



## **Joint Preservation Using Orthobiologic Therapies in Osteoarthritis**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Osteoarthritis is estimated to be the most prevalent musculoskeletal disorder in the world. Estimates show that the disease is prevalent in 18% and 10% in women and men that are aged >60 years old. The quality of life of the affected patients can also be significantly impacted due to the associated morbidities and functional loss. Many interventions have been proposed to preserve

the joint and enhance the functional outcomes in patients with osteoarthritis. In the present literature review, we have discussed the different orthobiologic therapies for patients with osteoarthritis for joint preservation and subsequent improvement in the functional and pain outcomes. Variable modalities that have been proposed in the literature include Bone Marrow Aspirate Concentrate (BMAC), gene therapy and platelet rich plasma (PRP). All of these modalities were reported with favorable outcomes and minimal complications. PRP has been reported to have a clinical efficacy that is boosted when co-administered with hyaluronic acid. However, it should be noted that the clinical efficacy is limited in the long term, and administration is continuously required. On the other hand, gene therapy is a promising technique that offers maintained favorable outcomes with no adverse events. However, further studies are still needed to indicate the effectiveness and cost-efficacy of this approach.

*Keywords: Osteoarthritis; orthobiologic; platelet-rich plasma; stem cell therapy; gene therapy; adipose-derived stromal cell therapy.*

## 1. INTRODUCTION

Osteoarthritis is estimated to be the most prevalent musculoskeletal disorder in the world. Estimates show that the disease is prevalent in 18% and 10% in women and men that are aged >60 years old [1]. It has been furtherly demonstrated that the knee joint is the most commonly affected, and most studies have been recruiting patients with knee osteoarthritis. The disease is characterized by a significant progressive degeneration of the bone and cartilaginous tissues leading to osteophyte and subchondral cyst formation [2,3]. The quality of life of the affected patients can also be significantly impacted due to the associated morbidities and functional loss [4].

Epidemiological studies indicate that the etiology of the condition is multifactorial, and many risk factors have been proposed [4,5]. For instance, being female, previous knee injuries, and obesity, and overweight are reported risk factors for developing knee osteoarthritis. Many interventions have been proposed to preserve the joint and enhance the functional outcomes in patients with osteoarthritis. In the present literature review, we aim to discuss the different orthobiologic therapies for patients with osteoarthritis for joint preservation.

## 2. ADIPOSE-DERIVED STROMAL CELL THERAPY

Evidence from the current investigations within the relevant literature indicates that these modalities are a great source for adequately obtaining adult stem cells that have been widely observed to effectively differentiate into tenocytes or chondrocytes [6]. It has been furtherly demonstrated that these modalities also

have supportive characteristics that can significantly aid in the repair and regeneration of the affected tissues [7]. Many previous investigations have reported the effectiveness of using adipose-derived stromal cell therapy (ATDs). A previous animal investigation by Toghraei et al. [8] reported that among the included 20 white New Zealand rabbits, that were indicated for osteoarthritis induction and after administration of ATDs, the frequency of subchondral sclerosis, joint space narrowing, and osteophyte development was significantly reduced among the included objects. Another similar investigation by Mei et al. [9] reported that after 8-12 weeks from the administration of ATD therapeutic modality in a rat model with osteoarthritis, it has been noticed that the gross and histological cartilage degeneration was significantly reduced. Among the studies in the literature, we have also noticed some articles that included the human population. For instance, a previous study by Spasovski et al. [10] reported that pain relief and clinical improvements were significantly noticed among their included nine patients with osteoarthritis at 18 months of follow-up following the administration of ATDs. Favorable events were also documented in a previous investigation by Koh et al. [11] that included 33 patients and were administered bone marrow-derived mesenchymal stem cells. Following the administration of intraarticular ATDs, Jo et al. [12] also indicated that the clinical outcomes in their included 18 patients were significantly improved. The authors also established an association between the administered dose (low, medium, or high) and the persistence of the therapeutic effect. It has been demonstrated that the favorable effects with the high doses were significantly maintained at two years since the initial administration, while the favorable effects

with the low and medium doses significantly deteriorated after one year. Swelling and pain were the only reported adverse events among these investigations and only lasted for 1-day maximum. Accordingly, it can be concluded that the current evidence strongly supports the administration of ATDs for joint preservation in patients with osteoarthritis as an efficacious and safe modality.

### **3. BONE MARROW ASPIRATE CONCENTRATE**

Investigations also studied the effects of the bone marrow aspirate concentrate (BMAC) for managing of the different musculoskeletal disorders because the modality has been previously approved by the US Food and Drug Administration [13]. Mesenchymal Stem Cells (MSCs), and Hematopoietic Stem Cells (HSCs) are the main significant modalities that are usually found in the BMAC in this concern [14]. Different clinical studies and in vitro investigations have assessed the efficacy of the administration of these modalities in patients with osteoarthritis. It has been demonstrated that injecting the modality in an affected tissue induces the formation and release of several cytokines, growth factors, and biomolecules including bone Morphogenetic Protein 2 and 7, Granulocyte-Macrophage Colony-Stimulating Factor, and stromal cell-derived factor (SDF-1). These factors were also reported to significantly lead to cartilaginous regeneration and preservation, which can remarkably lead to clinical improvement [15]. In a previous clinical trial, it has been demonstrated that improved clinical outcomes and reduced pain scores were significantly reduced after the intraarticular administration of BMAC in patients suffering from knee osteoarthritis [16]. Other investigations also demonstrated that in patients with moderate and severe joint osteoarthritis, the administration of intraarticular BMAC with platelet-rich plasma (PRP) resulted in a significant improvement in the short-term outcomes of these patients, in addition to patient satisfaction [17,18]. The same findings were also indicated in a previous meta-analysis that reported that after the injection of BMAC, a significant improvement in the quality of life and clinical outcomes were significantly improved among patients that suffered from focal chondral defects and/or joint osteoarthritis, especially those with Kellgren-Lawrence grade 4 osteoarthritis [19]. Evidence in the literature indicates that the favorable effects of administering BMAC start after one week of

administration and can last for up to 6 months among patients suffering from joint osteoarthritis [18]. Favorable effects for observed chondral lesions were also previously reported following the administration of BMAC. In this context, a previous investigation by Gobbi et al. [19] reported that functional outcomes and pain improvement were significantly reported among their included 50 patients that suffered from grade IV osteoarthritis following the administration of Hyaluronic Acid BMAC, and these effects were maintained for 2 years. Another research also showed that near normal and normal joint functions were reported by patients after 5 years of follow-up [20]. Some evidence furtherly indicates that the favorable effects with BMAC are even superior to the effects obtained by PRP. In a previous investigation by Krych et al. [20], the authors included 46 patients suffering from III and IV chondral lesions and divided them into three groups including the BMAC, PRP, and control group. The authors reported that after one year of follow-up, a similar T2 value was reported for the PRP and control groups, while the T2 values for the BMAC group were similar to the value for the superficial hyaline cartilage, in addition to observing more cartilage refill among patients in this group [21]. Although no significant adverse events were reported among these studies following the administration of BMAC, further research is still required to verify the volume, application, and timing of intraarticular BMAC administration for joint preservation among patients with osteoarthritis.

### **4. PLATELET RICH PLASMA**

The main function of platelets is to achieve hemostasis. However, researchers have evidenced further uses of these compounds [22]. Based on the evidenced functions that platelets have in the immunological and inflammatory responses, it has been demonstrated that they might have potential functions in regenerative medicine [23,24]. Many previous investigations have evaluated the efficacy and safety of using PRP in the management of osteoarthritis. In a previous meta-analysis, the authors compared the efficacy and safety of PRP administration compared to that of saline and hyaluronic acid administration for patients suffering from knee osteoarthritis [25]. It has been concluded that the efficacy of PRP in inducing pain relief and improving joint functions for the included patients was significantly higher than that of saline at six months of follow-up. Furthermore, the authors

elaborated that the efficacy was maintained for additional six months at the 12<sup>th</sup> follow-up month. On the other hand, no significance was estimated for the administration of PRP over hyaluronic acid. However, at 12 months of follow-up, the authors reported that the PRP group showed more significant improvements in joint functions and pain relief as compared to the hyaluronic acid group. In another context, a combination of PRP and hyaluronic acid was evaluated in a previous randomized controlled trial by Lana et al. [26] that showed that the combined use of both modalities significantly reduced the functional limitations and pain after treatment was inaugurated and was also maintained until 12 months of follow-up. Therefore, it has been concluded by further investigations that the combined administration of hyaluronic acid with PRP offers more notable effects than the administration of either of the therapeutic modalities alone [27-29]. Whether leukocytes are present or absent in the administered PRP for osteoarthritis has also been a point of concentration among the different investigations. This has been indicated in a previous meta-analysis that investigated the efficacies of leukocyte-poor PRP and leukocyte-rich PRP and found that the reported functional outcomes by the included investigations were significantly impacted by the presence and absence of leukocytes together with PRP [30]. It has been concluded that the functional outcomes were significantly improved with the administration of leukocyte-poor PRP. Moreover, no adverse events were reported with the administration of PRP as demonstrated by the authors of this investigation. However, it should be noted that the authors of this meta-analysis reported that the obtained quality of evidence in this investigation was of low quality. Another investigation by Gormeli et al. [27] also reported the ideal frequency and number of applications of PRP. They demonstrated that the functional outcomes and pain relief were significantly enhanced in their included patients after the administration of multiple PRP injections more than a single injection. Another investigation also indicated this finding. However, it has been concluded that the reported favorable effects that were observed with multiple injections are attainable within the early stages of the disease only while no significant differences were noticed regarding the frequency of injection of PRP in patients suffering from advanced osteoarthritis [28]. Despite the proven favorable events following the administration of PRP for patients suffering from osteoarthritis, evidence still needs

further validation to quantify the management protocols and reduce the heterogeneity among the current investigations. Finally, evidence supports the co-administration of hyaluronic acid with PRP to improve the functional outcomes and relief the associated pain in patients suffering from osteoarthritis.

## 5. GENE THERAPY

As a result of the current challenges regarding the frequent administration of the therapeutic agents that have been proposed to manage osteoarthritis and maintain functional outcomes, recent studies have focused on developing more advanced therapeutic modalities that can enhance the treatment with less frequent dosing systems. Gene therapy has been introduced as an outstanding modality that can enhance the long-term outcomes with no need for frequent administration of the different management modalities. In this context, various animal and clinical studies were conducted to prove the efficacy and safety of this approach in the management of osteoarthritis and joint preservation [31-35]. A previous randomized controlled trial by Ha et al. [36] reported that they induced transforming growth factor (TGF)- $\beta$ 1 overexpression among 12 patients suffering from end-stage knee osteoarthritis. The authors of this multicenter investigation reported that different doses of this modality were associated with enhanced functional outcomes and pain scores, with no serious adverse events. The same findings were also reported in other clinical trials by Lee et al. [34], Cherian et al. [37], and Kim et al. [38], which indicated that the included patients in the intervention groups had more favorable outcomes and less frequent administration of analgesics as compared to the placebo group. In 2018, the first gene therapy for osteoarthritis was announced in South Korea that was mainly based on encoding TGF- $\beta$ 1 [39,40]. Favorable cartilage thickness and improved clinical outcomes following the administration of IL-1Ra were also investigated in previous animal investigations and are still under observation in human studies [41]. Overall, gene therapy is a promising approach that can change the therapeutic concept of joint preservation in osteoarthritis and should be investigated by future investigations.

## 6. CONCLUSION

In the present literature review, we have discussed the different orthobiologic therapies for

patients with osteoarthritis for joint preservation and subsequent improvement in the functional and pain outcomes. Variable modalities that have been proposed in the literature include BMAC, gene therapy, ATDs, and PRP. All of these modalities were reported with favorable outcomes and minimal complications. PRP has been reported to have a clinical efficacy that is boosted when co-administered with hyaluronic acid. However, it should be noted that the clinical efficacy is limited in the long term, and administration is continuously required. On the other hand, gene therapy is a promising technique that offers maintained favorable outcomes with no adverse events. However, further studies are still needed to indicate the effectiveness and cost-efficacy of this approach.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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