Literature review

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Surgical methods of focal hyaline cartilage defect management in large joints (literature review)

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An articular cartilage lesion in large joints is a frequent pathology of the locomotor apparatus. More than 50 % of visits to a traumatologist or an orthopaedic surgeon in outpatient clinics are associated with pain in large joints. Conservative methods of treatment have not undergone significant changes lately what cannot be said about surgical interventions. Methods of chondrogenesis stimulation and restoration of the cartilaginous layer by repair of its defect with cell technologies continue to develop. This article reviews the literary sources on modern methods of treating articular cartilage lesions.
Keywords: hyaline cartilage, focal defect, microfracture, mosaic autochondroplasty, perforation tunneling, cell technology

INTRODUCTION

An articular cartilage lesion in large joints is a frequent pathology of the locomotor apparatus. More than 50 % of visits to a traumatologist or an orthopaedic surgeon in outpatient clinics are associated with pain in large joints [1]. A study of the results of 31,516 arthroscopic interventions performed for large joint damage and diseases showed that in 63 % of the cases were cartilage pathologies in varying stages [2, 3]. Conservative methods of treatment have not undergone significant changes in the recent years what cannot be said about surgical interventions. Methods of chondrogenesis stimulation and cartilaginous layer defect restoration with cellular technologies continue to develop rapidly [4, 5].

Attempts to restore the articular cartilage with conservative and surgical technologies have a long history. Early techniques were limited to performing transplantation of the articular bone end. In 1925, Lexer and co-authors described the first transplantation. Modern methods of chondrogenesis stimulation have originated from the technique of tunneling the articular cartilage defect zone, proposed by Pridie [6]. It was further developed by Ficat who called it spongialization. The technique consists in removing the damaged cartilage along with the subchondral bone to ensure the release of mesenchymal stem cells from the spongy bone, followed by their differentiation into fibrous tissue that fills in the defect. Gross et al. proposed the idea of allotransplantation of fresh osseo-cartilaginous grafts [7], and L. Peterson was the first to implant cultured chondrocytes of the first generation in an experiment [8]. Today, a variety of surgical techniques have been known for articular cartilage damage repair, but they all originate from these three methods.

Our article deals with a literature review of contemporary methods used to manage the damaged articular cartilage.

Bone marrow stimulation The essence of this method is to provide an exit of the cells contained in the bone marrow so that are able to move into the defect in order to improve the regeneration of the cartilage. Tunneling, abrasive arthroplasty, spongialization and microfracture can result in bleeding and subsequent formation of a fibrin clot that must cover the focal defect of the hyaline cartilage. Elements of the bone marrow, such as mesenchymal stem cells (MSC), leukocytes and growth factors contribute to the transformation of

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the fibrin clot into a cartilaginous fibrous tissue [4]. The mechanical and biochemical properties of such tissue are individual. However, the issue of the tissue' ability to resist various loads on the joint remains open.

Tunneling K. Pridie reported on the effectiveness of multiple drilling of the articular cartilage defect with the Kirschner wire. The operation was supposed to cause pronounced bleeding from the spongy bone with a possible formation of cartilaginous fibrous tissue at the defect site. Despite the fact that the method was developed more than 50 years ago, it has been still used nowadays during arthroscopic interventions on large joints. Thus, B.V. Malyuk in his PhD thesis entitled "Osteoperforation of the subchondral bone in osteochondritis dissecans of the femoral condyles of the knee joint" suggests that deep tunneling of the knee joint defect allows achieving a balanced course of osteo- and chondroregeneration to bridge the defect of the cartilage [9]. Some authors believe that indications for tunneling are damage to the cartilage due to osteochondritis dissecans or local idiopathic osteonecrosis. Removal of damaged osseocartilaginous fragments and deep drilling of the defect area with a wire (1.5–2 mm in diameter) or a thin drill (2.5–3.5 mm in diameter) is performed until bleeding starts (**Fig. 1**) [10]. The obvious shortcoming of perforation tunneling is the burn of adjacent tissues by incorrect drilling that results in minimal bleeding from the subchondral bone that may not be sufficient for formation of a full and stable cartilaginous-like fibrous tissue.

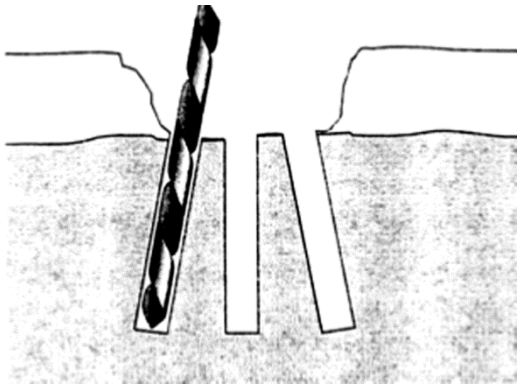

Fig. 1 Method of a focal cartilage defect tunneling

Abrasive arthroplasty Initially, the idea was to treat the damaged area of the cartilage and the underlying cortical plate with a 1–2 mm bur until bleeding appeared with an obligatory preservation of the integrity of the subchondral bone (**Fig. 2**). Later, this technique was modified to a deeper marginal resection of the cortical bone, down to the spongy bone. The authors believe that the technique provides remission of cartilage degeneration for up to 5 years in 70 % of patients and better outcomes in young people [11]. The merits of abrasion include a uniform formation of the regenerate and a better restoration of the shape of the joint surface as compared with tunneling [12]. The shortcoming of the method, like in case of tunneling, is the instability of the formed tissue and its inability to adequately withstand the load on the articular cartilage surface [13].

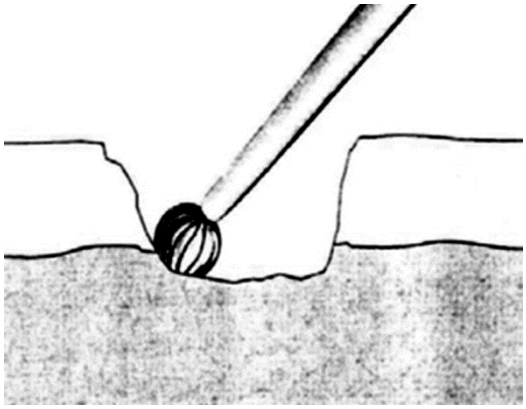

Fig. 2 Abrasive arthroplasty

Spongialization The principle is to clean the defect of the cartilage and remove the tissues along with the subchondral bone down to the spongy bone (**Fig. 3**). The author of the method reported 79 % of positive results after a 2-year follow-up. However, other studies could not reproduce such positive outcomes. The shortcomings caused by an excessive depth of resection include failures to cover the entire defect and a short remission period [14].

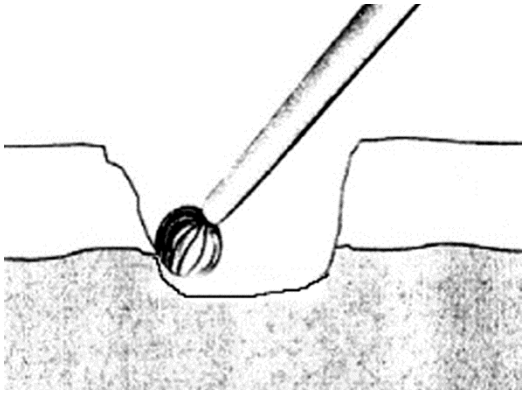

Fig. 3 Spongialization

Microfracturing Steadman was the first to report on the positive effect of microfractures on the restoration of focal defects of the articular cartilage in 1997. Microfractures of the subchondral bone in the cartilage defect are produced with a special awl to a depth of 4–5 mm (3–4 microfractures per 1 cm²) until bleeding appears (**Fig. 4**). Advantages of the method are the absence of burns, the preservation of a sufficient amount of the subchondral bone and an easy performance during arthroscopy [15]. Today, microfracturing continues to be successfully used for cartilage defects [16]. However, there is no unambiguous opinion on the maximum size of the defect for this method to be applied. Steadman reported good results in extensive cartilage defects, greater than 4 cm² [14]. However, Knutsen et al. obtained poor results for the same amount of damage [17]. A number of authors still object to the necessity of performing microfractures, considering that the resulting cartilaginous fibrous tissue is unstable to loads and could lyse fast [18].

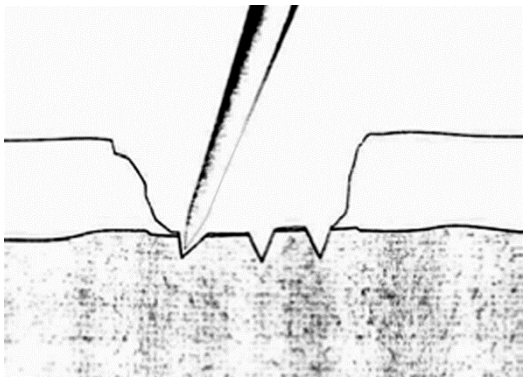

Fig. 4 Microfracture performance

It should be noted that good results are obtained with the mentioned variants of bone marrow stimulation only for a short period of time [11, 12].

Despite the fact that the methods of bone marrow stimulation were proposed more than half a century ago, they remain relevant today because they are easy to implement and inexpensive. We consider it advisable to use the microfracturing method for hyaline cartilage defect in the knee joint that amounts up to 4 cm² during the arthroscopic intervention.

Methods of cartilaginous layer restoration Today, allo- and autologous osteochondral grafts and periosteum transplantation methods as well as cell technologies, different in the content and volume of surgical intervention, have been developed, described, introduced and continue to develop actively.

Osseo-cartilaginous allografting As a rule, two types of grafts are used: fresh prepared and frozen. A. Gross in 1975 was the first to perform transplantation of fresh bone-and-cartilage grafts for large defects of the knee joint cartilage, harvested from the corpses no later than 12 hours after the death of the donor [7]. In 2008, he also reported on a 25-year survival of the graft [19]. Today, indications for such alloplasty can be osteochondral defects with a diameter of more than 3 cm². Undoubtedly, the advantage of this technique is the transplantation of viable, mature hyaline cartilage which completely restores the anatomy and function of the joint [20]. Shortcomings include the expected conflicting immunological graft rejection and the possibility of transmitting diseases [21]. The storage of extracted osseo-cartilaginous blocks reaches 28 days, as according to some studies. Therefore, there is a possibility of creating a bone-and-cartilage bank. W. Pearsall reports about 76 % of good results for frozen blocks for 4 years after grafting. The risk of disease transmission and immunological responses have decreased [3]. Some authors believe that conserved or frozen grafts lose plasticity, their proteins denature, and there happens destruction of cellular elements [22]. For this reason, fresh grafts are preferred [22].

Osseo-cartilaginous autologous grafting In 1992, L. Hangodi published a technique for arthroscopic autografting of bone-and-cartilage blocks of a cylindrical shape which were 4.5 mm in diameter, harvested from the non-loaded areas of the femoral condyles. The merits of this "mosaic" autochondroplasty include the possibility of complete closure of the defect and an increased survival of the hyaline cartilage with the preservation of its true morphological structure. This method has been very popular due to good clinical outcomes [23, 24, 25]. Nevertheless, some authors have a negative attitude to "mosaic" autohondroplasty and reported the presence of such deficiencies as painful donor zone, the lack of reliable integration of the transplanted block and the impossibility of covering large defects, partial lysis with the transformation of grafts into fibrous tissue [11, 15]. The work of S. Ulstein that compares the results of au-

tochondroplasty with the results of microfracturing [16] seems interesting as he did not reveal significant difference. There have been reports of good results of using grafts from the proximal tibio-fibular junction for autotransplantation [26].

Periosteum implantation The periosteum contains cells with the potential for regeneration of bone and cartilaginous tissues. It is conditionally a matrix for the delivery of growth factors and their source. These conditions make it possible to use the periosteum as a material for filling the hyaline cartilage defects. O'Driscoll was the first to show that the periosteum can produce chondrocytes in an animal experiment and thereby serve as a source for restoration of hyaline cartilage defects. Later, similar results were confirmed by other authors [27]. Today, there is no consensus on the position and orientation of the periosteum in the defect bed. O'Driscoll and Fitzsimmons [28] believe that the cambial layer should face the joint gap. Olivos-Meza reports good results using this method in combination with growth factors, especially in the treatment of defects in the patella hyaline cartilage [29]. Most authors opine that, despite good early results of transplantation of the periosteum, the long-term outcomes are unsatisfactory due to calcification and sequestration of the graft [30].

Autologous chondrocyte implantation (ACI) In 1994, Brittberg and Lindahl, two Swedish scientists, published the results of clinical use of ACI for management of post-traumatic defects of the hyaline cartilage in the knee joint [31]. The technique consists of two stepwise operations: 1) 200–300 mg of cartilage is harvested from the unloaded joint surface foolowed by cultivation of chondrocytes for 4–6 weeks; 2) introduction of chondrocytes into the defect covered with the periosteal flap [12, 32]. The described technique is classical and is used for defects greater than 2.5 cm^2. According to a number of authors, good results were observed in 80 % of patients following 10 years after the surgery [31]. The high risk of periosteal hypertrophy and arthrofibrosis, requiring interventions of revision and joint mobilization, is attributed to its shortcomings [32].

In view of the shortcomings described above, a variety of inert collagen membranes have preferably been used to cover the defect instead of the autologous periosteum [4, 33]. The second generation of ACI techniques includes debridement of the defect, its closure with a collagen membrane that is stitched with vicril to the edges of the preserved cartilage, and sealing the defect zone with fibrin glue. Chondrocytes are injected with a syringe through the membrane. This method provided good results but the problem of uneven distribution of chondrocytes in the defect remained [11].

In 2012, a third generation of ACI techniques based on the use of biological matrices was proposed. The latter helped maintain a differentiated phenotype of chondrocytes and correctly distribute them in the defect [34]. Biological matrices exclude the use of arthrotomy and all manipulations are performed arthroscopically [35]. Nevertheless, the treatment outcomes in patients using the 1st and 2nd generation of the ACI method do not significantly differ from the outcomes of the 3rd generation operations [36].

Autologous matrix induced chondrogenesis (AMIC) AMIC operations are performed using a matrix consisting of porcine collagen types I and III. Such matrices consist of two layers: the first layer is dense while the second is porous. The dense layer performs a protective function, preventing the stem cells from releasing from under the membrane. The porous layer that faces the subchondral bone promotes chondrogenesis [37]. Both sutures and fibrin glue can be used for fixation of the matrix. The merits of this technique are a one-stage operation without preliminary cartilage harvesting and its economic expediency, because there is no need for cultivation of chondrocytes [38]. Nowadays, many authors report better results of the AMIC technique when compared with the ACI 1 and 2 generation techniques [39, 40]. According to Ferruzzi and co-authors, the AMIC method achieves better results in comparison with 3rd generation of the ACI arthroscopic technique. At the same time, a high level of effectiveness is noted in both cases. According to one of the universities in Belgium, AMIC show better results in patello-femoral articulation lesions [41].

Mesenchymal stem cells (MSC) A number of authors opine that mesenchymal stem cells are a good alternative to ACI and AMIC [38, 42]. Cells are isolated from the bone marrow, synovial membranes, periosteum, and adipose tissue. Under the influence of various factors, they differentiate fur-

ther towards chondrogenesis [43, 44]. In experimental animal studies and clinical observations, the high potential of these cells for chondrogenesis was demonstrated [45]. MSCs are injected into the joint on some matrix if there is a cartilage defect or as an injection in case of a degenerative disease [44, 46]. According to some authors, intra-articular mesenchymal stem cell injection in gonarthrosis enables to achieve good clinical results for as long as 12 to 27 months [47]. There have been reports of the successful use of chondrocytes derived from mesenchymal stem cells to repair local cartilage defects of various sizes [48, 49]. High efficiency of MSC application does not exclude a number of shortcomings related to the possibility of uncontrolled expression of various genes in the body, which can have unpredictable consequences, and the high cost of the method [50].

Undoubtedly, the most common method of treating defects of the hyaline knee joint cartilage is mosaic autohondroplasty. We believe that this technology is effective for a cartilage defect of more than 4 cm². However, it should be mentioned that, according to our data, about 10 % of patients report pain in donor sites. Today, chondrogenesis technologies using cover membranes and specialized matrices for the filling of hyaline cartilage defects have been developing. Recent generations of such methods show good long-term outcomes. However, the high cost and complexity of implementation do not allow the introduction of these technologies in every circumstance. The use of cellular technologies, in our opinion, carries a high risk of autoimmune response and requires further investigation.

The methods of surgical hyaline cartilage defect repair continue to develop rapidly. However, each subsequent generation of the technologies has been more expensive. Given the economic feasibility and good clinical results, one should not abandon the use of classical methods such as microfracture or mosaic autochondroplasty.

REFERENCES

1. Beidik O.V., Levchenko K.K., Kireev S.I. Artroskopiia kolennogo sustava. Perspektivy razvitiia [Arthroscopy of the knee. Development prospects]. *Sbornik tezisov VIII s"ezda travmatologov-ortopedov Rossii. V 2 t.* [Proc. VIII Congress of traumatologists-orthopedists of Russia]. Samara, 2006, vol. 1, pp. 139-140. (In Russ.)
2. Curl W.W., Krome J., Gordon E.S., Rushing J., Smith B.P., Poehling G.G. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy*, 1997, vol. 13, no. 4, pp. 456-460.
3. Pearsall A. IV, Madanagopal S., Tucker J. The Evaluation of Refrigerated and Frozen Osteochondral Allografts in the Knee. *Surgical Science*, 2011, vol. 2, no. 5, pp. 232-241. DOI: 10.4236/ss.2011.25052.
4. Bozhokin M.S., Bozhkova S.A., Netyl'ko G.I. Vozmozhnosti sovremennykh kletochnykh tekhnologii dlia vosstanovleniia povrezhdennogo sustavnogo khriashcha (analiticheskii obzor literatury) [Potential of modern cell technologies for restoring the injured articular cartilage (An analytical review of the literature)]. *Travmatologiia i ortopediia Rossii*, 2016, no. 3, pp. 122-134. (In Russ.)
5. Vinokurov V.A., Norkin I.A. Khirurgicheskaia korrektsiia deformatsii kolennogo sustava i regeneratsiia gialinovogo khriashcha [Surgical correction of the knee deformity and regeneration of hyaline cartilage]. *Ortopediia, Travmatologiia i Vosstanovitel'naia Khirurgiia detskogo vozrasta*, 2015, vol. 3, no. 4, pp. 37-43. (In Russ.)
6. Pridie K.H. A method of resurfacing osteoarthritic knee joints. *J. Bone Joint Surg. Am*., 1959, vol. 41, pp. 618-619.
7. Gross A.E., Langer F., Houpt J., Pritzker K., Friedlaender G. Allotransplantation of partial joints in the treatment of osteoarthritis of the knee. *Transplant. Proc*., 1976, vol. 8, no. 2 Suppl., pp. 129-132.
8. Muller S., Breederveld R.S., Tuinebreijer W.E. Results of osteochondral autologous transplantation in the knee. *Open Orthop. J*., 2010, vol. 4, pp. 111-114. DOI: 10.2174/1874325001004020111.
9. Maliuk B.V. *Osteoperforatsii subkhondral'noi kosti pri rassekaiushchem osteokhondrite myshchelkov bedra kolennogo sustava*. Avtoref. Diss. kand. med. nauk [Osteoperforations of subchondral bone for dissecting osteochondritis /osteochondritis dissecans/ of the knee femoral condyles. Ext. Abstract of Cand. med. sci. diss.]. Minsk, 2014, pp. 15-16. (In Russ.)
10. Shevtsov V.I., Makushin V.D., Stupina T.A., Stepanov M.A. Eksperimental'nye aspekty izucheniia reparativnoi regeneratsii sustavnogo khriashcha v usloviiakh tunnelirovaniia subkhondral'noi zony s vvedeniem autologichnogo kostnogo mozga [The experimental aspects of studying articular cartilage reparative regeneration under subchondral zone tunneling with autologous bone marrow infusion]. *Genij Ortopedii*, 2010, no. 2, pp. 5-10. (In Russ.)
11. Jacobi M., Villa V., Magnussen R.A., Neyret P. MACI – a new era? *Sports Med. Arthrosc. Rehabil. Ther. Technol*., 2011, vol. 3, no. 1, p. 10. DOI: 10.1186/1758-2555-3-10.
12. Becerra J., Andrades J.A., Guerado E., Zamora-Navas P., López-Puertas J.M., Reddi A.H. Articular cartilage: structure and regeneration. *Tissue Eng. Part B Rev*., 2010, vol. 16, no. 6, pp. 617-627. DOI: 10.1089/ten.TEB.2010.0191.
13. Batty L., Dance S., Bajaj S., Cole B.J. Autologous chondrocyte implantation: an overview of technique and outcomes. *ANZ J. Surg*., 2011, vol. 81, no. 1-2, pp. 18-25. DOI: 10.1111/j.1445-2197.2010.05495.x.
14. Steadman J.R., Briggs K.K., Rodrigo J.J., Kocher M.S., Gill T.J., Rodkey W.G. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy*, 2003, vol. 19, no. 5, pp. 477-484. DOI: 10.1053/jars.2003.50112.
15. Kreuz P.C., Erggelet C., Steinwachs M.R., Krause S.J., Lahm A., Niemeyer P., Ghanem N., Uhl M., Südkamp N.

Is microfracture of chondral defects in the knee associated with different results in patients aged 40 years or younger? *Arthroscopy*, 2006, vol. 22, no. 11, pp. 1180-1186. DOI: 10.1016/j.arthro.2006.06.020.
16. Ulstein S., Årøen A., Røtterud J.H., Løken S., Engebretsen L., Heir S. Microfracture technique versus osteochondral autologous transplantation mosaicplasty in patients with articular chondral lesions of the knee: a prospective randomized trial with long-term follow-up. *Knee Surg. Sports Traumatol. Arthrosc*., 2014, vol. 22, no. 6, pp. 1207-1215. DOI: 10.1007/s00167-014-2843-6.
17. Knutsen G., Engebretsen L., Ludvigsen T.C., Drogset J.O., Grøntvedt T., Solheim E., Strand T., Roberts S., Isaksen V., Johansen O. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. *J. Bone Joint Surg. Am*., 2004, vol. 86-A, no. 3, pp. 455-464.
18. Ewers B.J., Dvoracek-Driksna D., Orth M.W., Haut R.C. The extent of matrix damage and chondrocyte death in mechanically traumatized articular cartilage explants depends on rate of loading. *J. Orthop. Res*., 2001, vol. 19, no. 5, pp. 779-784. DOI: 10.1016/S0736-0266(01)00006-7.
19. Gross A.E., Kim W., Las Heras F., Backstein D., Safir O., Pritzker K.P. Fresh osteochondral allografts for posttraumatic knee defects: long-term followup. *Clin. Orthop. Relat. Res.*, 2008, vol. 466, no. 8, pp. 1863-1870. DOI: 10.1007/s11999-008-0282-8.
20. Levy Y.D., Görtz S., Pulido P.A., McCauley J.C., Bugbee W.D. Do fresh osteochondral allografts successfully treat femoral condyle lesions? *Clin. Orthop. Relat. Res*., 2013, vol. 471, no. 1, pp. 231-237. DOI: 10.1007/s11999-012-2556-4.
21. Demange M., Gomoll A.H. The use of osteochondral allografts in the management of cartilage defects. *Curr. Rev. Musculoskelet. Med*., 2012, vol. 5, no. 3, pp. 229-235. DOI: 10.1007/s12178-012-9132-0.
22. Williams R.J. 3rd, Ranawat A.S., Potter H.G., Carter T., Warren R.F. Fresh stored allografts for the treatment of osteochondral defects of the knee. *J. Bone Joint Surg. Am*., 2007, vol. 89, no. 4, pp. 718-726. DOI: 10.2106/JBJS.F.00625.
23. Hangody L., Dobos J., Baló E., Pánics G., Hangody L.R., Berkes I. Clinical experiences with autologous osteochondral mosaicplasty in an athletic population: a 17-year prospective multicenter study. *Am. J. Sports Med*., 2010, vol. 38, no. 6, pp. 1125-1133. DOI: 10.1177/0363546509360405.
24. Solheim E., Hegna J., Oyen J., Austgulen O.K., Harlem T., Strand T. Osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee: results at 5 to 9 years. *Knee*, 2010, vol. 17, no. 1, pp. 84-87. DOI: 10.1016/j.knee.2009.07.007.
25. Solheim E., Hegna J., Oyen J., Austgulen O.K., Harlem T., Strand T. Results at 10 to 14 years after osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee. *Knee*, 2013, vol. 20, no. 4, pp. 287-290. DOI: 10.1016/j.knee.2013.01.001.
26. Espregueira-Mendes J., Pereira H., Sevivas H., Varanda P., da Silva M.V., Monteiro A., Oliveira J.M., Reis R.L. Osteochondral transplantation using autografts from the upper tibiofibular joint for the treatment of knee cartilage lesions. *Knee Surg. Sports Traumatol. Arthrosc*., 2012, vol. 20, no. 6, pp. 1136-1142. DOI: 10.1007/s00167-012-1910-0.
27. Singh R., Chauhan V., Chauhan N., Sharma S. Transplantation of free tibial periosteal grafts for the repair of articular cartilage defect: An experimental study. *Indian J. Orthop*., 2009, vol. 43, no. 4, pp. 335-41. DOI: 10.4103/0019-5413.55973.
28. O'Driscoll S.W., Fitzsimmons J.S. The role of periosteum in cartilage repair. *Clin. Orthop. Relat. Res.*, 2001, no. 391 Suppl., pp. S190-S207.
29. Olivos-Meza A., Fitzsimmons J.S., Casper M.E., Chen Q., An K.N., Ruesink T.J., O'Driscoll S.W., Reinholz G.G. Pretreatment of periosteum with TGF-beta1 in situ enhances the quality of osteochondral tissue regenerated from transplanted periosteal grafts in adult rabbits. *Osteoarthritis Cartilage*, 2010, vol. 18, no. 9, pp. 1183-1191. DOI: 10.1016/j.joca.2010.06.003.
30. Smith G.D., Knutsen G., Richardson J.B. A clinical review of cartilage repair techniques. *J. Bone Joint Surg. Br*., 2005, vol. 87, no. 4, pp. 445-449. DOI: 10.1302/0301-620X.87B4.15971.
31. Brittberg M., Lindahl A., Nilsson A., Ohlsson C., Isaksson O., Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N. Engl. J. Med*., 1994, vol. 331, no. 14, pp. 889-895. DOI: 10.1056/NEJM199410063311401.
32. Kozadaev M.N. Primenenie matrits na osnove polikaprolaktona dlia stimuliatsii regeneratsii sustavnogo khriashcha v usloviiakh eksperimenta [Use of matrtixes based on polycaprolactone (PCL) to stimulate articular cartilage regeneration experimentally]. *Teoreticheskie i Prikladnye Aspekty Sovremennoi Nauki*, 2014, no. 3-2, pp. 128-130. (In Russ.)
33. Ezhov M.Iu., Ezhov I.Iu., Kashko A.K., Kaiumov A.Iu., Zykin A.A., Gerasimov S.A. Nereshennye voprosy regeneratsii khriashchevoi i kostnoi tkani (obzorno-analiticheskaia stat'ia) [Unresolved problems of cartilaginous and bone tissue regeneration (a review-analytical article)]. *Uspekhi Sovremen. Estestvoznaniia*, 2015, no. 5, pp. 126-131. (In Russ.)
34. Caron M.M., Emans P.J., Coolsen M.M., Voss L., Surtel D.A., Cremers A., Van Rhijn L.W., Welting T.J. Redifferentiation of dedifferentiated human articular chondrocytes: comparison of 2D and 3D cultures. *Osteoarthritis Cartilage*, 2012, vol. 20, no. 10, pp. 1170-1178. DOI: 10.1016/j.joca.2012.06.016.
35. Kim M.K., Choi S.W., Kim S.R., Oh I.S., Won M.H. Autologous chondrocyte implantation the knee using fibrin. *Knee Surg. Sports Traumatol. Arthrosc*., 2010, vol. 18, no. 4, pp. 528-534. DOI: 10.1007/s00167-009-0905-y.
36. Iwasa J., Engebretsen L., Shima Y., Ochi M. Clinical application of scaffolds for cartilage tissue engineering. *Knee Surg. Sports Traumatol. Arthrosc*., 2009, vol. 17, no. 6, pp. 561-577. DOI: 10.1007/s00167-008-0663-2.
37. Benthien J.P., Behrens P. Autologous matrix-induced chondrogenesis (AMIC): combining microfracturing and a collagen I/II matrix for articular cartilage resurfacing. *Cartilage*, 2010, vol. 1, no. 1, pp. 65-68. DOI: 10.1177/1947603509360044.
38. Khan W.S., Johnson D.S., Hardingham T.E. The potential of stem cells in the treatment of knee cartilage defects. *Knee*, 2010, vol. 17, no. 6, pp. 369-374. DOI: 10.1016/j.knee.2009.12.003.
39. Zeifang F., Oberle D., Nierhoff C., Richter W., Moradi B., Schmitt H. Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation: a randomised clinical trial. *Am. J. Sports Med*., 2010, vol. 38, no. 5, pp. 924-933.
40. Welsch G.H., Mamisch T.C., Zak L., Blanke M., Olk A., Marlovits S., Trattnig S. Evaluation of cartilage repair tissue after matrix-associated autologous chondrocyte transplantation using a hyaluronic-based or a collagen based scaffold with morphological MOCART scoring and biochemical T2 mapping: preliminary results. *Am. J. Sports Med*., 2010, vol. 38, no. 5, pp. 934-942. DOI: 10.1177/0363546509354971.
41. Dhollander A., Moens K., Van der Maas J., Verdonk P., Almqvist K.F., Victor J. Treatment of patellofemoral cartilage defects in the knee by autologous matrix-induced chondrogenesis (AMIC). *Acta Orthop. Belg.*, 2014, vol. 80, no. 2, pp. 251-259.
42. Tepliashin A.S., Sharifullina S.Z., Chupikova N.I., Sepiashvili R.I. Perspektivy ispol'zovaniia mul'tipotentnykh mezenkhimnykh stromal'nykh kletok kostnogo mozga i zhirovoi tkani v regu- liatsii regeneratsii opornykh tkanei [Prospects of using multipo-

tent mesenchymal stromal cells of bone marrow and fatty tissue in regulation of support tissue regeneration]. *Allergologiia i Immunologiia*, 2015, vol. 16, no. 1, pp. 138-148. (In Russ.)
43. Demzhanova G., Karzhauov M.R., Sarsenova M.A. Kombinirovannoe vliianie mezenkhimal'nykh stvolovykh kletok, gialuronovoi kisloty i rostovykh faktorov tgf-β1 i bmp-4 na regeneratsiiu defektov khriashcha u krolikov [Combined effect of mesenchymal stem cells, hyaluronic acid and growth factors tgf-β1 and bmp-4 on regeneration of cartilage defect regeneration in rabbits]. *Materialy 54-i Mezhdunarodnoi nauchnoi studencheskoi konferentsii MNSK-2016* [Materials of the 54th International Scientific Student Conference MNSK-2016]. Novosibirsk, 2016, p. 24. (In Russ.)
44. Mafi R., Hindocha S., Mafi P., Griffin M., Khan W.S. Sources of adult mesenchymal stem cells applicable for musculoskeletal applications – a systematic review of the literature. *Open Orthop. J.*, 2011, vol. 5, no. Suppl. 2, pp. 242-248. DOI: 10.2174/1874325001105010242.
45. Bukach D.V., Beletskii A.V., Eismont O.L., Mokhammadi M.T., Isaikina Ia.I. Autotransplantatsiia mezenkhimal'nykh stvolovykh kletok dlia regenerativnogo vosstanovleniia povrezhdenii sustavnogo khriashcha (eksperimental'noe issledovanie) [Autotransplantation of mesenchymal stem cells for regenerative repair of articular cartilage (an experimental study)]. *Vestsi Natsyianal'nai Akademii Navuk Belarusi. Seryia medytsynskikh navuk*, 2015, no. 1, pp. 5-11. (In Russ.)
46. Zhai L.J., Zhao K.Q., Wang Z.Q., Feng Y., Xing S.C. Mesenchymal stem cells display different gene expression profiles compared to hyaline and elastic chondrocytes. *Int. J. Clin. Exp. Med*., 2011, vol. 4, no. 1, pp. 81-90.
47. Tanaka Y. Human mesenchymal stem cells as a tool for joint repair in rheumatoid arthritis. *Clin. Exp. Rheumatol*., 2015, vol. 33, no. 4 Suppl. 92, pp. S58-S62.
48. Kim Y.S., Choi Y.J., Lee S.W., Kwon O.R., Suh D.S., Heo D.B., Koh Y.G. Assessment of clinical and MRI outcomes after mesenchymal stem cell implantation in patients with knee osteoarthritis: a prospective study. *Osteoarthritis Cartilage*, 2016, vol. 24, no. 2, pp. 237-245. DOI: 10.1016/j.joca.2015.08.009.
49. Koh Y.G., Kwon O.R., Kim Y.S., Choi Y.J., Tak D.H. Adipose-derived mesenchymal stem cells with microfracture versus microfracture alone: 2-year follow-up of a prospective randomized trial. *Arthroscopy*, 2016, vol. 32, no. 1, pp. 97-109. DOI: 10.1016/j.arthro.2015.09.010.
50. Tan Q., Lui P.P., Rui Y.F. Effect of in vitro passaging on the stem cell-related properties of tendon-derived stem cells-implications in tissue engineering. *Stem Cells Dev*., 2012, vol. 21, no. 5, pp. 790-800. DOI: 10.1089/scd.2011.0160.

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