MEDS Clinical Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2023.040103
ISSN 2616-1907 Vol. 4 Num. 1

Research status and progress of bone marrow mesenchymal stem cells for osteonecrosis of femoral head

Peng Xu[1,a], Miao Tan[1], Mingming Wang[1], Yan Cheng[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang, 712046, China
[2]Shaanxi Hospital of Traditional Chinese Medicine, Xi'an, 710003, China
[a]1171644773@qq.com, [*]chy822@163.com
**Corresponding author*

Keywords: Bone marrow mesenchymal stem cells; osteonecrosis of femoral head; cardiac decompression; autogenous bone grafting; arterial interventional therapy; tissue engineering technology; summary

Abstract: Osteonecrosis of femoral head (ONFH) is a progressive, destructive disorder with no targeted treatment currently available. The etiology of this disease is complex and the pathogenesis is not clear. The main clinical manifestations are hip pain and mobility dysfunction, which threatens human health to a large extent. If not timely intervention and treatment in the early and middle stages of ONFH, femoral head deformation and even collapse are easy to occur, seriously affecting the prognosis of patients. Therefore, early identification and treatment of ONFH is very important. With the development and maturity of regenerative medicine and tissue engineering technologies, studies have shown that Bone marrow mesenchymal stem cells (BMSCs) combined with cardiac decompression, autologous bone transplantation, arterial interventional therapy, and tissue engineering techniques, it has certain curative effect on early and middle stage ONFH. This paper mainly discusses the research status and progress of BMSCs in the treatment of ONFH, in order to provide theoretical basis for the treatment of ONFH with BMSCs.

1. Introduction

ONFH is a destructive disease of the femoral head, mainly due to the interruption or damage of the blood supply of the femoral head, which leads to avascular necrosis of the bone marrow and osteocytes, and eventually causes changes in the internal structure of the femoral head and collapse [1]. Relevant data show that the cumulative number of ONFH patients in the United States is 300,000-600,000, and there are 20,000 new cases of osteonecrosis every year. About 12,000-24,000 new cases of osteonecrosis have been diagnosed in Japan in recent years [2]. In China, the total number of patients is about 8.12 million, and there are 150,000-200,000 new cases every year, among which the prevalence rate of males is significantly higher than that of females [3-4]. This disease is mainly related to corticosteroid drugs, excessive alcohol consumption, autoimmune diseases, coagulation diseases, caisson diseases, myeloproliferative diseases and radioactive necrosis [2,3,5,6], while smoking, obesity, pregnancy and other factors increase the risk of femoral head necrosis [7]. At present, the pathogenesis of this disease has not been fully defined, which may be closely related to intravascular coagulation,

abnormal lipid metabolism, lipid differentiation, apoptosis autophagy, gene polymorphism, etc. [8]. All of the above mechanisms will eventually cause blood circulation disorders of the femoral head, resulting in degeneration and necrosis of bone cells and bone marrow tissues, loss of bone repair and reconstruction function, changes in the internal microstructure of the femoral head, and eventually collapse of the femoral head. At present, the treatment of ONFH is mainly based on the stage of ARCO and the patient's own condition. However, due to the poor efficacy of hip preservation therapy in patients with advanced ONFH, it is of great importance to identify and treat ONFH as soon as possible [9]. In recent years, with the continuous development of stem cell research, relevant studies have shown that BMSCs have certain clinical efficacy in the treatment of ONFH, and it has gradually become a hot topic in orthopedics research field. This paper mainly introduces the biological characteristics of BMSCs and reviews the research status and progress in the treatment of ONFH, in order to provide reference for the treatment of ONFH.

2. Biological characteristics of bone marrow mesenchymal stem cells

Stem cells are self-renewing cells that can generate a variety of cell types at the same time, among which BMSCs are extremely important and usually come from the bone marrow of the iliac crest [10]. Related studies have confirmed that BMSCs can differentiate into osteoblasts and endothelial cells, which affect bone repair and blood vessel formation. In addition, BMSCs can secrete growth factors, cytokines, chemokines, microbubbles and exosomes through paracrine action, which can promote the chemotaxis, proliferation and differentiation of cells at the injured site after being secreted to the injured site. Exosomes play a key role in the process of intercellular transport, signal transduction and tissue regeneration. Therefore, BMSCs are considered as seed cells for regenerative therapy [11-12]. Relevant studies have shown that the decrease of BMSCs and changes in cell behavior are related to the occurrence and development of ONFH, indicating that BMSCs may be a good target for the treatment of ONFH [13]. In recent years, with the rapid development of cell biotechnology and tissue engineering techniques, the application of BMSCs in the treatment of ONFH has shown great potential.

3. Application of bone marrow mesenchymal stem cells in the treatment of femoral head necrosis

A large number of studies have confirmed that BMSCs transplantation alone has a high failure rate and poor efficacy in the treatment of ONFH, and some patients still need total hip replacement (THA). Therefore, in order to break through the current treatment status, relevant experts proposed BMSCs combined with current hip preservation therapy for the treatment of ONFH.

3.1 BMSCs combined with core decompression in treatment of ONFH

Ficat creatively invented core decompression (CD) in 1962, mainly through drilling decompression of the core necrotic area, on the one hand, the intraosseous pressure of the femoral head can be reduced, on the other hand, bone marrow edema can be reduced to improve the blood supply of the necrotic area of the femoral head, so as to reduce hip pain and delay the time of THA [14-15]. However, this technique cannot repair the femoral head and locally cannot provide effective structural support. Single application may increase the risk of femoral head collapse, and the medium and long-term efficacy is uncertain [16]. Studies have shown that BMSCs combined with CD has more significant efficacy than CD alone in the treatment of ONFH[17]. The combination of BMSCS and CD can improve the harris score of hip joint, delay the process of femoral head necrosis, and even reverse the stage of ONFH. With the gradual development of stem cell medicine, BMSCs transplantation

combined with CD has gradually become a new means to treat ONFH, which is worthy of promotion and application in orthopedic clinic. Wang Z et al. [18] found that BMSCs transplantation combined with CD could reduce the degree of postoperative pain in patients with ONFH at rest at six months, one year and two years after surgery. Moreover, it could reduce the volume of femoral head necrotic area, thus delaying the collapse of femoral head and reducing the proportion of THA. A systematic retrospective study by Liu Q et al. [19] showed that BMSCs implantation combined with CD could effectively delay 1-2 stages of femoral bone necrosis, relieve hip pain and improve hip joint function compared with CD alone. It has also been confirmed that BMSCs combined with CD can relieve pain, have better clinical outcomes, and improve survival. Liu Jiangfeng et al. showed that BMSCs transplantation combined with CD could improve the local blood supply of patients with ONFH, promote the absorption and repair of necrotic bone, and improve the success rate of hip preservation therapy [20]. This indicates that BMSCs transplantation combined with CD has certain advantages in the treatment of early and middle stage ONFH, but the efficacy of the treatment of late stage ONFH remains unclear and needs to be further observed.

3.2 BMSCs combined with autogenous bone transplantation in treatment of ONFH

The advantages of autogenous bone transplantation are mainly reflected in the following three aspects: (1) The graft is obtained from itself, so it has good bone induction, bone conduction and bone regeneration capabilities; (2) can clear necrotic lesions, reduce intraosseous pressure, improve pain symptoms; (3) Implantation of autogenous bone can effectively support the necrotic area, release the pressure in the necrotic area and prevent the collapse of the femoral head. Goto K et al. [21] performed BMSCs combined with autogenous bone transplantation on 10 patients with collapse of ONFH, and conducted 10 years of postoperative follow-up. The results showed that only 2 of the 10 patients needed THA surgery, and 5 of the 6 patients (collapse <3 mm) could avoid further collapse and changes in osteoarthritis within 10 years. These results indicate that BMSCs combined with autologous bone transplantation can effectively treat osteonecrosis after femoral head collapse. Kang JS et al. [22] conducted a study on the treatment of ONFH with iliac bone autograft combined with BMSCs, and found that the protection rate of femoral head for ARCO Stage II and ArCO Stage III lesions by this operation was 64.7% and 37.0%, respectively, and the surgical results were different with the size of the lesions and the stage. Relevant data show that this surgery is effective for early and mid-stage ONFH treatment, and can achieve similar results as other hip preservation operations, but the treatment effect of late ONFH is uncertain. At present, there are few relevant studies on BMSCs combined with autogenous bone transplantation in the treatment of ONFH in the available literature, and there is still a lack of strong clinical evidence to prove that this technology has a more significant effect on ONFH. Therefore, more credible basic and clinical studies are needed to support this.

3.3 BMSCs combined with arterial intervention in treatment of ONFH

As one of the important pathological changes of ONFH is the interruption of local blood supply to the femoral head, which leads to microcirculation disturbance and thus progresses to osteonecrosis, restoring local blood circulation to the femoral head is the key to treating the disease [23]. BMSCs are injected into the internal and lateral femoral arteries and obturator arteries through arterial interventional techniques, and blood circulation is used to carry stem cells to the necrotic lesions of the femoral head to promote bone and angiogenesis [24]. Although the technique is still immature and not widely accepted, this therapy has become an effective treatment for ONFH at present and has been widely used before the collapse of the femoral head. Liu N et al. [25] found that Mao et al. injected BMSCs into the internal circumflex artery to treat 62 patients with ONFH .The 5-year follow-up

observation showed that the treatment failure rate of ONFH patients in Ficat I-II stage was 4.4%, and the treatment failure rate of Ficat III cases was 30%, indicating that BMSCs combined with arterial intervention had a certain effect on early and middle ONFN, especially in the early stage.Jin H et al·[26] conducted an animal experimental study on the treatment of ONFH by arterial perfusion of BMSCs. The results showed that the volume of femoral head necrosis was significantly reduced in the arterial perfusion of BMSCs group, and the volume of bone trabeculae increased and the porosity decreased, further confirming that arterial perfusion of BMSCs could migrate to the femoral head necrosis area and differentiate into osteoblasts. Thereby delaying the necrotic process of the femoral head. Although this technology is still in the early stage of research, it can be seen from the existing conclusions that this technology may be a feasible and effective method for the treatment of ONFH.

3.4 BMSCs combined with tissue engineering in the treatment of ONFH

However, with the rapid development of bone tissue engineering and the maturity of stem cell biotechnology in recent years, BMSCs are co-cultured with biological scaffolds in vitro, and then implanted into the necrotic area of the femoral head, thus effectively solving the difficult problem of the reconstruction of the necrotic area of the femoral head, and are gradually applied in clinic. The mechanism of BMSCs combined with scaffolds in the treatment of ONFH is that BMSCs can differentiate into osteoblasts and promote bone regeneration. Combined with the mechanical structure stability of biological scaffolds, BMSCS jointly act on the necrotic area of the femoral head, thus delaying the progression of the disease and preventing the collapse of the femoral head. Bone scaffold materials should have the following advantages: good biocompatibility, appropriate porosity, certain mechanical strength, appropriate degradability, and can maintain cell activity and promote bone formation [27-28]. Currently, commonly used bone scaffold materials mainly include hydroxyapatite, calcium phosphate ceramics, porous tantalum rods, etc. Maruyama M et al. [29] found that in rabbit steroid-induced ONFH model, the use of new 3D printing customized functional grading scaffolds (FGS) combined with BMSCs to implant in the necrotic area of the femoral head can promote bone regeneration in the necrotic area, thus delaying the time of femoral head collapse. Wang G et al. [30] found in the experimental study of the rabbit model for the treatment of early ONFH that functional β-tricalcium phosphate (β-TCP) scaffold modified with DPI (a bone-marrow derived mesenchymal stem cell affinity peptide) was implanted into the ONFH region, and the results showed that the group had the lowest percentage of vacant bone space. This is because β-TCP scaffold modified with DPI peptide can recruit BMCSs to the necrotic femoral head, promote bone regeneration and angiogenesis, and enhance the repair ability of necrotic femoral head, thus obtaining better therapeutic effect. At present, BMSCs combined with tissue engineering technology in the treatment of ONFH is still in the early stage. Although preliminary research results have been achieved in rabbit experimental model, showing significant improvement in the treatment of ONFH, the clinical application experience is insufficient, and the efficacy and safety of this technology needs to be confirmed by higher level of evidence-based medical evidence.

4. Conclusion and outlook

Although ONFH is a common and frequently occurring disease in orthopedics, it is also a refractory disease. Due to poor efficacy of hip preservation treatment in the middle and late stages and high disability rate in the later stage, it causes serious physical and psychological damage to patients. Therefore, in order to seek better treatment methods and break through the dilemma of existing hip preservation treatment, Therefore, in recent years, the rapidly developed and mature stem cell transplantation technology has been applied to the treatment of ONFH. Studies have confirmed that the occurrence of ONFH is related to the destruction and reduction of BMSCs activity. At present,

hip preservation therapy is mainly focused on ARCO stage I and II. However, when the femoral head collapse occurs in patients with ONFH, the feasibility of hip preservation therapy is significantly decreased, and most patients need THA therapy. However, with the rapid development of bone tissue engineering and regenerative medicine in recent years, the application of BMSCs in the treatment of ONFH has gradually become the focus of research. The present status and progress of BMSCs combined with CD, autologous bone transplantation, arterial interventional therapy and tissue engineering in the treatment of ONFH were reviewed. The results showed that BMSCs combined with above therapeutic methods can promote bone regeneration and angiogenesis in the necrotic area of the femoral head and alleviate the outcome of ONFH. However, there are still many problems concerning the application of BMSCs in the treatment of ONFH that need to be further solved: (1) The number of BMSCs. Currently, there is no strong evidence to confirm the number of BMSCs needed in the treatment of ONFH to achieve the purpose of repair; (2) BMSCs quality problems, because the occurrence and development of ONFH is a chronic injury process, the activity of patients' own BMSCs is vulnerable to damage; (3) Survival rate of BMSCs. In vitro experiments, the growth environment of BMSCs was different from that of osteonecrosis area, and whether BMSCs could survive in large numbers after transplantation to the necrotic area due to different local microenvironment. 4. Safety of BMSCs. Since BMSCs continue to proliferate after implantation, it is not clear whether they have carcinogenic effects.

Although there are many doubts about the application of BMSCs technology in the treatment of ONFH, related research results in recent years have shown that BMSCs combined with other therapeutic methods show new hope in the treatment of ONFH. In the future, more basic experiments and clinical studies are needed to confirm the mechanism of action and molecular targets of BMSCs in the treatment of ONFH, so as to improve the prognosis of ONFH. With the continuous development and maturity of cell biology, molecular biology and tissue engineering technologies, it is believed that BMSCs will make great progress in the treatment of ONFH, and also provide new ideas for hip conservation therapy, so as to get rid of the treatment dilemma of ONFH.

Acknowledgement

Fund Project: Traditional Chinese Medicine Administration of Shaanxi Province, No.2021-GJ-LC011; "Nursery Cultivation Plan" Project of Shaanxi Hospital of Traditional Chinese Medicine (2021-23); Science and Technology Research and Development Program of Shaanxi Province, No.2015SF079

References

[1] Ma HY, Ma N, Liu YF, et al. Core Decompression with Local Administration of Zoledronate and Enriched Bone Marrow Mononuclear Cells for Treatment of Non-Traumatic Osteonecrosis of Femoral Head. Orthop Surg. 2021; 13(6):1843-1852.

[2] Jin Y, Zhu HX, Wei BF. Reduced serum and local LncRNA MALAT1 expressions are linked with disease severity in patients with non-traumatic osteonecrosis of the femoral head. Technol Health Care. 2021; 29(3):479-488.

[3] Zhao D, Zhang F, Wang B, et al. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). J Orthop Translat. 2020; 21: 100-110.

[4] Microsurgery Department of the Orthopedics Branch of the Chinese Medical Doctor Association; Group from the Osteonecrosis and Bone Defect Branch of the Chinese Association of Reparative and Reconstructive Surgery; Microsurgery and Reconstructive Surgery Group of the Orthopedics Branch of the Chinese Medical Association. Chinese Guideline for the Diagnosis and Treatment of Osteonecrosis of the Femoral Head in Adults. Orthop Surg. 2017; 9(1):3-12.

[5] Liu N, Zheng C, Wang Q, et al. Treatment of non-traumatic avascular necrosis of the femoral head (Review). Exp Ther Med. 2022; 23(5):321.

[6] Cui Q, Jo WL, Koo KH, et al. ARCO Consensus on the Pathogenesis of Non-traumatic Osteonecrosis of the Femoral

Head. J Korean Med Sci. 2021; 36(10):e65. Published 2021 Mar 15.
[7] Wang C, Wang Y, Meng H Y, et al. Application of bone marrow mesenchymal stem cells to the treatment of osteonecrosis of the femoral head [J]. International Journal of Clinical and Experimental Medicine, 2015, 8(3):3127-3135.
[8] Wen J F, Wei B F. Research progress in osteogenic differentiation of bone marrow mesenchymal stem cells in steroid-induced osteonecrosis of the femoral head [J]. Editorial Board of Medical Journal of Chinese People's Liberation Army, 2020(11).
[9] Li Z, Yang X, Liang S, et al. Imaging Observation of Nano-Artificial Bone in the Repair of the Defect in Osteonecrosis of the Femoral Head[J]. Journal of Nanoscience and Nanotechnology, 2020.
[10] Wang Pengzhi, Li Shenghua. Research progress of bone marrow mesenchymal stem cells in treatment of femoral head necrosis [J]. Clinical of Integrated Traditional Chinese and Western Medicine, 2018, 1:179-182.
[11] Xu Y, Jiang Y, Xia C, et al. Stem cell therapy for osteonecrosis of femoral head: Opportunities and challenges. Regen Ther. 2020; 15: 295-304. Published 2020 Nov 28.
[12] Zhang C, Su Y, Ding H,et al. Mesenchymal stem cells-derived and siRNAs-encapsulated exosomes inhibit osteonecrosis of the femoral head. J Cell Mol Med. 2020; 24(17):9605-9612.
[13] Song D, Wu ZS, Xu Q, et al. LRRC17 regulates the bone metabolism of human bone marrow mesenchymal stem cells from patients with idiopathic necrosis of femoral head through Wnt signaling pathways: A preliminary report. Exp Ther Med. 2021; 22(1):666.
[14] Talmaç MA, Kanar M, Sönmez MM, Özdemir HM, Dırvar F, Tenekecioğlu Y. The Results of Core Decompression Treatment in Avascular Necrosis of the Femoral Head. Sisli Etfal Hastan Tip Bul. 2018; 52(4):249-253. Published 2018 Dec 28.
[15] Zhao D, Liu B, Wang B, et al. Autologous Bone Marrow Mesenchymal Stem Cells Associated with Tantalum Rod Implantation and Vascularized Iliac Grafting for the Treatment of End-Stage Osteonecrosis of the Femoral Head[J]. Biomed Res Int, 2015, 2015:240506.
[16] Peng K, Wang Y, Zhu J, et al. Repair of non-traumatic femoral head necrosis by marrow core decompression with bone grafting and porous tantalum rod implantation. Pak J Med Sci. 2020; 36(6):1392-1396.
[17] Wang L, Tian X, Li K, et al. Combination use of core decompression for osteonecrosis of the femoral head: A systematic review and meta-analysis using Forest and Funnel Plots. Comput Math Methods Med. 2021; 2021: 1284149. Published 2021 Dec 6.
[18] Wang Z, Sun QM, Zhang FQ, et al. Core decompression combined with autologous bone marrow stem cells versus core decompression alone for patients with osteonecrosis of the femoral head: A meta-analysis. Int J Surg. 2019; 69: 23-31.
[19] Liu Q, Guo W, Li R, et al. Efficacy of various core decompression techniques versus non-operative treatment for osteonecrosis of the femoral head: a systemic review and network meta-analysis of randomized controlled trials. BMC Musculoskelet Disord. 2021; 22(1):948. Published 2021 Nov 15.
[20] Liu Jiangfeng. Core decompression combined with autologous bone marrow mesenchymal stem cell transplantation for treatment of femoral head necrosis [J]. Chin J Tissue Engineering Research, 2019, 29: 4599-4604.
[21] Goto K, Aoyama T, Toguchida J, et al. Ten-year results of mesenchymal stromal cell transplantation augmented with vascularised bone grafts for advanced osteonecrosis of the femoral head. J Orthop. 2021; 26:67-71. Published 2021 Jul 13.
[22] Kang JS, Moon KH, Kim BS, et al. Clinical results of auto-iliac cancellous bone grafts combined with implantation of autologous bone marrow cells for osteonecrosis of the femoral head: a minimum 5-year follow-up. Yonsei Med J. 2013; 54(2):510-515.
[23] Liu Pei, Liu Guojie, Ye Ye, et al. Research progress of mesenchymal stem cell transplantation in the treatment of femoral head necrosis [J]. Chinese Journal of Bone and Joint Surgery, 2021, 03:229-234.
[24] Pan J, Ding Q, Lv S, et al. Prognosis after autologous peripheral blood stem cell transplantation for osteonecrosis of the femoral head in the pre-collapse stage: a retrospective cohort study. Stem Cell Res Ther. 2020;11(1):83. Published 2020 Feb 26.
[25] Mao Q, Jin H, Liao F, et al. The efficacy of targeted intraarterial delivery of concentrated autologous bone marrow containing mononuclear cells in the treatment of osteonecrosis of the femoral head: a five year follow-up study. Bone. 2013; 57(2):509-516.
[26] Jin H, Xu T, Chen Q, et al. The Fate and Distribution of Autologous Bone Marrow Mesenchymal Stem Cells with Intra-Arterial Infusion in Osteonecrosis of the Femoral Head in Dogs. Stem Cells Int. 2016; 2016: 8616143.
[27] Kang Y, Xu C, Meng L, et al. Exosome-functionalized magnesium-organic framework-based scaffolds with osteogenic, angiogenic and anti-inflammatory properties for accelerated bone regeneration. Bioact Mater. 2022; 18: 26-41. Published 2022 Feb 18.
[28] Wang T, Wei Wang. Treatment of osteonecrosis of the femoral head with thorough debridement, bone grafting and bone-marrow mononuclear cells implantation [J]. Eur J Orthop Surg Traumatol, 2014, 24(2):197-202.

[29] Maruyama M, Nabeshima A, Pan CC, et al. The effects of a functionally-graded scaffold and bone marrow-derived mononuclear cells on steroid-induced femoral head osteonecrosis. Biomaterials. 2018; 187:39-46.
[30] Wang G, Li Y, Sun T, et al. BMSC affinity peptide-functionalized β-tricalcium phosphate scaffolds promoting repair of osteonecrosis of the femoral head. J Orthop Surg Res. 2019; 14(1):204. Published 2019 Jul 4.