Bone Marrow Cellular Therapies: Novel Therapy for Knee Osteoarthritis

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Abstract

Cellular therapies are emerging as potentially promising treatments for numerous musculoskeletal conditions, such as knee osteoarthritis (OA). As orthopaedic surgeons represent a sizable portion of the providers who deliver these therapies, it is particularly essential for them to understand their fundamental principles. One major principle is to identify the appropriate sources for obtaining these cells, with bone marrow being most common. Therefore, the purpose of this review was to provide an overview of cell-based therapies available for the treatment of knee OA with a focus on bone marrow-derived cellular therapies. Specifically, we discuss (1) bone marrow aspiration technique, (2) processing to bone marrow aspirate concentrate, and (3) the rational and clinical evidence for the use of bone marrow cellular therapies for the treatment of knee OA.

Keywords
- cell therapies
- knee osteoarthritis
- bone marrow cellular therapies
- bone marrow

Cell-based therapies are emerging as promising treatments for numerous musculoskeletal conditions.[1–4] Nevertheless, they are still at the proof-of-concept stage. Knee osteoarthritis (OA) is one of the most frequent targets of this therapy, since the marked burden of disability and morbidity that this condition poses on health care is quite sizable.[5] Despite knee OA occurring in more than 10% of individuals over 60 years and more than 75% over 75 years,[6,7] there is currently no validated nonsurgical disease modifying treatment.[8] Cell-based therapy for the treatment of knee OA may therefore be a promising approach to fill this gap.

A recent systematic review, which included only level of evidence III studies or higher (with control group), concluded that intra-articular cellular therapy injections for knee OA and focal cartilage defects showed clinical benefit with respect to safety.[9] However, the authors also noted that the improvement was modest, a high placebo effect could not be disregarded, and the overall quality of the reports was poor.[9] One major point raised in the study was that although stem and progenitor cell therapies may potentially perform as disease-modifying treatments for knee OA through proposed mechanisms of tissue regeneration or immunomodulation, this effect still needs to be further proven. Furthermore, there are multiple aspects of cellular therapy that are still not well understood or standardized, including multiple sources for obtaining cells (e.g., bone marrow, adipose tissue, periosteum, and synovium). In addition to cell sourcing, there are multiple technicalities with regard to the tissue collection and cell processing methods that affect the final sample of cells to be used as a therapy. Additionally, even in the scenario where the same standardized tissue collection and cell-processing technique is used, there are variations in stem and progenitor cell prevalence between patients leading to challenges in standardizing this technique.[10–13]

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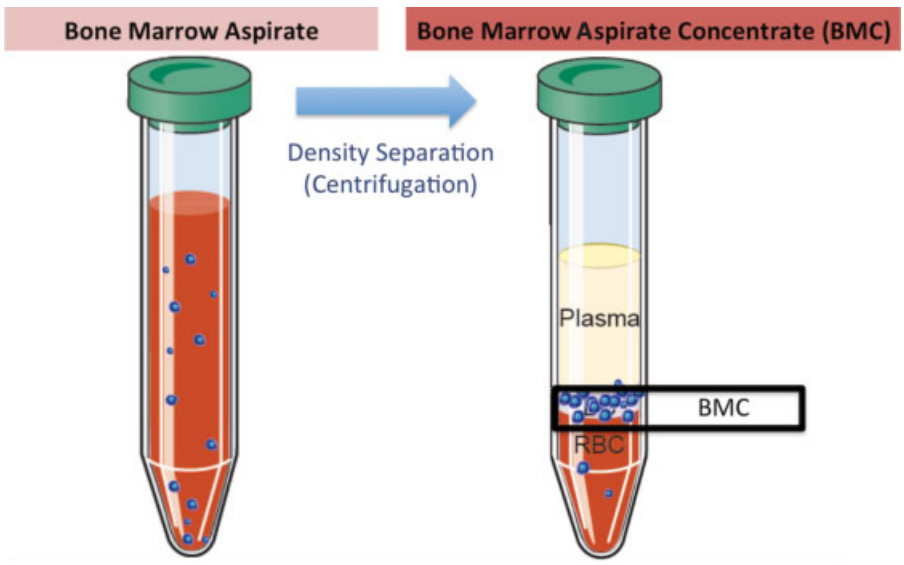
The field of cell-based therapy consists of a group of heterogeneous treatment methodologies. All of these variations constitute real challenges when trying to standardize this treatment. Among cellular therapies, bone marrow-derived cells have been the most frequently employed and reported on. This is likely due to the simplicity and low morbidity of bone marrow aspiration (BMA) and the essential advantage that this technique offers: a single cell suspension that can be easily processed. Therefore, the purpose of this review is to provide an overview of cell-based therapies available for the treatment of knee OA with a focus on bone marrow-derived cellular therapies including (1) BMA, (2) processing to bone marrow aspirate concentrate (BMC), and (3) the rational and clinical evidence for the treatment of knee OA.

Bone Marrow Aspiration

Autologous bone marrow collected through BMA has been one of the most frequently employed sources for cellular therapies. The simplicity and low morbidity of BMA as a percutaneous procedure makes it an appealing and practical approach. Additionally, when bone marrow is aspirated, it presents an important advantage that differentiates it from other cell sources: it offers a single cell suspension that can be immediately be processed with minimal manipulation.[13,14] Other cell sources, such as adipose tissue or synovium, require multistep processing, like mechanical dissociation and enzymatic digestion. In addition, the use of autologous bone marrow cells has been shown to be safe with low incidence of systemic or site-specific side effects.[15]

The site most frequently utilized for BMA is the iliac crest, which has been reported to be safe and to have a low rate of complications.[16] Furthermore, it has been reported that the concentration and yield of colony-founding units were greater when aspirates were obtained from the posterior iliac crest when compared with the anterior iliac crest, whereas the biological potential of the cells derived from these sites is comparable.[17] Nevertheless, both the anterior ant posterior iliac crest are common and viable sites for the harvesting of BMA.

BMA technique has a substantial effect on the yield of nucleated cells, and therefore on the stem and connective tissue progenitor cells (CTPs) collected. Probably the most essential aspect, which is often overlooked, is maintaining low aspiration volumes when performing a BMA. The reason for this is that bone marrow-derived stem/progenitor cells in BMA are diluted precipitously by blood as the volume of the aspirate in a given aspiration site is increased (►**Fig. 1**).[13] When doing a BMA, 85% of all of the marrow-derived cells available from a given aspiration site are collected in just the first 2 mL of aspirate, after which the rest of the aspirate is mainly composed of blood.[13] Therefore, a higher number of stem and CTPs per mL of BMA may be obtained by limiting each aspiration to 1 to 2 mL at a given site, followed by changing and advancing the needle location by 0.5 to 1 cm.[13] Additionally, the use of a 10 mL syringe as compared with a 50 mL syringe has provided a higher yield of CTPs.[18]



	BMA (1mL)	BMC (1mL)
Total Nucleated cells	+	++++
CTPs (CFU)	+	++++
Platelets	+	++++
Red blood cells	++	+
Growth factors and cytokines (PDGF, TGF-β2, VEGF, IL-8, etc.)	+	++++

Fig. 1 Bone marrow aspirate concentrate (BMC) is obtained by one or multiple bone marrow aspiration (BMA) centrifugations. After centrifugation (density separation), the buffy coat (BC), which lies in between the plasma and the red blood cells (RBC) containing most of the nucleated cells, (some of which are stem and progenitor cells), platelets, growth factors, and cytokines is obtained.

Bone Marrow Aspirate Concentrate: Density Separation (Centrifugation)

Bone marrow aspirate contains various components including plasma, red blood cells (RBC), platelets (PLT), total nucleated cells (TNC) including white blood cells (WBC), hematopoietic cells (HPC), CTPs, growth factors, and cytokines. With the intention of increasing the concentration of components of BMA that are believed to have a positive effect in the treatment of different conditions (as CTPs, growth factors, and cytokines), the most frequent and reported technique for processing bone marrow is centrifugation. Based on the different relative densities, sediment rates, and sizes, bone marrow components can be separated when a centrifugal force is applied. RBC have the highest density (1.1 g/L) and sediment to the bottom, while plasma (1.02 g/L) remains in the upper layer. In between the plasma and the RBCs, a "buffy coat" layer forms, which contains most of the nucleated cells including neutrophils (1.08 g/L), lymphocytes (1.05 g/L), as well as PLT (1.04 g/L). When BMC is obtained, this buffy coat is the fraction that is harvested.[19]

Therefore, when a density separation procedure is applied to a BMA sample, the concentration of stem and CTPs per mL increases.[19] In addition, the final BMC preparation (mostly buffy coat) has an increased concentration of PLT, growth factors, and cytokines (PDGF, TGF-β2, VEGF, IL-8, IL-1β, etc.), which may potentially have anabolic and anti-inflammatory effects on the osteoarthritic knee joint.[20,21]

A comprehensive understanding of the composition of BMC is still lacking. These preparations vary because of the unavoidable interpatient variability and the different processing techniques employed. The differences in the preparation of BMC include dissimilarities among centrifuge devices, settings or protocol, the time of each spin, the G-force generated in each spin, and diluents or anticoagulants added in the process.[21] All of these factors have an effect on the final yield in the desired sample on the number of stem and progenitor cells: (1) CTPs, assessed through colony forming unit assays; (2) hematopoietic stem cells; and (3) endothelial stem cells; which may have implications in their clinical efficacy. Furthermore, the concentration of stem and progenitor cells and other component such as PLT, growth factors, and cytokines needs to be better characterized, and future research will have to correlate their values in the final BMC product with subsequent clinical outcomes.

Bone Marrow Cellular Therapies Regulation

These preparations are classified clinically by the United States Food and Drug Administration (FDA) as Human Cell and Tissue Products (HCT/Ps) that are regulated under the 21 C.F.R. Part 1271 under the "361 exemption." For a product to qualify and be designated as a "361 product," and consequently be subject to minimal oversight, an HCT/P must meet each of the following four criteria (as BMC does): (1) minimally manipulated (e.g., centrifugation); (2) intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent; (3) not involving a combination cells or tissues with another article (e.g., drug); and (4) having a systemic effect or being dependent on the metabolic activity of living cells for its primary function. Also, is for (a) autologous use or (b) allogeneic use in a first-degree or second-degree blood relative. All these products are not subject to premarket review and approval requirements.

Rational and Clinical Evidence for the Use of Bone Marrow Cellular Therapies for the Treatment of Knee Osteoarthritis

Since half of the patients with radiographic evidence of knee OA do not experience daily knee pain, and most of these patients will not require a joint arthroplasty,[8,22] special attention should be placed on nonoperative treatments for OA. Furthermore, given that the prevalence of obesity is unlikely to decline, there will likely be an increase in the incidence of knee OA.[23] Therefore, early identification of at-risk patients and modifiable risk factors, in addition to the employment of prevention strategies with potential disease modifying effect (e.g., cellular therapies), is essential.[8] Knee OA results from a multifactorial, intricate interplay of many factors that ultimately culminate in a common phenotype that affects all of the tissues within and adjacent to the involved articular joint.[24,25] Historically, what was thought to be the mechanical result of "wear and tear" to the cartilage over years, is now perceived to be the consequence of the interaction between both constitutional and mechanical factors affecting the entire joint. These factors include joint integrity, mechanical forces, genetic predisposition, inflammation, as well as cellular and biochemical processes.[26–33] To date, the results obtained with structure modifying treatments for OA have been disappointing.[34,35]

Cellular therapies have the potential to provide an answer to this problem. However, to date there is insufficient evidence of efficacy to warrant a general recommendation to use bone marrow-derived cellular therapies.[9,21] Although there have been some encouraging results, the development of stem cell-based therapies for OA is at a critical juncture.[2] While limiting bias assessing their clinical efficacy through high-quality clinical trials, it is imperative to uncover the mechanism of action by which intra-articular bone marrow-derived cellular therapies act. Proposed mechanisms include (1) homing of cells to sites of degenerative or missing cartilage, (2) repopulating of stem and progenitor cell pools on the surface of damaged cartilage, and (3) modulation of the intra-articular milieu either by secretion of soluble factors or through cell-to-cell interactions and reducing inflammation and catabolic agents.[9,36]

As our understanding of bone marrow stem and progenitor cellular therapies improves, so should our understanding of the diseases we are treating. It is possible that cellular therapies will have a role in the treatment of knee OA; however, this treatment option may not prove to be best for all patients. As advocated by Karsdal et al, there is a need to segregate patients with different OA subtypes and pair them with optimal and specific treatments to yield an effective intervention.[37,38] This still needs to be defined and tested.

Table 1 Clinical studies on the use of BMC for the treatment of knee osteoarthritis

Author, year	LOE	Knees (*n*)	Follow-up (mean months)	Age (y)	Treatment	Concomitant treatment	K–L	Outcome (baseline)	Outcome (last follow-up)	Conclusion
Shapiro et al 2016[39]	II	25	6	60 (42–68)	BMC	None	I 2 (8%); II 11 (44%); III 12 (48%)	VAS pain 3.1 (0–8.1) ICOAP total pain 32 (18–91)	VAS pain 1.5 (0–6.8) ICOAP total pain 32 (18–91)	BMC was safe. Pain assessed by VAS and ICOAP decreased significantly from baseline, at 1 week, 3 months, and 6 months ($p < 0.19$) in each arm; however, the pain did not decreased significantly between treated knees ($p > 0.9$)
					Control—Saline	None	I 16 (64%); II 7 (28%); III 2 (8%)	VAS pain 2.9 (0–7) ICOAP total pain 32 (0–73)	VAS pain 0.8 (0–9.2) ICOAP total pain 9 (0–66)	
Centeno et al 2014[40]	IV	615	10.4	54 (SD, 14)	BMC	PRP, PL	I 223 (48%); II 145 (30%); III–IV 102 (21%)	LEFS 46.1 (SD,15.8) NPS 4 (SD, 2.3)	LEFS 54 (SD, 17.9) NPS 2.6 (SD, 2.3)	BMC injections showed encouraging outcomes and a low rate of adverse events. Adipose grafts did not provide detectable benefit over BMC alone
		224	10.7	59 (SD,10)	BMC	PRP, PL, adipose graft	I 69 (41%); II 58 (34%); III–IV 39 (23%)	LEFS 43.6(SD, 14.9) NPS 4.3 (SD, 2)	LEFS 54 (SD, 53.4) NPS 3 (SD, 2.3)	
Kim et al 2014[41]	IV	75	8.7	60.7 (53–80)	BMC	Adipose graft, arthroscopy, HTO	I 12 (16%); II 24 (32%); III 33 (44%); IV 6 (8%)	VAS 7(±0.5) IKDS 37.7(±4.4) SF-36 31.5(±1.7) KOOS 42(±6.3) Lysholm 37.3(±5.3)	VAS 3.3(±0.6) IKDS 69.3(±5.5) SF-36 47.7(±2.9) KOOS 70.6(±5.1) Lysholm 71(±6)	BMC significantly improved both knee pain and function Patients with more advanced K–L showed poorer results

Abbreviations: BMC, bone marrow aspirate concentrate; HTO, high tibial osteotomy; ICOAP, OARSI Intermittent and Constant Osteoarthritis Pain Questionnaire; IKDS, International knee Documentation Committee; K–L, Kellgren and Lawrence; KOOS, knee and osteoarthritis outcome score; LEFS, lower extremity functional scale; LOE, level of evidence; NPS, numerical pain scale; PL, platelet lysate; PRP, platelet-rich plasma; SF-36, short-form 36 healthy survey; VAS, visual analogue scale.

To date, there is limited evidence-based support for the use of BMC in the treatment of knee OA.[9] ►**Table 1** summarizes clinical studies published to date. Shapiro et al[39] performed a prospective, single-blind, placebo-controlled trial on 25 patients with bilateral knee OA, and reported that the use of BMC is safe. Regarding pain relief, they did not show any significant difference between BMC and the placebo group, although both groups showed improvement in pain at 1 week, 3 months, and 6 months. The two other studies reporting on the use of BMC for knee OA reported improvements in both pain and function; however, they lacked a control group,[40,41] and BMC injections were performed concomitant to other treatments including arthroscopy, PLT-rich plasma, and adipose grafts, which make interpretation of the results challenging. In general, there were no significant adverse events in these three studies.

Conclusion

The development of new therapeutic approaches with potential disease-modifying effects, such as cell-based therapies, may become a viable alternative for the treatment of knee OA. However, this will require overcoming multiple challenges including communicating early results obtained by basic scientists and clinical studies with good sample size and long-term follow-up. Autologous bone marrow collected through BMA has been one of the most frequently employed sources for cellular therapies. The simplicity and low morbidity of BMA make it an appealing and practical approach. Fundamental aspects of the BMA technique have a profound effect on the yield of stem and progenitor cells obtained. Therefore, multiple aspiration sites with a low aspiration volume (2 mL) in each should be used. Another fundamental advantage of bone marrow is that when aspirated it offers a single cell suspension that can be immediately be processed (e.g., centrifugation). Different processing techniques and protocols also have a profound effect on the yield of stem and progenitor cells, including the number of connective tissue progenitors, hematopoietic stem cells, or endothelial stem cells, which may influence the outcome of the disease conditions to treat. However, the role these cells have when injected in a patient's knee is still not clear. It is imperative to improve our understanding of the known and unknown areas related to these biologics, with a specific need to provide high-quality clinical trials to prove or disprove the efficacy of cell-based therapies for the treatment of knee OA. Effective clinical assessment and optimization of cellular therapies will demand high-quality methodology in blinded clinical trials, with special attention to standardized quantitative methods for cell harvesting, processing, characterization, delivery, and standardized reporting of clinical and structural outcomes.[9]

References

1 Filardo G, Madry H, Jelic M, Roffi A, Cucchiarini M, Kon E. Mesenchymal stem cells for the treatment of cartilage lesions: from preclinical findings to clinical application in orthopaedics. Knee Surg Sports Traumatol Arthrosc 2013;21(08):1717–1729

2 Diekman BO, Guilak F. Stem cell-based therapies for osteoarthritis: challenges and opportunities. Curr Opin Rheumatol 2013;25 (01):119–126
3 Marcucio RS, Nauth A, Giannoudis PV, et al. Stem Cell Therapies in Orthopaedic Trauma. J Orthop Trauma 2015;29(12, Suppl 12):S24–S27
4 Piuzzi NS, Chahla J, Schrock J, et al. Evidence for the Use of Cell-Based Therapy for the Treatment of Osteonecrosis of the Femoral Head: A Systematic Review of the Literature. J Arthroplasty 2017; 32(05):1698–1708
5 Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 2013;21(09):1145–1153
6 Felson DT, Nevitt MC. Epidemiologic studies for osteoarthritis: new versus conventional study design approaches. Rheum Dis Clin North Am 2004;30(04):783–797
7 Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol 2006;20(01):3–25
8 Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol 2016;12(02):92–101
9 Chahla J, Piuzzi NS, Mitchell JJ, et al. Intra-Articular Cellular Therapy for Osteoarthritis and Focal Cartilage Defects of the Knee: A Systematic Review of the Literature and Study Quality Analysis. J Bone Joint Surg Am 2016;98:1511–1521
10 Amini AR, Laurencin CT, Nukavarapu SP. Bone tissue engineering: recent advances and challenges. Crit Rev Biomed Eng 2012;40 (05):363–408
11 Muschler GF, Nitto H, Boehm CA, Easley KA. Age- and gender-related changes in the cellularity of human bone marrow and the prevalence of osteoblastic progenitors. J Orthop Res 2001;19(01):117–125
12 Muschler GF, Nakamoto C, Griffith LG. Engineering principles of clinical cell-based tissue engineering. J Bone Joint Surg Am 2004; 86-A(07):1541–1558
13 Muschler GF, Boehm C, Easley K. Aspiration to obtain osteoblast progenitor cells from human bone marrow: the influence of aspiration volume. J Bone Joint Surg Am 1997;79(11):1699–1709
14 Jäger M, Hernigou P, Zilkens C, et al. Cell therapy in bone healing disorders. Orthop Rev (Pavia) 2010;2(02):e20
15 Hernigou P, Homma Y, Flouzat-Lachaniette CH, Poignard A, Chevallier N, Rouard H. Cancer risk is not increased in patients treated for orthopaedic diseases with autologous bone marrow cell concentrate. J Bone Joint Surg Am 2013;95(24):2215–2221
16 Hernigou P, Desroches A, Queinnec S, et al. Morbidity of graft harvesting versus bone marrow aspiration in cell regenerative therapy. Int Orthop 2014;38(09):1855–1860
17 Pierini M, Di Bella C, Dozza B, et al. The posterior iliac crest outperforms the anterior iliac crest when obtaining mesenchymal stem cells from bone marrow. J Bone Joint Surg Am 2013;95(12):1101–1107
18 Hernigou P, Homma Y, Flouzat Lachaniette CH, et al. Benefits of small volume and small syringe for bone marrow aspirations of mesenchymal stem cells. Int Orthop 2013;37(11):2279–2287
19 Luangphakdy V, Boehm C, Pan H, Herrick J, Zaveri P, Muschler GF. Assessment of Methods for Rapid Intraoperative Concentration and Selection of Marrow-Derived Connective Tissue Progenitors for Bone Regeneration Using the Canine Femoral Multidefect Model. Tissue Eng Part A 2016;22(1-2):17–30
20 Cassano JM, Kennedy JG, Ross KA, Fraser EJ, Goodale MB, Fortier LA. Bone marrow concentrate and platelet-rich plasma differ in cell distribution and interleukin 1 receptor antagonist protein concentration. Knee Surg Sports Traumatol Arthrosc 2016. Doi: 10.1007/s00167-016-3981-9
21 Hegde V, Shonuga O, Ellis S, et al. A prospective comparison of 3 approved systems for autologous bone marrow concentration demonstrated nonequivalency in progenitor cell number and concentration. J Orthop Trauma 2014;28(10):591–598
22 Lawrence JS, Bremner JM, Bier F. Osteo-arthrosis. Prevalence in the population and relationship between symptoms and x-ray changes. Ann Rheum Dis 1966;25(01):1–24
23 Bryan D, Parvizi J, Austin M, et al; Workgroup of the American Association of Hip and Knee Surgeons Evidence Based Committee. Obesity and total joint arthroplasty: a literature based review. J Arthroplasty 2013;28(05):714–721
24 Sharma L. Osteoarthritis year in review 2015: clinical. Osteoarthritis Cartilage 2016;24(01):36–48
25 Arden NK, Leyland KM. Osteoarthritis year 2013 in review: clinical. Osteoarthritis Cartilage 2013;21(10):1409–1413
26 Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 2013;21 (01):16–21
27 Daghestani HN, Kraus VB. Inflammatory biomarkers in osteoarthritis. Osteoarthritis Cartilage 2015;23(11):1890–1896
28 Greene MA, Loeser RF. Aging-related inflammation in osteoarthritis. Osteoarthritis Cartilage 2015;23(11):1966–1971
29 Malfait AM. Osteoarthritis year in review 2015: biology. Osteoarthritis Cartilage 2016;24(01):21–26
30 Orlowsky EW, Kraus VB. The role of innate immunity in osteoarthritis: when our first line of defense goes on the offensive. J Rheumatol 2015;42(03):363–371
31 Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone 2012;51(02):249–257
32 Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? Joint Bone Spine 2013;80(06):568–573
33 Varady NH, Grodzinsky AJ. Osteoarthritis year in review 2015: mechanics. Osteoarthritis Cartilage 2016;24(01):27–35
34 Karsdal MA, Michaelis M, Ladel C, et al. Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future. Osteoarthritis Cartilage 2016;24(12):2013–2021
35 Kuyinu EL, Narayanan G, Nair LS, Laurencin CT. Animal models of osteoarthritis: classification, update, and measurement of outcomes. J Orthop Surg 2016;11(01):19
36 Evans CH, Kraus VB, Setton LA. Progress in intra-articular therapy. Nat Rev Rheumatol 2014;10(01):11–22
37 Karsdal MA, Christiansen C, Ladel C, Henriksen K, Kraus VB, Bay-Jensen AC. Osteoarthritis–a case for personalized health care? Osteoarthritis Cartilage 2014;22(01):7–16
38 Wyatt LA, Moreton BJ, Mapp PI, et al. Histopathological subgroups in knee osteoarthritis. Osteoarthritis Cartilage 2017;25 (01):14–22
39 Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MIA. A Prospective, Single-Blind, Placebo-Controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis. Am J Sports Med 2017;45(01):82–90
40 Centeno C, Pitts J, Al-Sayegh H, Freeman M. Efficacy of autologous bone marrow concentrate for knee osteoarthritis with and without adipose graft. BioMed Res Int 2014;2014:370621
41 Kim JD, Lee GW, Jung GH, et al. Clinical outcome of autologous bone marrow aspirates concentrate (BMAC) injection in degenerative arthritis of the knee. Eur J Orthop Surg Traumatol 2014;24 (08):1505–1511