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Systematic Review

Should I add orthobiologics to my knee osteotomy practice? A systematic review

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ABSTRACT

Importance: Orthobiologics has seen a renaissance over the last decade as an adjunct therapy during osteotomy due to the limited inherent regenerative potential of damaged intraarticular tissues.

Aim or objective: This systematic review aims to present the latest evidence regarding using orthobiologics with simultaneous high tibial osteotomy (HTO) for knee osteoarthritis. The results of this study may guide surgeons to improve their clinical results and clear the air regarding confusion over whether or not to add orthobiologics to HTO in clinical practice backed by scientific evidence.

Evidence review: According to PRISMA guidelines a systematic search for relevant literature was performed in the PubMed (MEDLINE), Scopus, EMBASE, and Cochrane Library databases of all studies published in English from January 1990 to May 2023. The following search terms were entered into the title, abstract, and keyword fields: "knee" or "osteotomy" AND "valgus" or "varus" AND "regenerative medicine" or "PRP" or "mesenchymal stem cells" or "stem cells" or "BMAC" or "bone marrow" or "growth factors" or "umbilical cord blood-derived mesenchymal stem cell" or "stromal vascular fraction". The AMSTAR-2 checklist was used to confirm the quality of the systematic review. Randomised controlled trials (RCTs), prospective and retrospective comparative cohort studies, case-control studies, and case series were included. Studies that reported clinical outcomes in patients treated with knee osteotomy for varus/valgus knee with concomitant adjunction of regenerative treatment [Platelet-rich plasma (PRP), Adipose-derived stem cells (ADSC), Human Umbilical Cord Blood-Derived (HUCBD), Mesenchymal Stem Cells (MSC), bone marrow aspirate concentrate (BMAC), stromal vascular fraction (SVF)] were included. The outcome measures extracted from the studies were the KOOS score, Lysholm score, Subjective IKDC, WOMAC Score, KSS, Tegner, HSS, radiographic tibiofemoral angle, posterior tibial slope and complications. The current systematic review is registered in the PROSPERO Registry (CRD42023439379).

Findings: Osteotomy for unicompartmental arthritis with adjunction of orthobiologics such as PRP, ADSC, HVCBD, MSC, BMAC, and SVF presents a consistent statistically significant clinical improvement compared to preoperative scores regardless of the treatment modality used and there were no notable complications associated with the use of these novel agents.

Conclusions and relevance: Orthobiologics and knee osteotomies could improve outcomes in patients with knee osteoarthritis desiring Knee preservation surgeries. However, only a few studies are available on the topic to conclude anything with certainty, the patients included in the studies could not be disintegrated based on the grade of osteoarthritis (OA), type, dosage and frequency of administration of orthobiologic and type of additional surgical procedures used. Therefore, better-structured RCTs are required to implement this finding into routine Orthopaedic practice.

Level of evidence: Level 4.

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What is already known?

- Various treatment modalities have been used for osteoarthritis, mainly focused on the correction of malalignment and prevention from overloading of specific joint compartments.
- Apart from the correction of mechanical factors, there could be a need to alter intra-articular biology as well. Orthobiologics has the potential to aid in the recovery and regeneration of damaged joint tissues. For this purpose, platelet-rich plasma could be a valuable augmentation to osteotomy surgery

What are the new findings?

- In recent times, apart from high tibial osteotomy and platelet-rich plasma, newer techniques have evolved which mainly focus on increasing the cartilage regeneration rate for osteoarthritis treatment.
- Newer modalities include specific growth factors, Alfa-2 macroglobulin (A2M), interleukin-1 receptor antagonist protein (IRAP), bone marrow stem cells and adipose-derived stromal cells and gene therapy.
- Orthobiologics are showing promising outcomes, but further accumulation of evidence is required so that the quest to find the targeted therapy is concluded and there are methods to address the disease pathology.

INTRODUCTION

Osteoarthritis (OA) is a degenerative disease of the joint, characterised by articular cartilage loss, remodelling of the adjacent bony structures, and joint inflammation [1]. OA is also associated with progressive angular knee deformity, which impairs a joint's function by altering the limb's mechanical axis and putting additional load on the arthritic medial compartment of the knee. OA is considered a degenerative joint disease that is inevitable with age and is stopped only when the joint is replaced by a prosthesis. Even today, there is no truly curative treatment [2,3]. Various treatment modalities have been employed for joint preservation in patients with osteoarthritis knee. These modalities mainly focus on correcting malalignment, thus adjusting the mechanical loading condition of the knee joint, leading to the reduction of joint degeneration.

High tibial osteotomy (HTO) effectively restores the mechanical alignment of the limb. However, it is noteworthy that up to 30% of patients undergo knee replacement surgery within ten years of HTO [4,5]. HTO, as a stand-alone procedure, does not consider and address the cartilage damage that has occurred in the affected limb, the altered internal environment of the joint, increased inflammatory mediators and the altered joint physiology, although a mechanical axis correction could

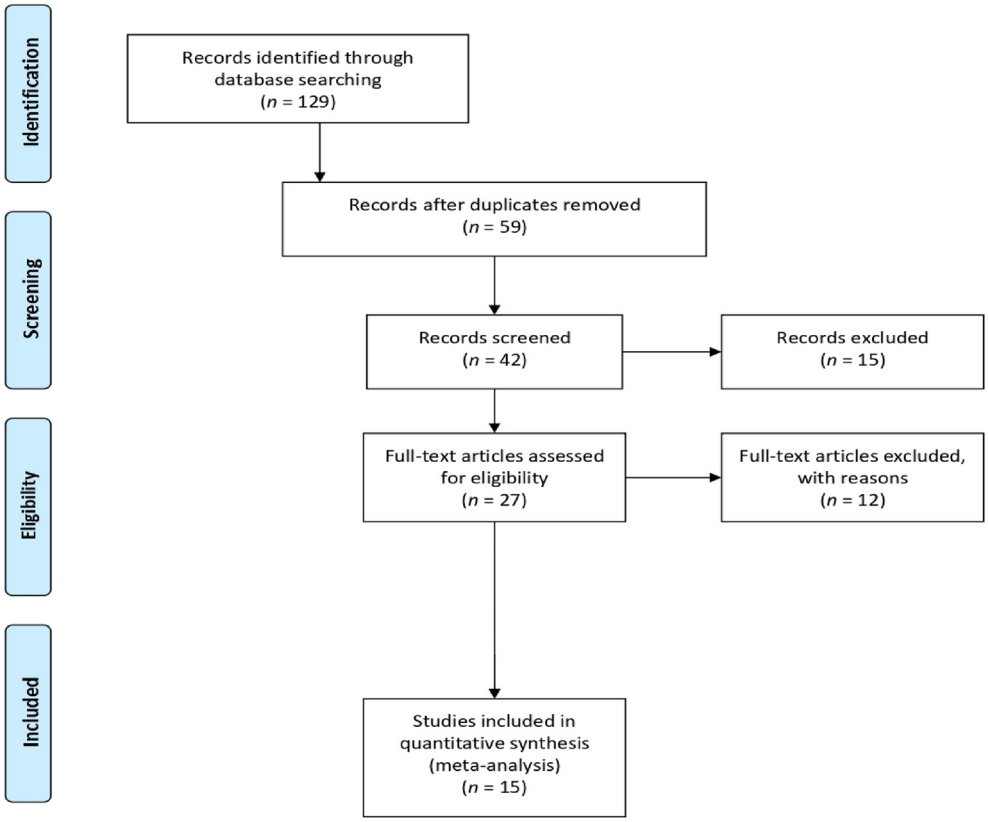

Fig. 1. A flowchart of the literature screening performed in this study.

facilitate biological change in the joint, due to poor vascularity of intraarticular structures involved in osteoarthritis like cartilage, meniscus etc; a solitary mechanical correction is not sufficient and will require something additional to promote repair in these joints [6]. Various surgical procedures like microfracture technique, abrasion arthroplasty, and autologous chondrocyte implantation have been tried along with HTO to address chondral lesions. Unfortunately, these have shown no clinical improvement compared to osteotomy alone [7].

In recent times, orthobiologics have gained attention, which could potentially promote joint repair and maintain homeostasis by various modes of action. Orthobiologics has the potential to aid in the recovery and regeneration of damaged cartilage [8]. For this purpose, PRP is most commonly used and has proved to be a valuable option. PRP contains various biologically active proteins, such as platelet-derived growth factor, fibroblast growth factor, tissue growth factor, and vascular endothelial growth factor, formed by the centrifugal ion of blood. It curbs inflammation and aids in cellular proliferation. PRP alleviates pain and improves outcome scores in patients with arthritis. The safety of intra--articular use of PRP was first described by Sánchez et al. [9]. Various authors compared its efficacy with hyaluronic acid (HA) and placebo (normal saline) and reported improved functional outcomes [10,11]. Intraarticular PRP injection has excellent patient-reported outcomes in early Osteoarthritis [12]. There is an unsettling urge among researchers to look for newer modalities like adipose-derived stem cells, human umbilical cord blood-derived mesenchymal stem cells, bone marrow aspirate concentrate, and stromal vascular fraction for the treatment of osteoarthritis. Orthobiologics are showing promising outcomes [13], but a proper evaluation is required so that the quest to find the targeted therapy is concluded and there are methods to address the disease pathology.

Based on the results as described above, these factors are promising to promote intraarticular tissue repair in osteoarthritis knee. Specifically, combined therapy with knee osteotomy could promote intraarticular condition as well as a clinical outcome as compared with conventional osteotomy surgery alone. The studies on orthobiologic use with concomitant knee osteotomies are scanty.

Therefore, this systematic review aims to guide surgeons offering knee preservation surgeries to suitable patients to improve their clinical results and clear the air regarding confusion over whether or not to add orthobiologics to HTO in clinical practice backed by scientific evidence. The hypothesis was that the concomitant use of orthobiologics and HTO would improve functional outcomes. The topic under question has significant implications and has the potential to influence the current guidelines for the management of OA knee in patients undergoing HTO.

MATERIALS AND METHODS

The current systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) and is registered in the PROSPERO Registry (CRD42023439379) [14]. The AMSTAR-2 checklist was used to confirm the quality of the systematic review [15].

Eligibility criteria

The literature selected for this study was based on the following criteria.

Study design

Randomised controlled trials (RCTs), controlled (nonrandomised) clinical trials (CCTs), prospective and retrospective comparative cohort studies, case-control studies, and case series were included.

Participants

Studies conducted on skeletally mature patients treated surgically for knee osteotomy with concomitant orthobiologic adjunction. Concurrent procedures were considered an exclusion criterion.

Interventions

Studies that reported clinical outcomes in patients treated with knee osteotomy for varus/valgus knee with concomitant adjunction of regenerative treatment (PRP, Adipose-derived stem cells [ADSCs], Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells, bone marrow aspirate concentrate, stromal vascular fraction)

Types of outcome measures

The outcome measures extracted from the studies were the Knee Injury and Osteoarthritis Outcome Score (KOOS), Lysholm score, Subjective IKDC, WOMAC Score, KSS, Tegner, HSS, radiographic tibiofemoral angle, posterior tibial slope and complications.

Information sources and search

A systematic search for relevant literature was performed in the PubMed (MEDLINE), Scopus, EMBASE, and Cochrane Library databases of all studies published in English from January 1990 to May 2023. The search was carried out in June 2023. Two independent reviewers (AM and RD) assisted in conducting and validating the search. The following search terms were entered into the title, abstract, and keyword fields: “knee” or “osteotomy” AND “valgus” or “varus” AND “regenerative medicine” or “PRP” or “mesenchymal stem cells” or “stem cells” or “BMAC” or “bone marrow” or “growth factors” or “umbilical cord blood-derived mesenchymal stem cell” or “stromal vascular fraction”. Finally, only papers published in English were included.

Data collection and analysis

Study selection

The retrieved articles were screened by title and, if found relevant, screened further by reading the abstract. After excluding studies not meeting the eligibility criteria, the entire content of the remaining articles was evaluated for eligibility. To minimise the risk of bias, the authors reviewed and discussed all the selected articles, references, and articles excluded from the study. In case of any disagreement between the reviewers, the senior investigator (ST) made the final decision. At the end of the process, further studies that might have been missed were manually searched by going through the reference lists of the included studies and relevant systematic reviews.

Data collection process

The first two authors extracted the data from the selected articles using a computerised tool created with Microsoft Access (Version 2010, Microsoft Corp, Redmond, Washington). Each article was validated again by the first author before analysis. For each study, data regarding the patients were extracted (age, sex), the surgical technique, orthobiologics treatment used, rehabilitation protocol, clinical outcomes, rate of complications and new surgeries.

Level of evidence

The Oxford Levels of Evidence set by the Oxford Centre for Evidence-Based Medicine was used to categorise the level of evidence [16].

Evaluation of the quality of studies

The quality of the selected studies was evaluated using the Methodological Index for Nonrandomized Studies (MINORS) score [17]. The

checklist includes 12 items, of which the last four are specific to comparative studies. Each item was given a score of 0–2 points. The ideal score was 16 points for noncomparative studies and 24 for comparative studies. Furthermore, according to AMSTAR-2 guidelines, every article was assessed using the ROBINS-I tool [15,18].

Statistical analysis

The extracted quantitative parameters (age, follow-up time and results of the PROMs) were given as mean ± standard deviation (SD) when provided in the articles. Otherwise, alternative values like median or range were extracted. Due to the high statistical and methodological heterogeneity in the included studies, a meta-analysis comparing the results of different treatments was not possible. Instead, a narrative description and comparison of the clinical outcomes were performed. Furthermore, tables and results were divided based on the treatment used.

RESULTS

Fifteen studies were included in the systematic review published between 2013 and 2023. The mean MINORS score was 18.7 ± 4.5 (11–23) (Table 1). The fifteen articles reported 20 different treatments, of which 4 (20%) involved ADSCs [19–22], 4 (20%) BMAC [23–26], 4 (20%) PRP [27–30], 1 (5%) PRP + SVF [30], 6 (30%) allogeneic human umbilical cord [21,24,25,31–33] and 1 (5%) SVF [28] (Table 1).

The score used were KOOS (7 studies – 45%), Lysholm (7 studies – 35%), Tegner (2 studies - 10%), IKDC (9 studies – 45%), WOMAC (7 studies – 35%), KSS (5 studies – 25%), HSS (3 studies – 15%) while for radiographic evaluation the femorotibial angle (14 studies – 70%) and anteroposterior tibial slope (7 studies – 35%).

Clinical results

All the studies reported a statistically significant difference compared to pre-operative scores ($p < 0.05$) regardless of the type of treatment used (Table 2).

Complications

No complications or failures were found in any study (Table 2).

ADSCs

A total of 4 studies [19–22] reported clinical results after ADSCs. The studies were published between 2018 and 2023 with Level of Evidence II or III, and 130 patients were included, of which 26 were male, 62 female and 42 unspecified, with a mean age of 58.15 ± 1.4 years. In all cases, an open-wedge high tibial osteotomy was performed. In two instances, ADSCs were harvested from the buttocks, in 1 from the abdomen while, in the other is not specified. Only in 1 case were the cells loaded into fibrin glue; in all other patients, they were injected intra-articularly. The mean follow-up was 25.9 ± 10.6 months. In one study all patients were suggested to undergo second-look arthroscopic surgery after explaining its purpose (to evaluate the medial arthritis lesion and the need for additional arthroscopic procedures such as debridement or synovectomy) before surgery. All patients reported a statistically significant difference ($p < 0.05$) without failure or complications.

Three studies reported KOOS scores, two studies Lysholm score, one study Tegner score, two studies IKDC, one study WOMAC and two studies radiographic evaluation including femorotibial and posterior tibial slope angles.

BMAC

Four studies [23–26] published between 2013 and 2021 reported clinical results after BMAC injections. All studies were level II and III and included 173 patients (49 male and 124 female) with a mean age of 56.58 ± 2.6 years. The mean follow-up was 29.23 ± 5.8 months. In all cases, an open-wedge high tibial osteotomy was performed, and BMAC were immersed in a patch or fibrin glue after performing microfracture.

All patients reported a statistically significant difference ($p < 0.05$) without failure or complications.

One study reported a KOOS score, one study Tegner, three studies IKDC, two studies WOMAC score, two studies KSS, one study HSS and one study Lysholm, while all three reported radiographic evaluation.

PRP

Four studies [27–30] reported clinical use of PRP and were published between 2014 and 2022. One study was level I, two level II and 1 level III for a total of 96 patients (27 male, 59 female, 10 unspecified) with a mean age of 53.9 ± 1.9 years and mean follow-up of 20.5 ± 5.2 months. In one study, PRP injection was performed one week after surgery and then at intervals of 1 week, in another study, PRP was injected 6 weeks after surgery, while in all other cases, it was performed during surgery. One study specified that PRP was pure-PRP (p-PRP), and only one study did not report the mean platelet count. An open-wedge high tibial osteotomy was performed in all patients. All patients reported a statistically significant difference ($p < 0.05$) without failure or complications.

One study reported a KOOS score, two studies Lysholm, two WOMAC and three femorotibial angle measurements.

PRP + SVF

Only one study [30] published in 2014 reported the use of PRP plus SVF on 21 patients (5 male, 16 female) with a mean age of 54.2 ± 2.9 years and a mean follow-up of 24.2 ± 2.7 months. SVF was harvested from the buttocks and injected (1.0 mL) in addiction with PRP (3.0 mL) during surgery (open-wedge high tibia osteotomy). Patients reported a statistically significant difference regarding the Lysholm score ($p < 0.05$) with no complications or failures.

ALLOGENIC HUMAN UMBILICAL CORD

Six studies [21,24,25,31–33] published between 2020 and 2023 reported using an Allogenic Human Umbilical Cord on 292 patients (76 male and 216 female) with a mean age of 57.32 ± 1.08 years and a mean follow-up of 22.69 ± 5.75 months. In all cases, stem cells were combined into a hydrogel and implanted where there were chondral lesions. All patients underwent high tibial osteotomy surgery. All patients reported a statistically significant difference ($p < 0.05$) without failure or complications. Patients were evaluated with IKDC in three studies, HSS, KOOS and WOMAC in two studies, and Tegner and KSS in one, while five studies evaluated radiographic evolution.

SVF

One study [28] reported outcomes after open-wedge high tibia osteotomy with SVF injections on ten patients (mean age 52.5 years) at a mean follow-up of 18 months. Patients reported a statistically significant difference regarding KOOS score and KSS ($p < 0.05$) with no complications or failures.

CONTROL GROUP

Only 8 studies report a control group with isolated HTO, of which 3 compared ADSCs, 2 BMAC, 2 PRP and 1 hUCB-MSCs. Overall, only 3 studies reported a statistically significant difference against the control group (Table 3).

DISCUSSION

The most important finding of this study was that osteotomy for unicompartmental arthritis with adjunction of orthobiologics such as

Table 1
Demographic details of included studies.

Authors, year	Minors	Level of evidence	Patients	M:F	Age	Surgical technique	Orthobiologics	Use of orthobiologics	Follow-up
Adipose-derived stem cells									
Magnanelli et al., 2020 [19]	12	III	42	n.a.	n.a.	Open-wedge high tibial osteotomy	ADSCs	Intra-articular injection	12 months
Kim et al., 2018 [20]	21	III	50	16/34	59.2 ± 4.5	Open-wedge high tibial osteotomy	ADSCs from patients' buttocks	Injected into the medial joint space under arthroscopic guidance	37.2 ± 4.3
Kim et al., 2023 [21]	22	III	25	8/17	56.0 ± 4.8	Open-wedge high tibial osteotomy	ADSCs stromal vascular fraction from gluteal regions	ADSCs loaded into the fibrin glue product were implanted into the cartilage lesion site under arthroscopic guidance	27.8 ± 3.6
Kim et al., 2022 [22]	23	II	13	2/11	58.3 ± 6.4	Open-wedge high tibial osteotomy	ADSCs from abdomen	Intra-articular injection	3,6,18,24 months
Bone Marrow Aspirate Concentrate									
Jin et al., 2021 [23]	18	III	48	11/37	56.9 ± 6.1	High tibial osteotomy	BMAC	BMAC immersed in the fibrin sealant patch fixed with fibrin glue after microfracture	33.6 ± 6.6 months
Lee et al., 2021 [24]	18	III	42	6/36	60.7 ± 4.1	High tibial osteotomy	BMAC	BMAC was fixed with fibrin glue after microfracture	20.7 ± 6.1 months
Yang et al., 2022 [25]	19	III	55	17/38	55.0 ± 7.3	Open-wedge high tibial osteotomy	BMAC	BMAC immersed in the fibrin sealant patch after microfracture	34.2 ± 8.4 months
Wong et al., 2013	23	II	28	15/13	53	Medial opening high tibial osteotomy	BMAC	Intra-articular injection 22 days after surgery. Marrow stimulation was achieved by performing microfracture	24.8 months
Platelet-Rich Plasma									
Dong et al., 2022	23	I	24	6/18	56.64 ± 8.32	Open-wedge high tibial osteotomy	PRP: 2 centrifugations–3 mL of injection. Mean platelet count: 142.14 × 10^4/uL.	1 week after HTO, which was requested again at intervals of 1 week for a total of four consecutive times	12 months
Prizov et al., 2022	12	III	10	n.a.	56.5	Medial opening wedge high tibial osteotomy	PRP (no information regarding type of PRP)	6 weeks after surgery	18 months
Zhang et al., 2022	23	II	39	15/24	52.7 ± 4.9	Open-wedge high tibial osteotomy	Pure-PRP: 2 centrifugations–4 mL of injection. Mean platelets: >1000 × 10^9/L; mean leukocytes: <0.2 × 10^9/L.	After the incision was closed, the prepared P-PRP was injected into the articular cavity	24 months
Koh et al., 2014	22	II	23	6/17	52.3 ± 4.9	Open-wedge high tibial osteotomy	PRP: 2 centrifugations – 3 mL of injection. Mean platelet count: 1303.27 × 10^3/mL	Injection was performed after the arthroscopic procedure by injection into the medial joint space under arthroscopic guidance	24.6 ± 6.4 months
Platelet-rich Plasma + Stromal Vascular Fraction									
Koh et al., 2014	22	II	21	5/16	54.2 ± 2.9	Open-wedge high tibial osteotomy	PRP + SVF	SVF from buttocks 1.0 mL of SVF + 3.0 ml of PRP injected under arthroscopy	24.2 ± 4.7
Allogenic Human Umbilical Cord									
Kim et al., 2023	22	III	25	9/16	56.4 ± 6.0	Open-wedge high tibial osteotomy	Human umbilical cord blood-derived MSCs	The hUCB-MSC and HA hydrogel composite was implanted into the drill holes in the cartilage lesion site from the base to the surface	28.2 ± 4.1
Lee et al., 2021	18	III	32	6/26	58.1 ± 3.6	High tibial osteotomy	Human umbilical cord blood-derived MSCs	Implanted into the holes with hydrogel in the lesion from the base to the surface	15.6 ± 2.8
Yang et al., 2021	19	III	55	13/42	56.4 ± 5.3	Open-wedge high tibial osteotomy	Human umbilical cord blood-derived MSCs	The hUCB-MSC and HA hydrogel composite was implanted into the drill holes in the cartilage defects from the base to the surface	31.0 ± 6.0

(*continued on next page*)

Table 1 (*continued*)

Authors, year	Minors	Level of evidence	Patients	M:F	Age	Surgical technique	Orthobiologics	Use of orthobiologics	Follow-up
Song et al., 2020	13	III	125	30/95	58.3 ± 6.8	High tibial osteotomy	Human umbilical cord blood-derived MSCs + Hyaluronic acid	Implanted into the drill holes	20.2 ± 6.5
Suh et al., 2021	21	III	43	15/28	56.5 (48–65)	High tibial osteotomy	Human umbilical cord blood-derived MSCs + HA	Implanted into the drill holes	18 months
Park et al., 2023	11	IV	12	3/9	54.3 ± 7.8	High tibial osteotomy	Human umbilical cord blood-derived MSCs	Implanted into the drill holes	2.9 years
Stromal Vascular Fraction Prizov et al., 2022	12	III	10	n.a.	52.5	Medial opening wedge high tibial osteotomy	SVF	n.a.	18 months

Abbreviations: n.a. = not available; ADSCs = adipose-derived stem cells; BMAC = bone marrow aspirate concentrate; PRP = platelet-rich plasma; VSF = stromal vascular fraction; hUCB-MSC = hllogenic human umbilical cord mesenchymal stem cells; HA = hyaluronic acid.

PRP, ADSC, HVCBD, MSC, BMAC, and SVF present a consistent statistically significant clinical improvement compared to preoperative scores regardless of the treatment modality used and there were no notable complications associated with the use of these novel agents. The literature review highlights an intriguing scenario with increased studies focused on orthobiologic use along with knee osteotomies over the past decade and a clear-cut interest in these agents amongst clinicians from around the globe.

Knee osteotomies have shown promising short to medium-term clinical results but are also associated with progressive deterioration over prolonged follow-up periods [34–36]. Insall et al. reported good to excellent results at two years in >97% of patients, with a decline to 61% ten years post-surgery [37]. This could be attributed to osteotomies only restoring the anatomy of a malaligned knee but failing to address the pathophysiological alterations that occur in an osteoarthritic knee joint. Various cartilage repair procedures and knee osteotomies have been tried to address the physiology. A study has shown that the result of chondral repair procedures combined with knee osteotomies are inconsistent when treating OA knee, and specific procedures like the microfracture technique also led to various complications [7]. This could be because the chondral repair is meant for otherwise healthy knees which is not the case in a setting of osteoarthritis, as cartilage healing is hampered in an environment with raised inflammatory mediators.

It is required to address the entire mile area of the knee. Knee osteotomy is only meant for unloading the diseased cartilage so that it can be repaired by addressing the inflammatory process activated by the disease process, severely affecting the healing potential of the diseased cartilage.

Orthobiologics target the generalised environment of the knee joint and hence are gaining increasing popularity among knee surgeons to address the OA knee [38]. Orthobiologics contains various bioactive substances like growth factors, MSCs, cytokines and other molecules that could promote cartilage healing. Various orthobiologics have been tried to augment the osteotomies done for OA knees like PRP, MSC-based products BMAC, etc, and the results are promising even in normally aligned knees with OA.

PRP contains various biologically active proteins, such as PDGF, FGF, TGF and VEGF. It limits inflammation and aid in cellular proliferation [39]. Different formulations and methods of PRP administration, like leukocyte-rich PRP or leukocytes, depleted PRP with or without activators. A newer modality is photoactivated PRP, which improves inflammatory mediators & has a synergistic action with PRP [40], and this review shows the beneficial effects of concomitant PRP administration along with knee osteotomy in terms of improved postoperative functional scores and patient-reported outcomes of the patient. PRP can easily be prepared from the patient's blood and is easy to administer, making it an accessible adjunct to knee osteotomy.

Similarly, Adipose-derived stem cells are easily extractable in the adult population; they have the highest pluripotency and can differentiate into chondrocytes and tenocytes. These can easily be harvested from fat-rich areas like buttocks by a simple procedure, and the aspirate can be processed to extract Stromal vascular fraction [41–43]. ADSCs and SVF, when combined with knee osteotomies, have yielded favourable functional outcomes which are statistically significant. The rate of complications following their use in these patients is also negligible, making this one of the preferable orthobiologics to use with knee osteotomy surgery [19,20,22,44].

BMAC is another orthobiologic used along with knee osteotomies to treat malalignment in osteoarthritis knee. BMAC has progenitor cells with excellent regenerative potential. It is rich in MSCs and has a high concentration of IL-1Ra and 1L-1beta, which are anti-inflammatory [45] and have been shown to improve the functional outcome of patients undergoing HTO for virus/valgus malalignment with OA knee [23–25].

Similarly, human umbilical cord blood MSCs are novel orthobiologics to be used in orthopaedics; apart from typical stem cell characteristics, these have rich sources and convenient material extraction. Compared

Table 2
Clinical and radiographic outcomes of included studies.

Authors, year	KOOS		Lysholm		Tegner		IKDC		WOMAC		KSS		Femorotibial angle (°)		Posterior tibial slope (°)		HSS		Failures/ complications
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Adipose-derived stem cells																			
Magnanelli et al., 2020 [19]	-	-*	-	-*	-	-*	-	-*											
Kim et al., 2018 [20]			55.7 ± 11.9	84.7* ± 16.1			36.5 ± 4.7	64.8* ± 13.4					3.2 ± 1.8	8.9* ± 2.6	10.2 ± 2.9	10.3* ± 2.5			
Kim et al., 2023 [21]	Pain 42.4 ± 5.3 Symptom 41.2 ± 5.2 ADL 52.2 ± 6.2 Sports 23.3 ± 4.5 QOL 31.4 ± 6.6	Pain 79.5* ± 5.7 Symptom 81.2* ± 6.4 ADL 83.6* ± 5.8 Sports 64.4* ± 4.9 QOL 73.7* ± 6.0					38.5 ± 4.1	72.4* ± 6.1					3.4 ± 0.6	8.8* ± 0.3	10.3 ± 0.9	10.3* ± 0.8			
Kim et al., 2022 [22]	Pain 57.1 ± 21.4 Symptom 57.1 ± 23.7 ADL 56.6 ± 16.7 Sports 23.5 ± 15.1 QOL 33.9 ± 19.5	Pain 74.6* ± 9.3 Symptom 78.0* ± 10.6 ADL 82.1* ± 9.7 Sports 30.0* ± 19.1 QOL 48.1* ± 10.9							Pain 8.0 ± 4.0 Stiffness 4.1 ± 2.1 Function 33.8 ± 12.0 Total 45.9 ± 17.1	Pain 2.9* ± 1.3 Stiffness 1.4* ± 0.8 Function 12.8* ± 5.9 Total 17.1* ± 7.6									
Bone marrow aspirate concentrate																			
Jin et al., 2021§ [23]							35.3 ± 12.6	71.3* ± 11.2	46.9 ± 13.9	16.3* ± 9.8	Pain 27.2 ± 7.6 Function 58.9 ± 13.3	Pain 42.6* ± 7.2 Function 91.0* ± 10.2	Valgus −7.5 ± 3.4	Valgus 2.9* ± 2.5	8.0 ± 3.6	9.0 ± 4.0			
Lee et al., 2021 [24]									43.9 ± 12.7	23.4* ± 11.6	Pain 30.8 ± 11.0 Function 62.3 ± 11.9	Pain 40.6* ± 9.1 Function 80.1* ± 15.0	HKA 8.6 ± 3.1	HKA 2.8* ± 3.2	8.5 ± 3.9	8.8 ± 4.5	57.9 ± 12.9	79.2* ± 11.5	
Yang et al., 2022 [25]	Pain 42.3 ± 5.7 Symptom	Pain 81.7* ± 6.4			2.3 ± 0.9	4.0* ± 0.5	36.2 ± 3.0	72.8* ± 5.8					HKA 7.6 ± 2.9	HKA −1.5* ± 2.3	7.7 ± 2.4	8.5* ± 2.5			

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Table 2 (*continued*)

Authors, year	KOOS		Lysholm		Tegner		IKDC		WOMAC		KSS		Femorotibial angle (°)		Posterior tibial slope (°)		HSS		Failures/ complications
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
	40.9 ± 5.1 ADL 52.0 ± 7.1 Sports 23.8 ± 7.0 QOL 31.1 ± 4.8	Symptom 79.2* ± 7.5 ADL 82.4* ± 5.0 Sports 62.0* ± 11.9 QOL 72.4* ± 6.8																	
Wong et al., 2013 [26]			41.9	83*			33.9	82*											
Platelet-rich plasma																			
Dong et al., 2022§ [27]									69.54 ± 12.83	18.54 ± 4.17*									
Prizov et al., 2022 [28]	-	-*									-	-*	8.3	1.6*					
Zhang et al., 2022 [29]			63.2 ± 11.3	76.3* ± 12.0					106.0 ± 17.6	80.3* ± 13.2			mMPTA 83.5 ± 3.5 mFTA 4.1 ± 4.0	mMPTA 92.5* ± 2.9 mFTA 7.7* ± 2.3					
Koh et al., 2014 [30]			56.7 ± 12.2	80.6* ± 13.5									FTA 2.8 ± 1.7	FTA 9.8* ± 2.4					
Platelet-Rich Plasma + Vascular Stromal Fraction																			
Koh et al., 2014 [30]			55.7 ± 11.5	84.7* ± 16.2									FTA 3.4 ± 3.0	FTA 8.7* ± 2.3					
Allogenic Human Umbilical Cord																			
Kim et al., 2023 [21]	Pain 42.0 ± 6.1 Symptom 42.9 ± 5.8 ADL 52.3 ± 5.3 Sports 23.2 ± 4.6 QOL 31.4 ± 6.0	Pain 78.7* ± 5.1 Symptom 79.3* ± 5.7 ADL 83.9* ± 5.4 Sports 64.0* ± 5.2 QOL 72.6* ± 6.0					37.9 ± 4.3	71.8* ± 6.1					3.3 ± 0.5	8.8* ± 0.3	10.3 ± 0.9	10.3* ± 0.8			
Lee et al., 2021 [24]									45.2 ± 8.8	19.5* ± 15.8	Pain 31.6 ± 10.4 Function 63.1 ± 11.2	Pain 42.8* ± 7.9 Function 82.4* ± 15.5					56.1 ± 10.6	84.6* ± 15.5	

(*continued on next page*)

Table 2 (*continued*)

Authors, year	KOOS		Lysholm		Tegner		IKDC		WOMAC		KSS		Femorotibial angle (°)		Posterior tibial slope (°)		HSS		Failures/ complications
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Yang et al., 2022 [25]	Pain 41.4 ± 6.5 Symptom 39.5 ± 6.9 ADL 51.5 ± 8.4 Sports 23.7 ± 9.2 QOL 29.8 ± 6.3	Pain 83.1* ± 8.3 Symptom 79.4* ± 8.8 ADL 83.1* ± 5.8 Sports 63.2* ± 10.97 QOL 73.8* ± 8.7	35.4 ± 5.5	73.3* ± 9.8	2.2 ± 0.8	4.1* ± 0.5							HKA 7.5 ± 2.7	HKA −1.6* ± 2.2	7.9 ± 2.1	8.2* ± 2.5			
Song et al., 2020 [31]							-	-*					HKA 7.6°						
Suh et al., 2021 [32]				92.5 ± 3.9				69.0 ± 7.7						Mechanical axis −1.5 ± 1.4				84.0 ± 11.2	
Park et al., 2023 [33]									46.6	12.3			Varus 6.7°	Valgus 2.2°					
Stromal vascular fraction																			
Prizov et al., 2022 [28]	-	-*									-	-*	6.2	1.2*					

* = Statistically significant improvement compared to pre-op; - = not reported; KOOS = Knee Injury and Osteoarthritis Outcome Score; IKDC = International Knee Documentation Committee: WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; KSS = Knee Society Score; HSS = Hospital for Special Surgery Knee-Rating Scale.

Table 3
Analysis of study with a control group (isolated osteotomy).

Authors, year	Group comparison	Patients	M: F	Age	Clinical outcomes treatment group	Clinical outcomes control group	p-value
Suh et al., 2021 [32]	hUCB-MSC vs control group	43 vs 57	15/28 vs 12/45	56.5 vs 58.6	Lysholm 92.5	Lysholm 90.2	ns
					IKDC 69.0	IKDC 62.1	0.002[b]
					HSS 84.0	HSS 79.2	ns
Dong et al., 2022 [27]	PRP vs placebo/control group	24 vs 25	6/18 vs 6/19	56.64 vs 56.07	WOMAC 18.54	WOMAC 30.10	<0.05
					VAS 1.72	VAS 3.21	<0.05
Jin et al., 2021 [23]	BMAC vs control group	48 vs 43	11/37 vs 13/30	56.9 vs 55.8	IKDC 71.3	IKDC 67.0	>0.05
					WOMAC 16.3	WOMAC 20.4	>0.05
					KSS Pain 42.6	KSS Pain 39.7	>0.05
					KSS Function 91.0	KSS Function 88.8	>0.05
Kim et al., 2018 [20]	ADSCs vs control group	50 vs 50	16/34 vs 16/34	59.2 vs 58.3	IKDC 64.8	IKDC 56.8	0.049
					Lysholm 84.7	Lysholm 80.5	0.041
Kim et al., 2022 [22]	ADSCs vs control group	13 vs 13	2/11 vs 5/8	58.3 vs 59.1	WOMAC Total 17.1	Womac Total 23.7	0.343
					KOOS Pain 74.6	KOOS Pain 76.9	0.733
					KOOS Symptoms 78.0	KOOS Symptoms 78.6	0.891
					KOOS ADL 82.1	KOOS ADL 80.4	0.699
					KOOS Sports 30.0	KOOS Sports 38.5	0.385
					KOOS QoL 48.1	KOOS QoL 52.8	0.695
Magnanelli et al., 2020 [19]	ADSCs vs control group	42 vs 43	n.a	n.a.	Tegner	Tegner	>0.05
					IKDC	IKDC	>0.05
					Lysholm	Lysholm	>0.05
					KOOS Pain	KOOS Pain	>0.05
					KOOS Symptoms	KOOS Symptoms	>0.05
					KOOS ADL	KOOS ADL	<0.05[b]
					KOOS Sports	KOOS Sports	>0.05
					KOOS QoL	KOOS QoL	>0.05
Wong et al., 2013 [26]	BMAC vs control group	28 vs 28	15/13 vs 14/14	53 vs 49	Tegner	Tegner	<0.05[a b]
					Lysholm	Lysholm	<0.05[a b]
					IKDC	IKDC	<0.05[a b]
Zhang et al., 2022 [29]	PRP vs control group	39 vs 41	15/24 vs 14/27	52.7 vs 51.7	Lysholm 76.3	Lysholm 74.2	0.682
					WOMAC 106.0	WOMAC 81.7	0.562
					VAS 16.5	VAS 15.2	0.765

Abbreviations: n.a. = not available; HTO = high tibial osteotomy; ADSCs = adipose-derived stem cells; KOOS = Knee Injury and Osteoarthritis Outcome Score; IKDC = International Knee Documentation Committee: WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; KSS = Knee Society Score; HSS = Hospital for Special Surgery Knee-Rating Scale; BMAC = Bone Marrow Aspirate Concentrate; PRP = platelet-rich plasma; VSF = stromal vascular fraction; hUCB-MSC = allogenic human umbilical cord mesenchymal stem cells; VAS = visual analogue scale for pain.

[a] After adjustment for age, baseline scores, and time of evaluation.

[b] Statistical significant difference.

with stem cells from other sources, they have increased potential for proliferation, immune regulation and differentiation. They protect cartilage, reduce inflammation and promote cartilage synthesis simultaneously. The same has been shown by various studies which show improved postoperative outcomes of knee osteotomies when combined with concomitant use of hUCB-MSCs [24,25,31,32].

The current systematic review shows promising results concerning orthobiologics with knee osteotomies in treating patients with OA and varus/valgus malalignment. These orthobiologics can easily be harvested and are relatively easy to administer, unlike various added surgical procedures like chondral repairs in these patients, yielding inconsistent outcomes regarding postoperative function. Another aspect of the results worth focusing upon is the minimal rate of complications associated with using this newer modality along with the surgery.

This systematic review is based on all the recent studies; hence, the evidence generated is reliable and applicable to the current practice. However, there are various intrinsic limitations in the studies' designs; it is challenging to disintegrate the patients based on the grade of OA and the orthobiologic used. The dosage and frequency of administration of the orthobiologics are different, making the analysis of this study easier and more convenient. The superiority of one orthobiologic compared to the other still needs to be understood. More studies are required to compare different agents and functional outcomes of the patients after their use and to explore the synergistic actions of orthobiologics when given in combination. The number of studies included in the current systematic review is less as the use of orthobiologics in orthopaedics is in its early stage, and we can expect the addition of a sizeable amount of data to our existing knowledge in the coming years as the number of studies and interest of orthopaedic surgeons is increasing in the topic exponentially. In the current systematic review, 8 studies had a control group (isolated HTO) and out of these 8 studies, only 3 studies reported significant clinical differences against the control group. Therefore, further research is needed comparing isolated HTO vs HTO along with concomitant orthobiologics use.

The results can guide clinicians on using orthobiologics to improve the outcomes of knee-preserving surgeries, considering the importance of addressing the knee physiology, which is altered in osteoarthritis, and their practice can be backed by scientific evidence.

CONCLUSION

Orthobiologics and knee osteotomies could improve outcomes in patients with knee osteoarthritis desiring Knee preservation surgeries. However, only a few studies are available on the topic to conclude anything with certainty, the patients included in the studies could not be disintegrated based on grade of OA, type, dosage and frequency of administration of orthobiologic and type of additional surgical procedures used. Therefore, better-structured RCTs are required to implement this finding into routine Orthopaedic practice.

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Authors' contribution

Conceptualization, AM, AM, RD, MA, LF, NN, ST and MO; writing—original draft preparation, AM, RD, MA, AM, LF, ST and MO; writing—review and editing, AM, RD, MA, AM, LF, ST, NN and MO; supervision, ST, NN and MO; all authors interpreted the data, critically reviewed the work, made important contributions to the manuscript with their suggestions for improvement, approved the published version and agreed to be responsible for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

Informed consent

Not Applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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