenous cortical and cancellous bone grafts for osteonecrosis of the femoral head. *J Bone Joint Surg Br*. 1998 Jan;80(1):56-62. doi: 10.1302/0301-620x.80b1.7989
30. Li Y, Han R, Geng C, Wang Y, Wei L. A new osteonecrosis animal model of the femoral head induced by microwave heating and repaired with tissue engineered bone. *Int Orthop*. 2009 Apr;33(2):573-580. doi: 10.1007/s00264-008-0672-2
31. Hamazoe R, Maeta M, Murakami A, Yamashiro H, Kaibara N. Heating efficiency of radiofrequency capacitive hyperthermia for treatment of deep-seated tumors in the peritoneal cavity. *J Surg Oncol*. 1991 Nov;48(3):176-179. doi: 10.1002/jso.2930480307
32. Filippenko VA, Malyshkina SV, Dedukh NV, Kulish NI, Pankov EIa, Zhigun AI. [The way of modeling aseptic necrosis of the femoral head]. Authors' license no. 1141444 SSSR, 1985. (In Russ.)
33. Malizos KN, Quarles LD, Seaber AV, Rizk WS, Urbaniak JR. An experimental canine model of osteonecrosis: characterization of the repair process. *J Orthop Res*. 1993 May;11(3):350-357. doi: 10.1002/jor.1100110306
34. Conzemius MG, Brown TD, Zhang Y, Robinson RA. A new animal model of femoral head osteonecrosis: one that progresses to human-like mechanical failure. *J Orthop Res*. 2002 Mar;20(2):303-309. doi: 10.1016/S0736-0266(01)00108-5
35. Martel J, Bueno A, Domínguez MP, Llorens P, Quirós J, Delgado C. Percutaneous radiofrequency ablation: relationship between different probe types and procedure time on length and extent of osteonecrosis in dog long bones. *Skeletal Radiol*. 2008 Feb;37(2):147-152. doi: 10.1007/s00256-007-0416-1
36. Le TX, Andrews RT. Thermal osteonecrosis of the rib after radiofrequency ablation in the thorax. *J Vasc Interv Radiol*. 2008 Jun;19(6):940-944. doi: 10.1016/j.jvir.2008.02.017
37. Encalada I, Richmond JC. Osteonecrosis after arthroscopic meniscectomy using radiofrequency. *Arthroscopy*. 2004 Jul;20(6):632-636. doi: 10.1016/j.arthro.2004.04.075
38. Cetik O, Cift H, Comert B, Cirpar M. Risk of osteonecrosis of the femoral condyle after arthroscopic chondroplasty using radiofrequency: a prospective clinical series. *Knee Surg Sports Traumatol Arthrosc*. 2009 Jan;17(1):24-29. doi: 10.1007/s00167-008-0604-0
39. Bonutti PM, Seyler TM, Delanois RE, McMahon M, McCarthy JC, Mont MA. Osteonecrosis of the knee after laser or radiofrequency-assisted arthroscopy: treatment with minimally invasive knee arthroplasty. *J Bone Joint Surg Am*. 2006 Nov;88 Suppl 3:69-75. doi: 10.2106/JBJS.F.00533
40. Manggold J, Sergi C, Becker K, Lukoschek M, Simank HG. A new animal model of femoral head necrosis induced by intraosseous injection of ethanol. *Lab Anim*. 2002 Apr;36(2):173-180. doi: 10.1258/0023677021912460
41. Pozharskii VP, Egorova SA, Egorov NA, Pozharskii AV. [The way of modeling epiphyseal aseptic necrosis in experiment]. Patent RF no. 2300812, G09B 23/28, 2003. (In Russ.)
42. Boiko A.S. *Kompleksnoe lechenie bolezni Legg-Kalve-Pertesa u detei. Diss. kand. med. nauk* [Complex treatment of Legg-Calve-Perthes disease in children. Cand. med. sci. diss.]. Rostov-na-Donu, 2006, 94 p. (In Russ.)
43. Wada M, Kumagai K, Murata M, S-Yamashita Y, Shindo H. Warfarin reduces the incidence of osteonecrosis of the femoral head in spontaneously hypertensive rats. *J Orthop Sci*. 2004;9(6):585-590. doi: 10.1007/s00776-004-0829-9
44. Suzuki M, Kumagai K, Osaki M, Murata M, Tomita M, Miyata N, Hozumi A, Niwa M. Osteonecrosis of femoral head in the stroke-prone spontaneously hypertensive rats, especially old rats. *Clin Exp Hypertens*. 2008 Oct;30(7):689-697. doi: 10.1080/10641960802251883
45. Mont MA, Jones LC, Hungerford DS. Nontraumatic osteonecrosis of the femoral head: ten years later. *J Bone Joint Surg Am*. 2006 May;88(5):1117-1132. doi: 10.2106/JBJS.E.01041
46. Xu J, Gong H, Lu S, Deasey MJ, Cui Q. Animal models of steroid-induced osteonecrosis of the femoral head-a comprehensive research review up to 2018. *Int Orthop*. 2018 Jul;42(7):1729-1737. doi: 10.1007/s00264-018-3956-1
47. Fang S, Li Y, Chen P. Osteogenic effect of bone marrow mesenchymal stem cell-derived exosomes on steroid-induced osteonecrosis of the femoral head. *Drug Des Devel Ther*. 2018 Dec 18;13:45-55. doi: 10.2147/DDDT.S178698
48. Iwakiri K, Oda Y, Kaneshiro Y, Iwaki H, Masada T, Kobayashi A, Asada A, Takaoka K. Effect of simvastatin on steroid-induced osteonecrosis evidenced by the serum lipid level and hepatic cytochrome P4503A in a rabbit model. *J Orthop Sci*. 2008 Sep;13(5):463-8. doi: 10.1007/s00776-008-1257-z
49. Kuribayashi M, Fujioka M, Takahashi KA, Arai Y, Ishida M, Goto T, Kubo T. Vitamin E prevents steroid-induced osteonecrosis in rabbits. *Acta Orthop*. 2010 Feb;81(1):154-160. doi: 10.3109/17453671003587101
50. Takao M, Sugano N, Nishii T, Sakai T, Nakamura N, Yoshikawa H. Different magnetic resonance imaging features in two types of nontraumatic rabbit osteonecrosis models. *Magn Reson Imaging*. 2009 Feb;27(2):233-239. doi: 10.1016/j.mri.2008.07.001
51. Zhang X, Liu Y, Ren K, Liu J, Zhu B, Sun Z. [Secondary total hip arthroplasty for osteonecrosis of femoral head after failed internal fixation of femoral neck fracture]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2010 Mar;24(3):257-261. (in Chinese)
52. Cui Q, Wang GJ, Su CC, Balian G. The Otto Aufranc Award. Lovastatin prevents steroid induced adipogenesis and osteonecrosis. *Clin Orthop Relat Res*. 1997 Nov;(344):8-19.
53. Xavier A, Toumi H, Lespessailles E. Animal Model for Glucocorticoid Induced Osteoporosis: A Systematic Review from 2011 to 2021. *Int J Mol Sci*. 2021 Dec 29;23(1):377. doi: 10.3390/ijms23010377
54. Irisa T, Yamamoto T, Miyanishi K, Yamashita A, Iwamoto Y, Sugioka Y, Sueishi K. Osteonecrosis induced by a single administration of low-dose lipopolysaccharide in rabbits. *Bone*. 2001 Jun;28(6):641-649. doi: 10.1016/s8756-3282(01)00460-4
55. Sakaguchi O, Kokuryo S, Tsurushima H, Tanaka J, Habu M, Uehara M, Nishihara T, Tominaga K. Lipopolysaccharide aggravates bisphosphonate-induced osteonecrosis in rats. *Int J Oral Maxillofac Surg*. 2015 Apr;44(4):528-534. doi: 10.1016/j.ijom.2014.08.011
56. Tsuji T, Sugano N, Sakai T, Yoshikawa H. Evaluation of femoral perfusion in a non-traumatic rabbit osteonecrosis model with T_2*-weighted dynamic MRI. *J Orthop Res*. 2003 Mar;21(2):341-351. doi: 10.1016/S0736-0266(02)00144-4
57. Zhang G, Sheng H, He YX, Xie XH, Wang YX, Lee KM, Yeung KW, Li ZR, He W, Griffith JF, Leung KS, Qin L. Continuous occurrence of both insufficient neovascularization and elevated vascular permeability in rabbit proximal femur during inadequate repair of steroid-associated osteonecrotic lesions. *Arthritis Rheum*. 2009 Oct;60(10):2966-2977. doi: 10.1002/art.24847
58. Sun Y, Feng Y, Zhang C. The effect of bone marrow mononuclear cells on vascularization and bone regeneration in steroid-induced osteonecrosis of the femoral head. *Joint Bone Spine*. 2009 Dec;76(6):685-690. doi: 10.1016/j.jbspin.2009.04.002
59. Wu X, Yang S, Duan D, Zhang Y, Wang J. Experimental osteonecrosis induced by a combination of low-dose lipopolysaccharide and high-dose methylprednisolone in rabbits. *Joint Bone Spine*. 2008 Oct;75(5):573-578. doi: 10.1016/j.jbspin.2007.11.004
60. Okazaki S, Nishitani Y, Nagoya S, Kaya M, Yamashita T, Matsumoto H. Femoral head osteonecrosis can be caused by disruption of the systemic immune response via the toll-like receptor 4 signalling pathway. *Rheumatology* (Oxford). 2009 Mar;48(3):227-232. doi: 10.1093/rheumatology/ken462
61. Wang Y, Yin L, Li Y, Liu P, Cui Q. Preventive effects of puerarin on alcohol-induced osteonecrosis. *Clin Orthop Relat Res*. 2008 May;466(5):1059-1067. doi: 10.1007/s11999-008-0178-7
62. Jaffré C, Rochefort GY. Alcohol-induced osteonecrosis--dose and duration effects. *Int J Exp Pathol*. 2012 Feb;93(1):78-79; author reply 79. doi: 10.1111/j.1365-2613.2011.00798_1.x
63. Lehner CE, Adams WM, Dubielzig RR, Palta M, Lanphier EH. Dysbaric osteonecrosis in divers and caisson workers. An animal model. *Clin Orthop Relat Res*. 1997 Nov;(344):320-332.

64. Eismont OL. [Orthobiological technologies in the treatment of osteoarthritis of the joints]. *Meditsinskie Novosti*. 2020;(8):45-48. (In Russ.)
65. Obana KK, Schallmo MS, Hong IS, Ahmad CS, Moorman CT 3rd, Trofa DP, Saltzman BM. Current Trends in Orthobiologics: An 11-Year Review of the Orthopaedic Literature. *Am J Sports Med*. 2022 Sep;50(11):3121-3129. doi: 10.1177/03635465211037343
66. Dolzhikov A.A., Dolzhikova I.N. [The problem of experimental model choice in biomedical researches of implants (review)]. *Nauchnye Rezultaty Biomeditsinskikh Issledovanii*, 2018;4(3):49-62. (In Russ.) doi: 10.18413/2313-8955-2018-4-3-0-5
67. Aerssens J, Boonen S, Lowet G, Dequeker J. Interspecies differences in bone composition, density, and quality: potential implications for in vivo bone research. *Endocrinology*. 1998 Feb;139(2):663-670. doi: 10.1210/endo.139.2.5751
68. Gong JK, Arnold JS, Cohn SH. Composition of trabecular and cortical bone. Anat. Rec., 1964 Jul;149:325-331. doi: 10.1002/ar.1091490303
69. Slizovskiy GV, Kuzhelivskiy II, Sitko LA, Bochmaga YaYa. [A method of modeling aseptic necrosis of the femoral head]. *Mat i Ditia v Kuzbasse*. 2017;(1):33-36. (In Russ.)
70. Kuzhelivskiy II, Slizovskiy GV, Anikina EYu. [Method for modeling aseptic necrosis of the femoral head]. Patent RF no. 2626567, 2016. (In Russ.)

The article was submitted 23.03.2022; approved after reviewing 17.05.2022; accepted for publication 16.12.2022.

Information about the authors:

1. Anastasia V. Sertakova – Candidate of Medical Sciences, anastasiya-sertakova@yandex.ru, https://orcid.org/0000-0002-4375-0405;
2. Vladimir Yu. Ulyanov – Doctor of Medical Sciences, Associate Professor, v.u.ulyanov@gmail.com, https://orcid.org/0000-0002-9466-8348;
3. Elmira A. Magomedrasulova – M.D.

Conflict of interests and funding *This work was performed as part of the Advanced Research Project of the Saratov State Medical University named after V.I. Razumovsky Ministry of Health of Russia "Development of a system for evaluating the effectiveness of orthobiological methods for the treatment of degenerative diseases of major joints in children" No. SSMU-2022-010 (state registration number R&D 122031400732-9).*