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*EDITORIAL*

# Osteoarthritis, an old wine in a new bottle!

Sathish Muthu

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## Abstract

Osteoarthritis (OA) is the most common form of arthritis that has a major impact on patient morbidity and health care services. Despite its prevalence and impact, we do not have any effective management strategy to prevent or control their manifestations. Several decades of pharmacological development have failed to deliver a disease-modifying solution to OA. This editorial article outlines the lacunae in the research efforts of the past, the challenges that we are facing at present, and the exciting opportunities we have in the future for the management of OA. OA research has to be made more personalized concerning the phenotypic and endotypic disease variants. To begin with, robust disease classification criteria need to be defined for early OA, and biomarkers to detect such early diseases to aid in patient stratification. We also need to refine our clinical research design to make them more objective to meet the demands of the patient and the regulatory agencies. Embracing the current technologies such as artificial intelligence along with the use of genomic profiling from the omics platforms, the future of OA is more promising in developing appropriate management of OA.

**Key Words:** Osteoarthritis; Management; Phenotypes; Endotypes; Theratypes

**Core Tip:** We analyzed the current landscape of management of osteoarthritis (OA) and identified the challenges we are facing to develop an effective management strategy for OA at present and commented on the exciting opportunities available in the future. We also detailed the patient stratification based on the phonotypic and endotypic disease variants. We suggest that by embracing the current technologies such as artificial intelligence, and genomic profiling of patients, personalized management of OA is amenable with predictable results tailored for individual patient needs.

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## INTRODUCTION

Osteoarthritis (OA) remains the most common form of arthritis causing a huge burden on the health care system[1]. The prevalence of the disease keeps on increasing due to the aging population compounded by the increasing obesity epidemic. But we do not find comparable progress in disease control and its management options[2]. Over the past 3 decades, all the pharmacological ventures to develop a disease-modifying OA drug (DMOADS) have resulted in disappointing results making OA a "graveyard of drug development"[3]. Any drug that is being developed for OA cannot impact the structure of the joint as seen by radiographs and this has been the key reason for failure in the past decades of drug development for OA[4]. The clear expectations of the regulatory agencies such as the United States Food and Drug Administration for any DMOADs involve establishing the impact of the drugs on the subjective patient feeling, improvement in their function, and prolonged joint survival following the treatment[5].

## OA PHENOTYPES

OA is now being understood as a multifaceted heterogeneous disease with multiple causative factors, clinical phenotypes, and molecular endotypes[6]. The clinical phenotypes in OA refer to the cluster of visible properties such as associated mechanical deformities that individualize the disease expression in a certain group of patients[7]. Similarly, a comprehensive set of such visible parameters including age, sex, race, disease duration, symptoms, and radiological features such as joint space narrowing, osteophytes, and subchondral sclerosis needs to be utilized to characterize the patient's response to the treatment outcomes. The various phenotypes proposed for OA include chronic pain phenotype, inflammatory phenotype, metabolic syndrome phenotype, mechanical overload phenotype, minimal joint disease phenotype, senescent phenotype, endocrine phenotype, and sarcopenic phenotype as shown in Figure 1[6,8,9]. Prospective studies are needed to validate the efficacy of these phenotypic subtype-based management methods to surpass or prevent symptoms at an early stage before progressive and irreversible changes occur[10].

## OA ENDOTYPES

While the clinical phenotypes describe the presenting features of the OA individual, endotypes refer to the compilation of disease mechanisms that explains the disease expression in the group of patients. In OA, the disease expression is mostly based on a few typical endotypes such as inflammatory endotype, metabolic syndrome endotype, senescent endotype, endocrine endotype, and senescent endotype with characteristic biomarkers in serum and synovial fluid of the joint[6]. The biomarkers used in defining a characteristic endotype involve cartilage matrix destruction markers, proteases, subchondral bone matrix destruction markers, signaling markers, synovial inflammatory markers, and systemic inflammatory markers[11,12]. Hence a typical OA endotype may present as various OA phenotypes and on the contrary, every OA phenotype may have an overlap with various OA endotypes as illustrated in Figure 1 before presenting as an end-stage disease. Angelini *et al*[11] in their endotypic stratification based on clustering of biochemical marker data was proved to potentially drive the stratification of the clinical studies and contribute to precision medicine strategies for OA progression in the future.

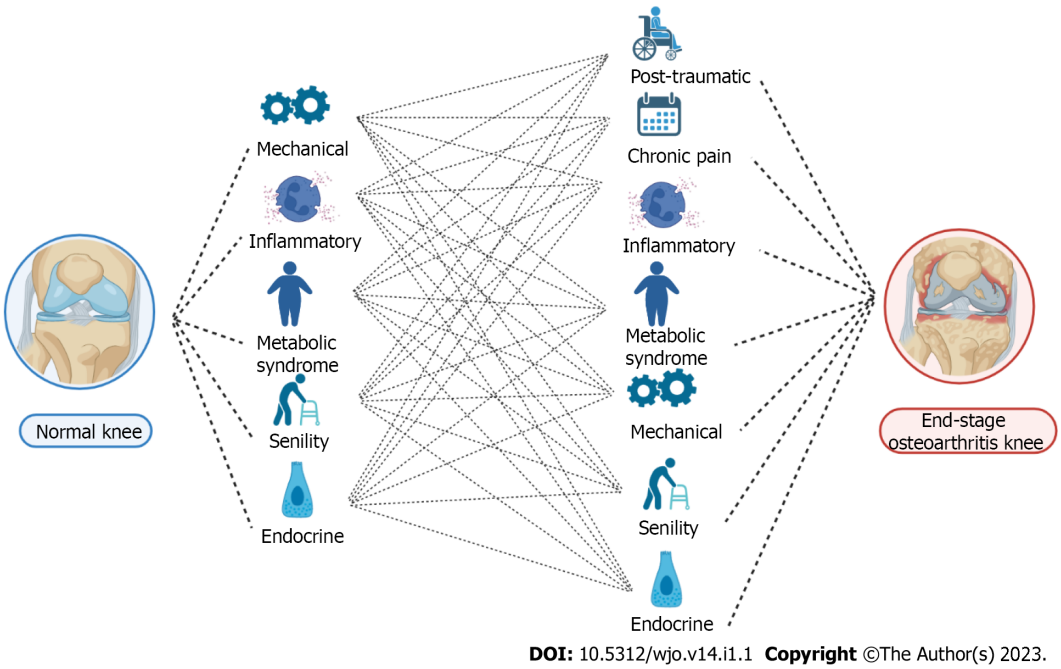


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**Figure 1 Illustration of the interplay between the various endotypes and phenotypes proposed in osteoarthritis.**

## CURRENT CHALLENGES

Having identified OA to be a multifactorial, heterogenous, multi-dimensional complex disease, the challenges before us to develop DMOADs include the introduction of the OA phenotypes and endotypes into clinical study designs to test the efficacy of biomarkers and newly developed DMOADs. Although we have various newer ortho-rheumatological tools to grade joint degeneration[13], we do not have a defined early disease identification and categorization tool to embark on the enrolment of patients in clinical studies. We do not have the necessary genetic and polyomic tools to stratify patients into therapeutic subgroups to test their efficacy. However, by harmonizing the data collection from the clinical studies in OA, true stratification of the patients by clinical data from all the interventional and observational studies provides the future to predict the response to treatment[14]. Current research has identified various key biomarkers such as oncostatin M, a cytokine from the interleukin-6 family, and metabolite of C-reactive protein was identified as candidate biomarkers to stratify the patients of inflammatory subtype[12]. However, the list is not sufficient to comprehensively enlist all the OA subtypes into their appropriate phenotypic and endotypic subclassification to tailor their clinical management algorithms.

## FUTURE RESEARCH PERSPECTIVES

Before the development of therapeutic DMOADs, measures to develop a robust early classification criterion for OA need to be established. The other main focus of future research in OA involves identifying the key biomarkers that would enable the categorization of OA patients into individual subtypes for optimal management. This involves studying the disease at a molecular level in the early stages without evident radiographic changes which enables us to distinguish between the molecular endotypes and corresponding phenotypes before all the phenotypes coalesce into a final common presentation as classical end-stage OA as shown in Figure 1.

Further, research on the key biomarkers that differentiate between the different subgroups of OA needs to be identified. The current platforms (*e.g.*, omics techniques) help in the assessment of a panel of markers to find their relationship with a particular phenotype rather than just a few markers tested in the conventional methods. The ideal substrate suitable for such categorization might be the local biochemical markers (*e.g.*, synovial fluid) that better distinguishes the molecular endotypes free from the systemic sources with noise such as comorbidities. With the identified phenotypic and endotypic markers in OA, we can identify the potential theratypes in OA where predicted treatment responses could be contemplated based on their endotypic categorization.

## CONCLUSION

Tailoring an effective early management strategy for OA involves the development of early disease identification methods, and disease stratification algorithms based on the distinctive phenotypic and endotypic expression in the individuals using their molecular signature patterns. The future of OA management is focussed more on prevention and early identification of disease process rather than redemption of the joint from an end-stage disease.

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*MINIREVIEWS*

# Update on surgical procedures for carpal tunnel syndrome: What is the current evidence and practice? What are the future research directions?

Valerio Pace, Fabrizio Marzano, Giacomo Placella

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## Abstract

Carpal tunnel syndrome (CTS) is a multifactorial compression neuropathy. It is reported to be very common and rising globally. CTS's treatment varies from conservative measures to surgical treatments. Surgery has shown to be an effective method for more severe cases. However few unclear aspects and room for further research and improvements still remains. We performed a narrative literature review on the most up to date progress and innovation in terms of surgical treatments for CTS. The simple algorithm of leaving the choice of the surgical method to surgeons' preference and experience (together with consideration of patients' related factors) seem to be the best available option, which is supported by the most recent metanalysis and systematic reviews. We suggest that surgeons (unless in presence of precise indications towards endoscopic release) should tend to perform a minimally invasive open approach release, favoring the advantage of a better neurovascular structures visualization (and a consequent higher chance to perform a complete release with long term relief of symptoms) instead of favoring an early reduction (in the first postoperative days) of immobilization and pain. Research towards a universally accepted standardization should be aimed for by the researchers, who have failed to date to sufficiently limit bias and limitations.

**Key Words:** Carpal tunnel; Carpal tunnel release; Transverse ligament; Endoscopic release; Open release

**Core Tip:** After reviewing the most up to date literature, it could be said that evidence of superiority of one technique over the others is lacking from a high level of evidence point of view. Specific advantages and disadvantages of surgical methods can however be taken into account when choosing among treatments. The simple algorithm of leaving the choice of the surgical method to surgeons' preference and experience (together with consideration of patients' related factors) seem to be the best available option, which is supported by the most recent metanalysis and systematic reviews.

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## INTRODUCTION

Carpal tunnel syndrome (CTS) is a multifactorial neuropathy caused by compression of the median nerve at the carpal tunnel. Its symptoms include pain, tingling or numbness affecting mainly the thumb, index and middle finger (sometimes the ring finger is also involved), with this sensation that could travel up the arm; hand weakness (mainly the thumb's pinching muscles).

The incidence of CTS in the general population is thought to be about 3%-4%; although it could reach 8% in the working population. Figures vary quite significantly among continents and countries, but unequivocally the trends suggest the CTS incidence and subsequent surgical management are rising globally[1-3].

The majority of cases seem to be idiopathic. Other causes such as fractures, infections and systemic diseases should also be taken into account. In fact the primary diseases should be properly assessed and treated, together with CTS in order to achieve complete resolution of symptoms[1-4].

The diagnosis is made with accurate history taking and clinical examination, supported by electromyography (EMG) and nerve conduction studies. Ultrasound has been used to aid diagnosis. Most people with mild to moderate symptoms are initially treated non-operatively. However surgery is thought to provide more effective and durable symptom relief, especially for the most severe cases[4].

Various surgical methods have been proposed and studied, with contradictory results. In fact little agreement on the best surgical procedure to treat CTS has been reached. Most of studies are characterized by significant limitations, which do not allow the clinicians to achieve a consensus on the matter [4,5].

Our aim is to present an update on surgical procedures for carpal tunnel syndrome, highlighting what the current evidence is, with advantages and limitations of the studied surgical methods. The final goal is to provide the most up to date scientific information in order to help the clinicians to maintain good practice with decisions based on the highest possible level of evidence.

## DIAGNOSIS

Accurate physical examination is warranted (after full history taking). It should include Tinel sign and Phalen sign, which are commonly utilized to reveal median nerve compression at the carpus. Durkan's compression test could also be used, but it is not useful to discriminate between symptomatic patients with and without EMG disturbances. The closed fist test is specific in these situations. Two-point discrimination is considered positive if greater than 4 mm. EMG shows that the median nerve transmission rate decreases and the latency period extends beyond normal values. Ultrasounds are sometimes used to aid diagnosis[4-7].

## SURGICAL MANAGEMENT

Surgical management is recommended after failure of conservative measures (splinting, physiotherapy, manual therapy, steroid injections, platelet-rich plasma injections, Kinesio taping, neurodynamic techniques, gabapentin, therapeutic ultrasound, and extracorporeal shockwave therapy) for mild and moderate cases of CTS, or for the most severe cases (numbness in the hand, atrophy of the hand muscles, restricted hand function). No high-grade clinical evidence currently supports specific surgical

indications. Surgery should be aimed at reduce the compression on the median nerve at the carpus, at the level of the transverse ligament. The cause of CTS should also be clearly identified, as the primary disease should be treated and resolved as well. However most of cases are thought to be idiopathic. For those cases, a carpal tunnel release is indicated[4,6-8].

## SURGICAL PROCEDURES

The first reported surgically treated cases of CTS we could found in the literature are the ones presented by Herbert Galloway in 1924. Since then, surgical methods have become more and more common. Many surgical options have been studied and proposed, but in the end the main open uncertainty is about the choice between open surgery and endoscopic assisted surgery. Ultrasound guided methods have also been developed[6-9].

### *Open carpal tunnel release*

Surgeons could use a traditional incision or a mini-incision. The landmarks for the traditional incision are the radial border of the hypothenar muscle, where the incision should be started and extended proximally till the distal wrist crease. 5 cm is the most common length of the incision, but it can be further extended to better visualize the structures. The mini-incision techniques include a transverse incision of about 2 cm on the ulnar side of the wrist stripes or a longitudinal incision starting from the mid-palm and ending at the most proximal portion of the palm. The main issues when using the two latter options are increased complexity, scar pain and increased chance of incomplete transverse ligament release. Other options such as double mini-incisions or other slightly different longitudinal incision options have been presented with promising results. Many studies have proved that all mini-incision technique are safe and provide good results[6,10,11].

After skin incision, the surgeon should go through the palmar fat and fascia, trough which the flexor retinaculum should be visualized. When adequately exposed, it should be completely split longitudinally, with decompression and visualization of the median nerve. Wound closure (skin stitches) and a wound dressing are the last surgical steps. Some authors have presented a method of open release through a small incision using a set of specially designed instruments, retaining advantages of observing the pathology under direct vision and avoiding complications of hazardous injuries to important structures. The instruments consist of a thin metal guide with a groove in the center to accommodate an angled knife holder. The procedure has been performed since 1997 with no complications[10,11].

Open carpal tunnel release (OCTR) has been reported to be a safe procedure overall. Only few cases of wound infections are reported. Scar formation on the palm could also be a complication, especially for traditional size incisions. The palmar nerve branch of the median nerve could also be damaged inadvertently during surgical exposure, as it arises at the distal part of the forearm palmarly and it divides into a medial and lateral branch, passing superficial to the flexor retinaculum of the hand. Another nerve that might be injured is the recurrent motor nerve branch of the median nerve, which normally supplies the thenar muscles. His injury might significantly affect the thumb function[9,11,12].

### *Endoscopic carpal tunnel release*

Single-portal and two-portal endoscopic carpal tunnel release (ECTR) have been reported. The first was introduced in 1986 by Okutsu *et al*[13] who started using the aid of endoscopy to perform carpal ligament release. This technique was used and modified by several other authors in the years, such as Agee and Linvatec[14].

Agee used an entry portal between the palmaris longus and the flexor carpi ulnaris at the level of the proximal wrist striatum. The palmaris longus tendon is then exposed after soft tissue dissection. The endoscope is then placed at the level of the ulnar side of the transverse ligament through the portal, and the ligament is cut from distal to proximal. Not good visualization of the neurovascular structures is the main issue of this approach[14-17].

Linvatec introduced a similar single-portal technique. The main characteristic and difference compared to the previous described technique is that the transverse ligament is cut from proximal to distal[14-17].

Among the two-portal ECTR, the Chow technique is the most widely used method. The first portal is made similarly to Agee method's entry portal, whilst the second portal is made in the palm surface (0.5-0.75 ncm in length) on the bisect line of the angle formed from the distal border of the fully abducted thumb and the third web space and approximately 1 cm proximal to the junction of these lines[18,19].

The surgeon should than push the sleeve till it enters into carpal tunnel from the entry portal and exits through the exit portal with the flexor tendon sliding. Cutting tools are then inserted into the sleeve and surgeons can cut the transverse ligament bilaterally under endoscopic monitoring[18,19].

It is thought that two-portal techniques allow a better visualization of the neurovascular structures and therefore they carry the lowest risk of complications and the higher chance to completely cut the transverse ligament. On the other hand, given the quite distal incision of the Chow technique, we must

say that the risk of injury to the arcus volaris superficialis is higher than in other endoscopic techniques, together with a higher risk of excessive palmar scar formation[15,16,18,19].

### *Comparison among surgical procedures*

A huge amount of work has been carried out and lots of papers published on the matter. Several reviews and metanalysis are also available. From the most up to date evidence it seems that no significant differences exist among the different surgical methods. However it must be said that relevant limitations often bias the results[12,15-17].

Results related to differences among mini-incision and traditional incision surgery are various and contradictory. There are studies reporting good outcomes and lower complication rates with mini-incision techniques. Undoubtedly a smaller approach results in less invasive surgery and this could contribute to better esthetic results both on the short and long run, with potential better patients' satisfaction. However symptoms resolution on the long run is the main objective of the performed surgery, and it is unclear whether open surgery could allow better results due to better visualization of the structures and reduced revision surgery rate. Similar results among mini and conventional approach have also been reported[19-24].

Despite what one could hypothesize regarding potential benefits of endoscopic procedures *vs* open surgery in terms of complication rate, operative time and outcomes and patients' satisfaction, overall data do not clearly highlight such advantages. Moreover most of papers present similar results. More evidence is present with regards to postoperative hand pain and recovery time, in favor of endoscopy procedures, allowing a quicker return to work and his consequent reduction of costs and resources. In fact open surgery (particularly the traditional approach) may prolong the immobilization time and augment postoperative pain and the risk for hypertrophic or hypersensitive scar formation. However the better visualization of the neurovascular structures allowed by the open procedures makes the latter safer from this point of view. However it must be said that most noted nerve injuries were transient, and patients still achieved full recovery after surgery. It should be taken as a worrying sign that often the choice between open and endoscopic surgery is left to surgeons' preference and experience, together with patients' related factors. It seems that a lack of universally accepted evidence on one of the most common syndromes and related surgical management still exist[15,16,20-23].

Among the endoscopic techniques, the majority of the studies have focused their attention on the two-portal technique, whilst fewer studies have reported the results of the Agee's technique. The latter is claimed to be used for his potentials of reducing the higher complication rates of the Chow's technique reported by some authors. Better results in terms of recovery time and return to work has been reported in favor of the single-portal techniques. However the utilization of just one portal could cause a not perfect visualization of the structures (including the transverse ligament), and this could lead to incomplete ligament section and the consequent recurrence of symptoms and the need of revision surgery[22-27].

Intuitively one could relate the endoscopic techniques to mini-incision techniques, as they are based on the same objectives (a smaller approach able to provide good or even better results). In fact surgeons utilizing these techniques aim to a better appearance of the scar (and less complications related to scarring processes) and a quicker recovery, with better patients' satisfaction and acceptance of the procedure. However insufficient evidence with regards of comparison between the two techniques is still present[26-29].

A mention to ultrasound-guided percutaneous carpal tunnel release is needed. Several authors have performed carpal tunnel release with such modality, reporting good results and claiming that it could be an effective treatment for CTS. However the overall level of evidence has been reported by review and metanalysis to be very low, with several studies with at least moderate risk of bias. A low complication rate and fast recovery have often been reported after such procedures[29-32].

Another special mention should be given to epineurotomy and flexor tenosynovectomy. They are often considered as a useful adjunct to the basic surgical procedure, but their indications are still controversial. It seems that tenosynovectomy is only recommended for patients with rheumatic disease (or inflammatory risk factors), or patients undergoing chronic hemodialysis. The intraoperative finding of excessive or abnormal synovial tissues makes a tenosynovectomy also indicated[33-37] Table 1.

## CONCLUSION

There has been controversy regarding the superiority of ECTR over OCTR in the last decades. Many original articles have been published on this issue; moreover, several meta-analyses have compared ECTR with OCTR as treatment options for CTS, but relevant bias and limitations have commonly been reported. Therefore a universal consensus has not been achieved yet, even if CTS is a very common pathology and his surgery is routinely and widely performed[26,27].

Over the years the wrist anatomy knowledge has improved and various surgical instruments and methods have been studied and presented. Sufficient effectiveness has always been reported, but a high quality evidence is lacking.

**Table 1 Advantages of surgical options (risk of hypertrophic or hypersensitive scar formation should be considered secondary, despite temporary discomfort for the patients)**

| Advantages of open release | Advantages of endosopic release |
|---|---|
| Good outcomes | Good outcomes |
| Low complication rates | Low complication rate (slightly better the open release) |
| Mini-incision: best approach and better patients' satisfaction | Better esthetic results (much smaller scars) |
| Reduced revision surgery rate | Reduced risk for hypertrophic or hypersensitive scar formation |
| Better visualization of structures | Reduced postoperative hand pain |
| Safest approach for neurovascular structures | Reduced recovery time |
| Possibility to use a mini-incision approach | Quicker return to work |
| Possibility to perform epineurotomy and flexor tenosynovectomy | Reduced costs and resources |

Many studies determined that ECTR was superior to OCTR in terms of higher satisfaction rates, improved key pinch strengths, earlier recovery times, and fewer scar-related complications. This suggests that patients with CTS can be effectively managed with ECTR; however, the possibility of transient nerve injury should be considered. However most of studies are characterized by significant limitations, which do not allow the clinicians to achieve a consensus on the matter. Clear and high level of evidence advantages of one technique over the others have not been provided yet, and sufficient results seem to be provided with any of the studied methods[4,5,26-29,38].

We believe that the lack of high level of evidence regarding the surgical techniques should be taken as a worrying sign, especially because clear evidence is most of the time provided for the most common diseases and related management options. In fact it seems that often the choice between open and endoscopic surgery is left to surgeons' preference and experience, together with patients' related factors. To date, this simple algorithm has shown to be able to provide the best results. Surgeons should refrain from attempting potentially less invasive procedures if not familiar with the technique, as the risks of arming would outweigh the potential better results.

Relevant authors tend to strongly recommend their proposed technique, commonly providing evidence of excellent results and elements in favor of their method over the other ones. However when it comes to systematic reviews and metanalysis, data suggest that relevant bias and limitations do not allow standardization and do not provide sufficient evidence of the superiority of a technique over the others.

We suggest that surgeons (unless in presence of precise indications towards endoscopic release) should tend to perform a minimally invasive open approach release, favoring the advantage of a better neurovascular structures visualization (and a consequent higher chance to perform a complete release with long term relief of symptoms) instead of favoring an early reduction (in the first postoperative days) of immobilization and pain. Moreover, in view of higher chances to obtain long term symptoms relief, the risk of hypertrophic or hypersensitive scar formation should be considered secondary, despite temporary discomfort for the patients Table 1.

We believe there is room for further research evidence, possibly high level of evidence works (level 1 or 2) which should separately study specific aspects and provide detailed and clear advantages and disadvantages of every single treatment option. Cohorts should be sufficiently big and bias reduced to the minimum. The problem of the current heterogeneity should also be overcomed.

CTS is becoming more and more common, as is its surgical management. This constitutes a significant economic burden for societies. All surgical techniques have provided satisfactory results and have been proven to be effective options. After reviewing the most up to date literature, it could be said that evidence of superiority of one technique over the others is lacking from a high level of evidence point of view. Specific advantages and disadvantages of surgical methods can however be taken into account when choosing among treatments. The simple algorithm of leaving the choice of the surgical method to surgeons' preference and experience (together with consideration of patients' related factors) seem to be the best available option, which is supported by the most recent metanalysis and systematic reviews. Research towards a universally accepted standardization should be aimed for by the authors, who have failed to date to sufficiently limit bias and limitations.

## FOOTNOTES

**Author contributions:** Pace V, Marzano F, and Placella G designed the article, performed research and literature review, analyzed data and wrote the review.

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*MINIREVIEWS*

# Polydactyly: Clinical and molecular manifestations

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## Abstract

Polydactyly is a malformation during the development of the human limb, which is characterized by the presence of more than the normal number of fingers or toes. It is considered to be one of the most common inherited hand disorders. It can be divided into two major groups: Non-syndromic polydactyly or syndromic polydactyly. According to the anatomical location of the duplicated digits, polydactyly can be generally subdivided into pre-, post-axial, and mesoaxial forms. Non-syndromic polydactyly is often inherited with an autosomal dominant trait and defects during the procedure of anterior-posterior patterning of limb development are incriminated for the final phenotype of the malformation. There are several forms of polydactyly, including hand and foot extra digit manifestations. The deformity affects upper limbs with a higher frequency than the lower, and the left foot is more often involved than the right. The treatment is always surgical. Since the clinical presentation is highly diverse, the treatment combines single or multiple surgical operations, depending on the type of polydactyly. The research attention that congenital limb deformities have recently attracted has resulted in broadening the list of isolated gene mutations associated with the disorders. Next generation sequencing technologies have contributed to the correlation of phenotype and genetic profile of the multiple polydactyly manifestations and have helped in early diagnosis and screening of most non-syndromic and syndromic disorders.

**Key Words:** Polydactyly; Gene; Syndromic; Non-syndromic; Preaxial; Postaxial

**Core Tip:** The molecular basis of hand and foot polydactyly, syndromic or non- syndromic, is diverse. There are several phenotypes of the disorder which are correlated to a specific molecular profile and other whose molecular basis is still unclear. We summarize and provide an overview of gene mutations that cause hand and foot polydactyly as an isolated disorder or as part of a syndrome and present the clinical manifestations that they cause.

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## INTRODUCTION

Non-syndromic (Table 1) or syndromic polydactyly (Table 2) is often inherited with an autosomal dominant trait with variable penetrance[1]. It is related with a disturbance of the anterior–posterior axial development procedure of the limb[2] and is classified into preaxial, axial (central), and postaxial polydactyly[3]. Preaxial polydactyly is defined as an extra digit affecting the radial/tibial digits while postaxial involves the ulnar/peroneal digits. The rare type of axial (central) polydactyly refers to the duplication of three central hand or foot digits. Mirror-image polydactyly and Haas-type polysyndactyly are rare and distinct types, not fitting to the three categories[4].

Many specific phenotypes, including all types of hand and foot polydactyly, have been identified and correlated to gene mutations[5].

Since polydactyly is often a part of a syndrome, the ability to identify the potential syndromes associated with this anomaly is very important for the clinician. Additionally, it is important to distinguish between syndromic and non-syndromic cases for reasons of genetic counselling. In this paper, we review the recent progress in the molecular genetics, including clinical and molecular manifestations of disorders, and present some representative syndromes including polydactyly as a phenotype.

## CLINICAL AND MOLECULAR MANIFESTATIONS OF NON-SYNDROMIC HAND AND FOOT POLYDACTYLY

### *Preaxial polydactyly*

The preaxial form of polydactyly is the second most common phenotype behind the postaxial with a reported prevalence of approximately 0.8 to 2.3 in 10000 live births. It is characterized by an extra digit on the tibial/radial side of limb (Figure 1). The following classification has been suggested:

Preaxial polydactyly type I, which is thumb polydactyly (*OMIM 174400*)[6]—characterized by duplication of one or more skeletal elements of a biphalangeal thumb.

Preaxial polydactyly type II, which is polydactyly of a triphalangeal thumb (*OMIM 174500*).

Preaxial polydactyly type III, which is polydactyly of the index finger, characterized by the presence of one or two triphalangeal digits (*OMIM 174600*).

Preaxial polydactyly type IV and syndactyly of various degrees involving the middle and ring finger/second and third toe (*OMIM 174700*) or hallux polydactyly (*OMIM 601759*)[7].

**Preaxial polydactyly type I:** Thumb polydactyly is usually observed in unilateral form. In bilateral cases, hands are more often affected and the left hand is also more often affected than the right. It follows an autosomal dominant inheritance model[7]. However, a recent study in a Pakistani family has revealed a rare autosomal recessive form of preaxial polydactyly, linked to a novel variant (c.1517T>A; p. Leu506Gln) in the *GLI1* gene on chromosome 12q13.3[8].

The most commonly used classification is Wassel classification which divides thumb duplication into six subtypes according to the level and the extent of duplication (partial or complete)[9]. Hallux polydactyly is known to exist as a predominant presentation or an isolated disorder. The incidence of hallux duplication is 2.4/100000 as compared to thumb polydactyly incidence in South America, which is 1.65/10000.

Preaxial type I polydactyly is caused by sequence variants in the sonic hedgehog (*SHH*) enhancer, called zone of polarizing activity (*ZPA*) regulatory sequence (*ZRS*), which is regulated by *LMBR1* gene.

**Table 1 Mutated genes isolated in non-syndromic polydactyly**

| Preaxial | Central | Postaxial | Complex |
|---|---|---|---|
| *CEP290* | *CPLANE1* | *GLI3* | *MIPOL1* |
| *RPGRIP1* | | *ZNF141* | *PITX1* |
| *TMEM216* | | *DACH1* | *LMBR1* |
| *FBN1* | | *GLI1* | |
| *CEP164* | | | |
| *MEGF8* | | | |
| *LMBR1* | | | |
| *ZRS* | | | |
| *GLI3* | | | |
| *ZNF141* | | | |
| *STKLD1* | | | |
| *GLI1* | | | |
| *KIAA0586* | | | |
| *EVC* | | | |
| *HES1* | | | |

**Table 2 Mutated genes isolated in syndromic polydactyly**

| Syndrome | Mutated gene(s) |
|---|---|
| Bardet-Biedl | *CCDC28B, ARL6, MKS1, BBS8, SDCCAG8, LZTFL1, WDPCP, BBS4, BBS12, TMEM67, BBS1, BBS2, BBS6, BBS10, BBS9, BBS7, BBS5, CEP290, TRIM32, BBIP1, ALMS1, MKKS* |
| McKusick-Kaufman | *MKKS* |
| Carpenter | *P4HB, RAB23* |
| Saethre-Chotzen | *TWIST1, FGFR2* |
| Poland syndrome | - |
| Greig cephalopolysyndactyly | *GLI3* |
| Short-rib polydactyly | *ATD1, LBN, DYNC2H1, IFT81* |
| Pallister-Hall | *GLI3* |
| Triphalangeal thumb-polydactyly | *LMBR1* |
| Smith-Lemli-Opitz | *DHCR7* |

Mutations in *CEP290, RPGRIP1, TMEM216, FBN1, CEP1*, and *MEGF8* genes have been isolated and suspected to play a role in Wassel III and Wassel IV manifestations[10]. Recently, a mutation in *STKLD1* gene, located on chromosome 9q34.2, was found and correlated with the disease phenotype in all members of the studied family[11]. Another molecular study of the *SHH/GLI* signaling axis, identified *HES1* gene as a downstream modifier which can cause preaxial polydactyly[12].

Next generation sequence analysis in a large four-generation family with isolated preaxial polydactyly revealed a new *ZRS* mutation (g.101779T>A) which can cause the disease phenotype[13]. Another recent genetic analysis of 20 Chinese patients with preaxial polydactyly identified two novel mutations in *GLI3* gene (c.G2844A) and in *EVC* gene (c.1409_1410del). Mutations in *KIAA0586* gene, which are related with ciliopathies (*OMIM 610178*), were also detected[14].

**Preaxial polydactyly type II:** Preaxial polydactyly type II is characterized by the presence of a usually opposable triphalangeal thumb with or without additional duplication of one or more skeletal components of the thumb. The thumb appearance can differ widely in shape or it can be deviated in the radio-ulnar plane. It can also be associated with Holt-Oram syndrome and Fanconi anemia. *LMBR1* and its related pathways *Wnt/Notch* and *Hedgehog* play a significant role in the development of the disorder. The disease gene locus was mapped to chromosome 7q36[15]. Mutations in the *SHH* regulatory factor

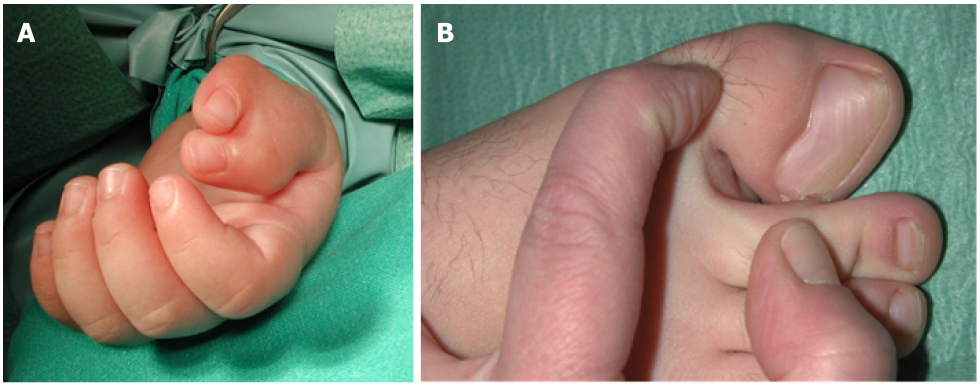


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**Figure 1 Preaxial polydactyly.** A: Preaxial/radial hand polydactyly phenotype; B: Preaxial/tibial foot polydactyly phenotype.

were also reported[16]. Two mutations, a 739A>G transition near the 5- end of the *ZRS* and a 621C>G mutation in the *ZRS* of the *LMBR1* gene, were identified[17]. Triphalangeal thumb-polysyndactyly can manifest as a syndrome. It is an isolated limb deformity characterized by pre- and postaxial polysyndactyly of hands and feet. Mutations in *ZRS* have been identified[18,19].

**Preaxial polydactyly type III:** Preaxial polydactyly type III is an autosomal dominant disorder which is characterized by a malformation of fingers, where the thumb is replaced by one or two triphalangeal digits with dermatoglyphic pattern specific for the index finger. It can occur unilaterally and bilaterally. No responsible gene has been identified[20].

**Preaxial polydactyly type IV:** Preaxial polydactyly type IV is an autosomal dominant disorder which can be described as mild duplication of the thumb, syndactyly that affects the third and fourth hand/foot fingers/toes, duplication of the first or second toes, and toes syndactyly. There are patients who have only foot malformations. *GLI3* gene mutations are associated with the disorder. Genetic analysis in two families with the phenotype were found heterozygous for p.L1216PfsX31 and p.R290X mutations in the *GLI3* gene[21].

### *Postaxial polydactyly*

Postaxial polydactyly is a frequent congenital hand malformation characterized by fifth digit duplications in hands and/or feet (Figure 2). Its prevalence is estimated between 1/630 and 1/3300 in Caucasian race and between 1/100 and 1/300 in Black race. Two phenotypic categories have been described: Type A, the extra digit is well formed and articulates with the fifth or an extra metacarpal; Type B, there is a rudimentary extra fifth digit which is usually represented by an extra skin tag. Both types can be inherited by autosomal dominant or recessive trait[22]. There are six subcategories of type A postaxial polydactyly.

**Postaxial polydactyly type A1:** In postaxial polydactyly type A1, the extra digit is well-formed and articulates with the fifth or a sixth metacarpal/metatarsal. Genetic analysis in an Indian family resulted in the identification of association of *GLI3* gene mutations with the phenotype[23]. It was mapped to 7pl5-q11.23. Mutation in the C- and the N-terminal or the zinc finger domain of the *GLI3* gene causes isolated postaxial polydactyly type A1 and is also linked to Greig cephalopolysyndactyly syndrome, while a mutation in the post-zinc finger region is incriminated for Pallister–Hall syndrome[24]. A recent genetic study in a Chinese family with isolated postaxial polydactyly revealed a new mutation of *GLI3* (c.1180C>TT, p.P394fs18x)[25]. A *DACH1* gene mutation was identified in a patient with bilateral postaxial polydactyly who was subjected to whole exome sequencing[26]. New mutations of the *GLI1* gene have been incriminated for postaxial polydactyly according to a novel study which aims to help in prevention of the disorder[27].

**Postaxial polydactyly type A2:** It consists of Type A polydactyly phenotypes with an extra digit well-formed. A genetic study of an Indian kindred revealed disease gene locus of postaxial polydactyly type A2 (*OMIM 602085*) which was mapped to 13q21-q32[28]. The underlying gene for the disorder has not been identified.

**Postaxial polydactyly type A3:** It manifests with polydactyly phenotypes Type A/B in hands and feet. Genetic analysis of a Chinese family discovered incomplete penetrance of the phenotype and identified the disease gene locus which was mapped to 19p13.2-p13.1[29]. There is not an identified gene responsible for the disorder.

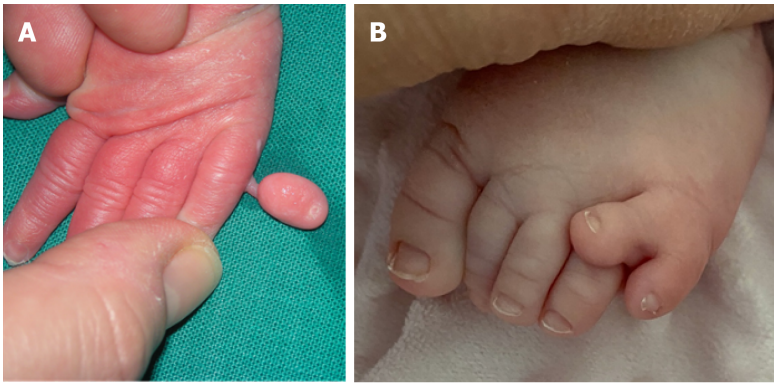


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**Figure 2 Postaxial polydactyly.** A: Postaxial/ulnar hand polydactyly phenotype; B: Postaxial/fibular foot polydactyly phenotype.

**Postaxial polydactyly type A4:** It is characterized by polydactyly phenotypes Type A/B in hands and feet and two to three finger/toe syndactyly. The disease locus (*OMIM 608562*) was mapped to 7q21-q34 by genetic analysis in a Dutch family with an autosomal dominant inheritance of the phenotype[30]. Until now there is no candidate gene for this manifestation.

**Postaxial polydactyly type A5:** It is characterized by polydactyly of hands and feet, minor syndactyly, and five to six metacarpal synostoses. Two Indian families and a Sicilian family were identified to have this type of autosomal recessive postaxial polydactyly[31]. Postaxial polydactyly type A5 (*OMIM 263450* ) was mapped to 13q13.3- 13q21.2 region. The underlying gene for this phenotype has not yet been identified.

**Postaxial polydactyly type A6:** The phenotype is characterized by an extra functionally developed digit in hands and/or feet. Mutations in the *ZNF141* gene are considered to cause postaxial polydactyly type A6 (*OMIM 615226*). Exome sequencing in a Pakistani family resulted in showing autosomal recessive inheritance of A6 phenotype. The *ZNF141* gene consists of four exons[32]. The final protein is expressed in many different tissues and it is still unclear whether it plays a role in embryogenesis[33].

**Postaxial polydactyly type B:** It is the most common type of polydactyly. There is a vestigial nonfunctional, partially formed, ulnar (or fibular) digit with no bony attachments, attached by a narrow neurovascular pedicle to the lateral aspect of the hand or foot[25]. *GLI3* gene mutations are associated with this often manifestation.

### *Central polydactyly*

Central polydactyly (*OMIM 174200*) is a very rare phenotype which is characterized by duplication of one of the three middle digits of the hand and foot. It can be an isolated defect or can be accompanied with other anomalies. The most often manifestation of hand central polydactyly is duplication of the fourth digit[3]. Foot central polydactyly is very rare and the second toe is most commonly duplicated [34]. Central polydactyly is related to split-foot malformation with mesoaxial polydactyly and Holzgreve syndrome. *CPLANE1* is the only known gene which is associated with central polydactyly.

### *Complex types*

**Mirror image polydactyly:** This rare non-syndromic limb malformation (*OMIM 135750*) presents with mirror-image hand or foot polydactyly. The malformation can be unilateral, bilateral, and very rarely tetramelic. It can be associated with other congenital anomalies or can present isolated. *MIPOL1* and *PITX1* gene mutations have been identified and incriminated for this disorder. A recent German study in a patient with the phenotype showed a heterozygous deletion of 4.9 Mb on 5q31 including *PITX1*[35].

**Haas-type polysyndactyly:** Haas-type polysyndactyly (*OMIM 186200*) is characterized by complete cutaneous syndactyly of all hand fingers and occasionally foot toes are affected. It frequently presents with polydactyly with six digits and six metacarpals. It is inherited with an autosomal dominant trait. It is usually classified as syndactyly type IV. The locus for Haas-type polysyndactyly was mapped on 7q36 by linkage and haplotype analysis of a Chinese family[36]. Mutations of the *ZRS* region of *LMBR1* gene and other *ZRS* point mutations were found in families presenting with the clinical sings of Haas-type polysyndactyly according to two recent studies[37,38].

## CLINICAL AND MOLECULAR MANIFESTATIONS OF SYNDROMIC HAND AND FOOT POLYDACTYLY

### *Bardet-Biedl syndrome*

Bardet-Biedl syndrome (*OMIM 209900*) is an autosomal or digenic recessive disorder which can present with vision loss, obesity, hand and/or foot polydactyly, intellectual disabilities, and hypogonadism. Mutations in at least 20 genes have been identified and associated with the syndrome[39]: *CCDC28B*, *ARL6*, *MKS1*, *BBS8*, *SDCCAG8*, *LZTFL1*, *WDPCP*, *BBS4*, *BBS12*, *TMEM67*, *BBS1*, *BBS2*, *BBS6*, *BBS10*, *BBS9*, *BBS4*, *BBS7*, *CEP290*, *TRIM32*, *BBIP1*, *IFT27,* and *IFT172*genes are examples of them. A recent study in four Iranian children with a clinical diagnosis of Bardet-Biedl syndrome identified in three children one previously reported mutation in *BBS12* gene (c.265-266delTT, p.L89fs) and two newly detected mutations in *MKKS* (c.1196T>G, p.L399X) and *BBS7* gene (c.1636C>T, p.Q546X). A new mutation in *ALMS1* gene was isolated in the other child[40].

### *McKusick-Kaufman syndrome*

McKusick-Kaufman syndrome's phenotype (*OMIM 236700*) consists of the following features: Genitourinary malformations (hydrometrocolpos, glanular hypospadias, and prominent scrotal raphe), postaxial hand and/or foot polydactyly, and rarely cardiac defects. *MKKS* gene mutations are associated with McKusick-Kaufman syndrome and they are inherited with an autosomal recessive trait [41].

### *Carpenter syndrome*

Carpenter syndrome (*OMIM 201000*) is characterized by craniosynostosis, involving a pointed head (acrocephaly), syndactyly of certain fingers or toes, and polydactyly. It appears most commonly with foot polydactyly, rarely hand polydactyly and hand or toe cutaneous syndactyly. *RAB23* gene mutations are associated with the syndrome, which appears with autosomal recessive inheritance[42]. Recent molecular studies have identified two new mutations in *RAB23* gene (NM_001278668:c.T416C:p.Leu139-Pro and NM_016277.5:c.398+1G>A)[43] and a new mutation in *P4HB* gene [44].

### *Saethre-Chotzen syndrome*

Saethre-Chotzen syndrome's phenotype (*OMIM 101400*) is characterized by premature closure of cranial sutures, hand syndactyly, and foot polydactyly. Foot polydactyly most often involves the first toe. *TWIST1* and *FGFR2* gene mutations are usually incriminated and inherited with an autosomal dominant trait[45].

### *Poland syndrome*

Poland syndrome (*OMIM 173800*) involves underdeveloped pectoralis muscles on one side of chest wall and ipsilateral hand abnormalities, including short fingers and syndactyly (symbrachydactyly); however, there are rare cases of preaxial polydactyly manifestations in the literature[46]. Most cases of Poland syndrome are not related with a family history, and they are sporadic. Rarely it is inherited with an autosomal dominant trait through generations in families. There are no isolated gene mutations correlated with Poland syndrome.

### *Greig cephalopolysyndactyly syndrome*

Greig cephalopolysyndactyly (*OMIM 175700*) syndrome is an autosomal dominant syndrome, which presents with hypertelorism, macrocephaly, and polydactyly. The polydactyly is most commonly preaxial of the feet and postaxial in the hands. Greig cephalopolysyndactyly is associated with *GLI3* mutations[47]. Recently, molecular studies have broadened the spectrum of known *GLI3* mutations correlated with the syndrome[48,49].

### *Pallister-Hall syndrome*

Pallister-Hall syndrome (*OMIM 146510*) is a rare disorder which affects many parts of the body. Very often manifestation of the syndrome is postaxial polydactyly and cutaneous syndactyly of hands and toes. *GLI3* gene mutations are considered responsible for this autosomal dominant disorder[50].

### *Short-rib polydactyly*

Jeune syndrome, Ellis-van Creveld syndrome, Saldino-Noonan syndrome, and Majewski syndrome are called short-rib polydactyly syndromes (*OMIM 613091*). They belong to a group of lethal congenital disorders characterized by shortening of the ribs and long bones, hand and/ or foot polydactyly, and a range of extraskeletal phenotypes. *ATD1* gene is considered to be responsible for Jeune syndrome. *LBN* gene mutations cause Ellis-van Creveld syndrome and individuals carrying *DYNC2H1* gene mutations can present with Saldino-Noonan and Majewski syndromes. Novel exome sequencing studies have isolated two new mutations in *DYNC2H1* gene (c.8077G>T and c.11741_11742delTT) and a new mutation in *IFT81* gene, causing malformation of the cilia[51,52]. Short-rib polydactyly syndromes are

usually inherited with an autosomal recessive trait[53].

### *Triphalangeal thumb-polydactyly syndrome*

Triphalangeal thumb-polydactyly syndrome (*OMIM 173800*) consists of triphalangeal thumbs, pre- or post-axial polydactyly, and syndactyly. *LMBR1* gene is considered to be responsible for this manifestation. It is inherited with an autosomal dominant genetic trait. Typically, the syndrome presents with duplicated triphalangeal thumbs and typical phenotypic findings include duplicated triphalangeal thumbs and syndactyly between middle, ring, or little finger[54].

### *Smith-Lemli-Opitz syndrome*

Smith-Lemli-Opitz syndrome (*OMIM 173800*) is a multi-malformation syndrome. The responsible gene for this syndrome is considered to be *DHCR7* gene and it is inherited with an autosomal recessive pattern[55]. Its phenotype contains foot syndactyly (usually of 2$^{nd}$ and 3$^{rd}$ toes) and postaxial hand polydactyly.

## CONCLUSION

Genetic mechanisms which combine epigenetic and environmental factors play a significant role in foot and hand polydactyly manifestations[56]. Proper genotype-phenotype correlations might help in future genetic testing and enhance our knowledge about identified diseases and their associated genes. Recent genetic analysis techniques of extra foot or hand digit formation highlight the existence of nongradual transitions in phenotypes, suggesting a distinction between continuous and discontinuous variation in evolution. Genome sequencing will probably lead to the discovery of a number of new gene mutations responsible for non-syndromic or syndromic polydactyly. Clinical manifestation and genetic profile correlation of polydactyly types will be further established by use of bioinformatics analysis of gene mutations. Progress of prenatal diagnosis, which is still mostly postnatal, prenatal operative treatment planning, and potential future gene modification treatment will be enhanced and unknown molecular background of diseases, which is to date unclear, will be elucidated.

## FOOTNOTES

**Author contributions:** Kyriazis Z wrote the paper and participated in the collection of the data; Dailiana ZH, Kollia P, and Grivea I participated in the conception of the study, and interpretation and collection of the literature data; Stefanou N and Sotiriou S participated in the collection of the literature data; all authors have read and approved the final manuscript.

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META-ANALYSIS

# Comparative effectiveness of adipose-derived mesenchymal stromal cells in the management of knee osteoarthritis: A meta-analysis

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## Abstract

***BACKGROUND***

Osteoarthritis (OA) is the most common joint disorder, is associated with an increasing socioeconomic impact owing to the ageing population.

***AIM***

To analyze and compare the efficacy and safety of bone-marrow-derived mesenchymal stromal cells (BM-MSCs) and adipose tissue-derived MSCs (AD-MSCs) in knee OA management from published randomized controlled trials (RCTs).

***METHODS***

Independent and duplicate electronic database searches were performed, including PubMed, EMBASE, Web of Science, and Cochrane Library, until August 2021 for RCTs that analyzed the efficacy and safety of AD-MSCs and BM-MSCs in the management of knee OA. The visual analog scale (VAS) score for pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, Tegner score, magnetic resonance observation of cartilage repair tissue score, knee osteoarthritis outcome score (KOOS), and adverse events were analyzed. Analysis was performed on the R-platform using OpenMeta (Analyst) software. Twenty-one studies, involving 936 patients, were included. Only one study compared the two MSC sources without patient randomization; hence, the results of all included studies from both sources were pooled, and a comparative critical analysis was performed.

***RESULTS***

At six months, both AD-MSCs and BM-MSCs showed significant VAS improvement ($P = 0.015$, $P = 0.012$); this was inconsistent at 1 year for BM-MSCs ($P < 0.001$, $P = 0.539$), and AD-MSCs outperformed BM-MSCs compared to controls in measures such as WOMAC ($P < 0.001$, $P = 0.541$), Lysholm scores ($P = 0.006$; $P = 0.933$), and KOOS ($P = 0.002$; $P = 0.012$). BM-MSC-related procedures caused significant adverse events ($P = 0.003$) compared to AD-MSCs ($P = 0.673$).

***CONCLUSION***

Adipose tissue is superior to bone marrow because of its safety and consistent efficacy in improving pain and functional outcomes. Future trials are urgently warranted to validate our findings and reach a consensus on the ideal source of MSCs for managing knee OA.


**Key Words:** Mesenchymal stromal cell; Adipose tissue-derived mesenchymal stromal cell; Bone-marrow derived mesenchymal stromal cell; Cartilage regeneration; Knee osteoarthritis; Meta-analysis; Efficacy; Safety



**Core Tip:** With the ongoing rise in the exploration of the clinical efficacy of mesenchymal stromal cells (MSCs) in the management of osteoarthritis (OA), there is an imminent need to identify the ideal source of MSCs to be utilized. Our meta-analysis has brought out the lacunae in the literature for studies to evaluate the impact of the source of MSCs in the management of OA. From a single-arm meta-analysis of available studies on the two commonly used sources such as bone marrow (BM) and adipose tissue, we found the adipose tissue to be superior to BM concerning the safety and consistent efficacy in improving pain and functional outcomes. However, considering the paucity of evidence, we recommend future trials to validate our findings and reach a consensus on the ideal source of MSCs for managing knee OA.

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## INTRODUCTION

Osteoarthritis (OA) of the knee is the world's leading cause of degenerative joint disease leading to

articular cartilage damage resulting in pain, stiffness, and loss of joint mobility[1]. Owing to the hypovascular and aneural nature, the articular cartilage has a decreased integrity for intrinsic repair mechanisms[2]. The management of OA knee aims to provide painless functional joint with a full range of motion. To minimize the morbidity in the surgical management of OA knee, regenerative and translational medicine has paved a way to manage the articular cartilage defects with orthobiological products due to the limited potential for redifferentiation of chondrocytes[3,4].

Cell-based therapy has revolutionized its usage in the area where disease-modifying pharmacological agents or biological therapies are unavailable to treat the disorders. Mesenchymal stromal cells (MSCs) have proven the benefits in the formation of articular cartilage in the OA knee[5,6]. There are various sources of MSCs available namely bone marrow (BM), adipose tissue, synovium, peripheral blood, placenta, menstrual fluid, and amniotic fluid where the regenerative potential of all these sources of MSCs varies[7]. Out of all these sources of MSCs, the most commonly used sources are BM and adipose tissue for cartilage regeneration.

Adipose tissue possesses higher stem cell yield than BM[8]. One gram of adipose tissue yields approximately 0.35-1 million MSCs whereas one gram of BM yields 500-50000 MSCs[9]. BM-derived MSCs (BM-MSCs) show early senescence during expansion than adipose-derived MSCs (AD-MSCs)[10]. Mohamed-Ahmed *et al*[11] have demonstrated that AD-MSCs continued to proliferate up to 21 d than BM-MSCs and AD-MSCs showed considerable chondrogenic capacity, but less than BM-MSCs. Im *et al*[12] stated that osteogenic and chondrogenic potentials of BM-MSCs and AD-MSCs differ. The difference in potentiality exponentiated when an equal amount of bioactive factors are seeded and AD-MSCs demonstrated inferior regenerative potential to differentiate into bone and cartilage when compared with BM-MSCs[12]. However, Jeyaraman *et al*[13] demonstrated the efficacy, safety, and superiority of AD-MSCs transplantation when compared to BM-MSCs in OA knee management. With the conflicting evidence in literature[14-16], we aim to critically analyze the clinical efficacy and patient safety in the use of BM-MSCs and AD-MSCs in the management of OA of the knee.

## MATERIALS AND METHODS

We conducted this meta-analysis in accordance with the guidelines from the Back Review Group of Cochrane Collaboration[17] and we followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18].

### Search strategy

We conducted an independent and duplicate electronic literature search for studies evaluating the ideal source of MSC therapy for knee OA. The literature databased searched the relevant studies include: PubMed, EMBASE, Web of Science, Reference Citation Analysis, and the Cochrane Library up to August 2021. We did not apply any language or date restrictions to the search query. We used the following keywords in the search strategy "Knee Osteoarthritis", "Knee Degeneration", "Stem Cell Therapy" and "Mesenchymal Stromal Cells", "Bone marrow", "Adipose". We have presented a sample search strategy utilized for retrieving the relevant studies from one of the included databases in Supplementary Table 1. Apart from the above databases, we also searched to identify studies not identified in the primary search from the reference list of potential articles shortlisted. Based on the criteria identified as a priori for inclusion and exclusion of studies, eligible studies were identified and included for meta-analysis. In case of discrepancy among the reviewers in study selection, discussion was made until a consensus was obtained. PRISMA flow diagram of the selection of the studies included in the analysis is given in Figure 1.

### Inclusion criteria

Studies were included for quantitative review if they met the following PICOS criteria: Population: Patients with OA of knee. Intervention: AD-MSC therapy. Comparator: BM-MSC therapy. Outcomes: Visual analog score (VAS) for Pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm Knee Scale (Lysholm), Magnetic resonance observation of cartilage repair tissue (MOCART) Score, knee osteoarthritis outcome score (KOOS), Tegner Activity Score (TAS) and reported adverse events. Study design: Randomized controlled trials.

### Exclusion criteria

We excluded studies from analysis if they were of the following characteristics: (1) *In-vitro* studies involving stem cell therapy; (2) Studies of observational nature and interventional studies without appropriate comparison group; (3) Studies conduction animal models of knee OA investigating stem cell therapy; and (4) Review articles and *in-vitro* studies involving stem cell therapy.

### Data extraction

We made an independent and duplication extraction of the following data from the included studies: (1) Study characteristics: Name of the author, publication year, country, total number of patients enrolled in

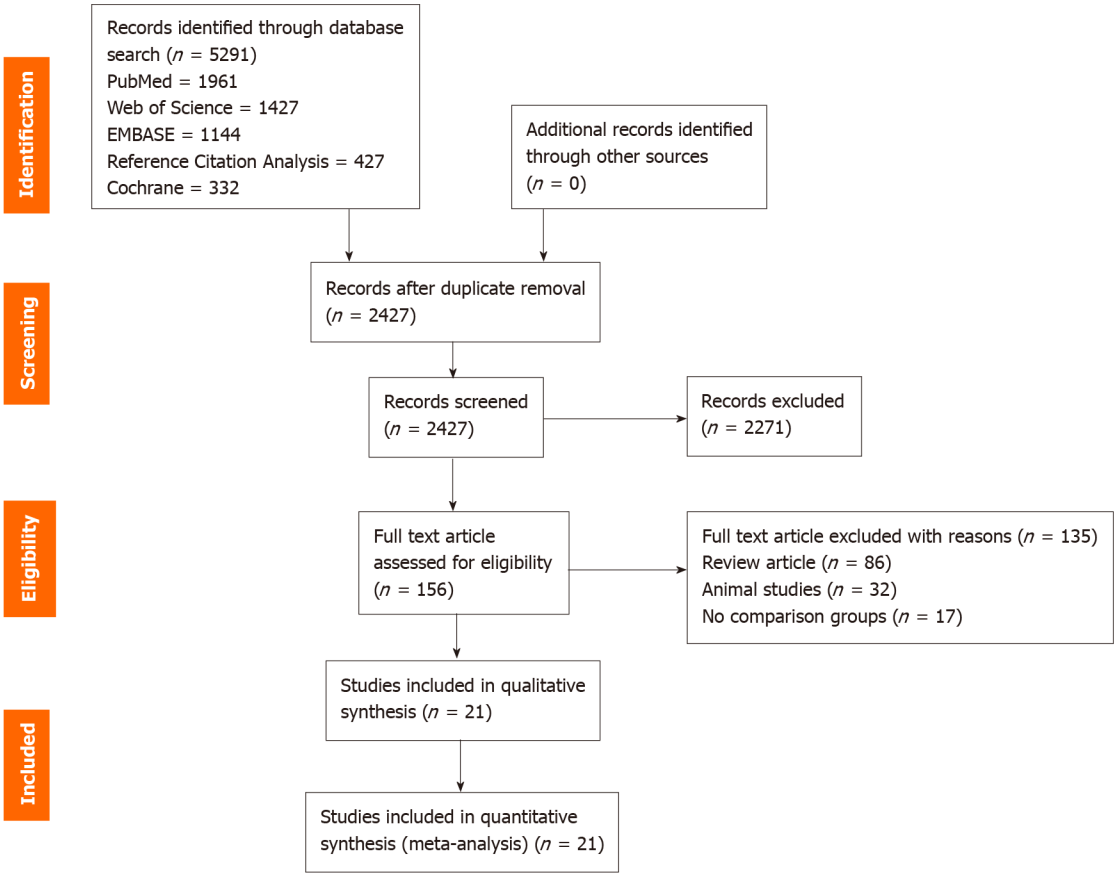


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**Figure 1 PRISMA flow diagram of the included studies.**

the study and level of evidence of the study; (2) Baseline characteristics: Age (mean with standard deviations), gender proportions of the individual groups, Kellgren Lawrence grades of OA, type of MSC source used in them, protocol of intervention utilised for both the groups, mean duration of follow-up of the study population and parameters used for assessment of clinical measures. We grouped studies utilizing BM based therapies involving BM concentrates and isolated expanded BM-MSCs into one group and another group involving studies using stromal vascular fraction (SVF) and isolated expanded AD-MSCs; (3) Efficacy outcomes: Pain outcomes using VAS, functional outcomes using WOMAC score, Lysholm score, KOOS, TAS, and radiological outcomes like MOCART score; (4) Safety outcomes: Reported adverse events; and (5) In case of any disagreement in data collection, discussion was made until a consensus was attained.

### *Risk of bias and quality assessment*

We performed an independent and duplicate analysis of the methodological quality of the included studies by two reviewers based on the ROB2 tool of Cochrane Collaboration for randomized studies. The tool has five domains of bias assessment including randomization process followed in the studies, bias in application of the intended intervention, bias in the presentation of the study outcome data, bias in the measurement of measured outcome, and bias in reporting of results of the study[19].

### *Statistical analysis*

We performed the analysis in the R platform using OpenMeta(Analyst) software[20]. We used risk ratio (RR) with 95% confidence interval (CI) for analysing dichotomous variable outcomes and weighted mean difference (WMD) with 95%CI for continuous variable outcomes. We analysed the heterogeneity observed in the results analysed using the $I^2$ test [21]. We used fixed-effects model to evaluate the outcomes if the value of $I^2 < 50\%$ and $P > 0.1$. We used random-effects model if the value of $I^2 > 50\%$ and $P < 0.1$. We considered a $P$-value < 0.05 to be significant. We performed sensitivity analyses in case of heterogeneity among the reported results from the studies included for analysis. We used Funnel plot, Egger regression test, and normal quantile plot to analyse the publication bias for the outcomes in the included studies.

## RESULTS

### Search results

Our initial electronic database screening yielded 4864 articles, which upon removal of the duplicate articles resulted in 2427 articles. We then performed title and abstract screening and shortlisted 156 eligible articles and excluded 2271 articles. We made a full-text review of the 156 articles qualified articles and excluded 135 of them for the reasons listed in the PRISMA flow diagram for study selection (Figure 1). Among the included studies, we found only one study by Estrada *et al*[22] to make a direct comparison of the adipose tissue and BM as a source of MSC and found no significant difference among the groups compared despite observing a significant improvement from the baseline. The study had a selective allocation of the subjects based on the stage of the disease and utilized adipose tissue-based cellular therapy for high-grade disease and BM-based therapy for intermediate grade disease and platelet-based therapy for early disease. To objectively evaluate the results of the study across all the grades of disease, we pooled the results of all the included studies of both sources and made a combined comparative quantitative analysis of all 21 included studies[22-42] with 936 patients. 9/21 studies[22,26,27,29,31,36-40] utilized MSC of adipogenic origin, of which 1 study utilized AD-MSC of allogenic source while rest 8 studies utilized AD-MSCs of autogenous source. 12/21 studies[22-25,28,30,32-35,41,42] utilized MSC of BM origin, of which 2 studies utilized BM-MSCs of allogenic sources, and the rest 10 studies utilized autogenous sources of BM-MSC. We did not note a standardised utilization of the dose of the MSCs transplanted in the included studies. We did not note uniformity among the included studies for the measures of outcomes assessment employed. We presented the general characteristics of the included studies in Table 1. The protocol of intervention used in the case and control groups along with the measures of outcome assessment were given in Table 2.

### Quality assessment

We utilised RoB2 tool for the evaluation of the methodological quality of the included studies and presented in Figure 2. We did not note the included studies to have high risk of bias to warrant exclusion from the analysis.

### Efficacy outcomes

**Visual analog scale for pain:** We analysed 7 studies[16,17,21,26-28,30], 5 studies[26,27,31,36,40], and 1 study[39] reporting the VAS outcome at 6, 12, and 24 mo respectively using adipose tissue as the source of MSCs. There was a significant heterogeneity observed between the included studies. ($I^2$ > 80%, $P$ < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant reduction in VAS score was noted compared to their controls at 6 mo [WMD = -13.414, 95%CI: (-24.175)-(-2.653), $P$ < 0.015; Figure 3A], 12 mo [WMD = -21.498, 95%CI: (-33.819)-(-9.177), $P$ < 0.001; Figure 3B), and 24 mo [WMD = -6.000, 95%CI: (-9.079)-(-2.921), $P$ < 0.05; Figure 3C] compared to their controls as shown in Figure 3. Similarly, we analysed 5 studies[24,25,28,32,33], 4 studies[23,24,28,33], and 1 study[24] reporting the VAS outcome at 6, 12, and 24 mo respectively using BM as the source of MSCs. There was a significant heterogeneity observed between the included studies. ($I^2$ > 80%, $P$ < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant reduction in VAS score was noted compared to their controls at 6 mo [WMD = -11.028, 95%CI: (-19.605)-(-2.450), $P$ < 0.012; Figure 3A), and 24 mo [WMD = -17.589, 95%CI: (-22.486)-(-12.692), $P$ < 0.001; Figure 3C), with a drop in the pain control at 12 mo [WMD = -2.366, 95%CI: (-9.912)-5.180, $P$ = 0.539; Figure 3B], period compared to their controls.

On critical analysis of the pain reduction potential of both the sources, it is noted as shown in Figure 4 that despite the inconsistency in the pain reduction at 12 mo with BM, we noted a rising trend curve in pain reduction which favors the therapy. Although both the sources were capable of significant pain reduction compared to their controls, adipose tissue demonstrated consistent results across all the time points. However, the inconsistencies in the results of BM could also be accounted to the heterogeneity in the studies included for analysis.

**WOMAC score:** We analyzed 6 studies[27,31,36,37,39,40], and 6 studies[27,31,36-39] reporting the WOMAC scores at 6, and 12 mo respectively using adipose tissue as the source of MSCs. There was a significant heterogeneity observed between the included studies. ($I^2$ > 80%, $P$ < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant reduction in WOMAC scores were noted compared to their controls at 6 mo [WMD = -21.317, 95%CI: (-27.146)-(-15.488), $P$ < 0.001; Figure 3D], and 12 mo [WMD = -19.341, 95%CI: (-30.544)-(-8.138), $P$ < 0.001; Figure 3E] compared to their controls as shown in Figure 3. Similarly, we analyzed 7 studies[24,25,28,32-35], and 6 studies[24,25,28,33-35] reporting the WOMAC outcome at 6, and 12 mo respectively using BM as the source of MSCs. There was a significant heterogeneity observed between the included studies ($I^2$ > 80%, $P$ < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, we did not note any significant reduction in WOMAC scores compared to their controls at 6 mo [WMD = -1.958, 95%CI: (-10.273)- 6.357, $P$ = 0.644; Figure 3D], and 12 mo [WMD = -1.944, 95%CI: (-8.183)-4.294, $P$ = 0.541; Figure 3E] compared to their controls.

**Table 1 Characteristics of included studies**

| Sl. No | Ref. | Country | Nature of study | Kellgren Lawrence Grade | Sample size | Treatment/ control | Mean age (SD) | | Male/female | | MSC type | MSC source | Follow-up (mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Treatment group | Control group | Treatment group | Control group | | | |
| 1 | Vega *et al*[23], 2015 | Spain | RCT | II, III, IV | 30 | 15/15 | 56.6 ± 9.24 | 57.3 ± 9.09 | 06/09 | 05/10 | BM | Allo | 12 |
| 2 | Vangsness *et al*[24], 2014 | United States | RCT | NR | 55 | 36/19 | 44.6 ± 9.82 | 47.8 ± 8 | 25/11 | 13/06 | BM | Allo | 24 |
| 3 | Garay-Mendoza *et al*[25], 2018 | Mexico | RCT | NR | 61 | 30/31 | 55.57 ± 12.02 | 59.32 ± 10.85 | 07/23 | 09/22 | BM | Auto | 6 |
| 4 | Kuah *et al*[26], 2018 | Australia | RCT | I, II, III | 20 | 16/4 | 50.8 ± 7.29 | 55.0 ± 10.42 | 11/05 | 01/03 | AD | Allo | 12 |
| 5 | Estrada *et al*[22], 2020 | Argentina | RCT | I, II, III | 89 | 60/29 | 61 ± 12 | 61 ± 12 | NR | NR | BM / AD | Auto | 12 |
| 6 | Freitag *et al*[27], 2019 | Australia | RCT | II, III | 30 | 20/10 | 54.6 ± 6.3 | 51.5 ± 6.1 | 11/09 | 01/09 | AD | Auto | 12 |
| 7 | Ruane *et al*[41], 2021 | United States | RCT | I, II, III | 32 | 17/15 | 58.06 ± 9.14 | 58.6 ± 8.05 | 09/08 | 10/05 | BM | Auto | 12 |
| 8 | Lamo-Espinosa *et al*[28], 2016 | Spain | RCT | II, III, IV | 30 | 20/10 | 65.9 | 60.3 | 12/08 | 07/03 | BM | Auto | 12 |
| 9 | Garza *et al*[29], 2020 | United States | RCT | II, III | 39 | 26/13 | 60.5 ± 7.9 | 57.1 ± 9.1 | 15/11 | 7/6 | AD | Auto | 12 |
| 10 | Wong *et al*[30], 2013 | Singapore | RCT | NR | 56 | 28/28 | 53 | 49 | 15/13 | 14/14 | BM | Auto | 24 |
| 11 | Lu *et al*[31], 2019 | China | RCT | I, II, III | 53 | 27/26 | 55.03 ± 9.19 | 59.64 ± 5.97 | 03/24 | 03/23 | AD | Auto | 12 |
| 12 | Lv *et al*[42], 2015 | Huang | RCT | I, II | 80 | 40/40 | 55.9 ± 8.1 | 55.1 ± 6.8 | 14/26 | 13/27 | BM | Auto | 12 |
| 13 | Emadedin *et al*[32], 2018 | Iran | RCT | II, III, IV | 43 | 19/24 | 51.7 ± 9.2 | 54.7 ± 5.3 | 12/07 | 15/09 | BM | Auto | 6 |
| 14 | Gupta *et al*[33], 2016 | India | RCT | II, III | 60 | 40/20 | 58.10 ± 8.23 | 54.90 ± 8.27 | 12/28 | 4/16 | BM | Allo | 12 |
| 15 | Bastos *et al*[34], 2020 | Brazil | RCT | I, II, III, IV | 47 | 30/17 | 55.7 ± 7.8 | 55.9 ± 13.4 | 15/15 | 09/08 | BM | Auto | 12 |
| 16 | Wakitani *et al*[35], 2002 | Japan | | I, II | 24 | 12/12 | NR | NR | NR | NR | BM | Auto | 16 |
| 17 | Tran *et al*[36], 2019 | Taiwan | RCT | II, III | 33 | 15/18 | 58.2 ± 5.70 | 59.0 ± 6.04 | 03/12 | 05/13 | AD | Auto | 24 |
| 18 | Lee *et al*[37], 2019 | South Korea | RCT | II, III, IV | 24 | 12/12 | 62.2 ± 6.5 | 63.2 ± 4.2 | 03/09 | 03/09 | AD | Auto | 6 |
| 19 | Koh *et al*[38], 2012 | South Korea | RCT | IV | 50 | 25/25 | 54.2 ± 9.3 | 54.4 ± 11.3 | 08/17 | 08/17 | AD | Auto | 16 |
| 20 | Koh *et al*[39], 2014 | South Korea | RCT | I, II, III | 44 | 23/21 | 52.3 ± 4.9 | 54.2 ± 2.9 | 06/17 | 05/16 | AD | Auto | 24 |
| 21 | Hong *et al*[40], 2019 | China | RCT | II, III | 32 | 16/16 | 51 ± 5.95 | 53 ± 10.97 | 03/13 | 03/13 | AD | Auto | 12 |

AD: Adipose derived; Allo: Allogenic; Auto: Autologous; BM: Bone marrow; MSC: Mesenchymal stem cell; NR: Not reported; RCT: Randomized controlled trial; SD: Standard deviation.

On critical analysis of the WOMAC score reduction potential of both the sources, it is noted as shown in Figure 3 that most of the studies that utilized BM did not report any significant improvement compared to their controls, despite their heterogeneity in results at both 6 mo and 12 mo. Since the WOMAC score concentrates more on the functional efficiency of the intervention apart from pain reduction, adipose tissue stands superior to BM as a dependable source of MSC to give better functional results consistently across both time points.

**Lysholm knee score:** We analyzed 3 studies[36,36,38], and one study[39] reporting the lysholm score at 12, and 24 mo respectively using adipose tissue as the source of MSCs. There was a significant heterogeneity observed between the included studies. ($I^2$ > 80%, $P$ < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant improvement in scores was noted compared to their controls at 12 mo (WMD = 6.494, 95%CI: 1.889-11.100, $P$ = 0.006; Figure 3F). However, at 24 mo, the improvement in scores was not sustained [WMD = 4.100, 95%CI: (-4.757)-12.9557, $P$ = 0.757; Figure 3G] compared to their controls as shown in Figure 3. Similarly, we analyzed 3 studies[22, 24,30], and 2 studies[24,30] reporting Lysholm scores outcome at 12 and 24 mo respectively using BM as the source of MSCs. There was a significant heterogeneity observed between the included studies. ($I^2$ > 80%, $P$ < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, we did not note any significant improvement in Lysholm score compared to their controls at both 12 mo [WMD = 0.232, 95%CI: (-5.133)-5.597, $P$ = 0.933; Figure 3F], and 24 mo [WMD = 4.412, 95%CI: (-0.801)-9.626, $P$ = 0.097; Figure 3G] respectively. On critical analysis of the improvement of the Lysholm score of both the sources, it is noted only in studies utilizing adipose tissue as the source of MSC significant improvement in the functional outcomes is noted which is in corroboration with the WOMAC score results.

### *KOOS & MOCART Score*

We analyzed the quality of life outcomes such as KOOS reported in 3 studies[22,27,39] using adipose tissue and 3 studies[22,34,41] utilizing BM as the source of MSCs. There was a significant heterogeneity observed between the included studies ($I^2$ > 80%, $P$ < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant improvement in scores was noted in both adipose tissue (WMD = 13.124, 95%CI: 4.745-21.502, $P$ = 0.002; Figure 3H) and BM (WMD = 2.642, 95%CI: 0.587-4.698, $P$ = 0.012; Figure 3H) as the sources compared to their controls, despite the inconsistencies noted earlier in the functional outcomes such as WOMAC or Lysholm scores.

Similarly, we analyzed 2 studies that objectively analyzed the regenerate cartilage tissue using magnetic resonance imaging with MOCART score between the two sources[30,40]. There was a significant heterogeneity observed between the included studies ($I^2$ > 80%, $P$ < 0.001). Hence, the random-effects model was used for analysis. We noted significant improvement in the MOCART scores at 12 mo in both the sources (WMD = 31.625, 95%CI: 7.481-55.769, $P$ = 0.010; Figure 3I) compared to their controls. As shown in Figure 3, although both the sources had significantly improved KOOS and MOCART scores at 12 mo, the improvement noted with adipose tissues stands relatively high compared to the BM.

**Table 2 Stem cell transplantation protocol of the included studies**

| Ref. | MSC type | MSC source | MSC preparation | MSC count ($10^7$ cells) | Treatment group intervention | Control group intervention | Outcome measures |
|---|---|---|---|---|---|---|---|
| Vega *et al*[23], 2015 | BM | Allo | CE-BMMSC | 4 | sIA injection of MSC | sIA Injection of 60 mg HA | VAS, WOMAC |
| Vangsness *et al* [24], 2014 | BM | Allo | CE-BMMSC | 5/15 | sIA injection of MSC + 20 mg HA | sIA Injection of 20 mg HA | VAS, Lysholm Score |
| Garay-Mendoza *et al*[25], 2018 | BM | Auto | BMC | NA | 600 μg/d G-CSF for 3 consecutive days before the procedure + sIA injection of MSC | Oral acetaminophen, 500 mg every 8 h for 6 mo | VAS, WOMAC |
| Kuah *et al*[26], 2018 | AD | Allo | CE-ADMSC | 0.39-0.67 | sIA injection of MSC | Placebo sIA injection of cell culture media and cryopreservative | VAS, WOMAC, MRI assessment |
| Estrada *et al*[22], 2020 | AD | Auto | BMC | NA | sIA injection of BM concentrate | sIA injection of PRP | IKDC, Lysholm Score, KOOS |
| Estrada *et al*[22], 2020 | BM | Auto | SVF | NA | sIA injection of lipoaspirate | sIA injection of PRP | |
| Freitag *et al*[27], 2019 | AD | Auto | CE-ADMSC | 10 | sIA injection of MSC ± 2 $^{nd}$ injection at 6 mo | Conservative management | VAS, WOMAC, KOOS, MRI assessment |
| Ruane *et al*[41], 2021 | BM | Auto | BMC | NA | sIA injection of BM concentrate + PRP | Gel-One® Cross-Linked hyaluronate injection | VAS, KOOS |
| Lamo-Espinosa *et al*[28], 2016 | BM | Auto | CE-BMMSC | 1 | sIA injection of MSC + 60 mg HA | sIA injection of 60 mg HA | VAS, WOMAC, MRI assessment |
| Garza *et al*[29], 2020 | AD | Auto | SVF | NA | sIA injection of MSC | Placebo injection without cells | WOMAC, MRI assessment |
| Wong *et al*[30], 2013 | BM | Auto | CE-BMMSC | 1.46 | HTO + microfracture + sIA injection of MSC + 20 mg HA | HTO + microfracture + sIA injection of 20 mg HA | Tegner Score, Lysholm Score |
| Lu *et al*[31], 2019 | AD | Auto | CE-ADMSC | 5 | 2 IA injection of MSC at 0, 3 wk and sham injection at 1, 2 wk | 4 IA injection of 25 mg HA at 0, 1, 2, 3 wk | VAS, WOMAC |
| Lv *et al*[42], 2015 | BM | Auto | CE-BMMSC | 3.82 | 3 × monthly IA injection of MSC + 20 mg HA | sIA injection of 20 mg HA | Tegner Score, Lysholm Score |
| Emadedin *et al* [32], 2018 | BM | Auto | CE-BMMSC | 4 | sIA injection of MSC | Placebo sIA injection of normal saline | VAS, WOMAC |
| Gupta *et al*[33], 2016 | BM | Allo | CE-BMMSC | 2.5-15 | sIA injection of MSC + 20 mg HA | Placebo sIA injection of 20 mg HA | VAS, WOMAC, MRI assessment |
| Bastos *et al*[34], 2020 | BM | Auto | CE-BMMSC | 4 | sIA injection of MSC in 10 mL of PRP | sIA injection of 4 mg dexamethasone | KOOS, MRI assessment |
| Wakitani *et al* [35], 2002 | BM | Auto | CE-BMMSC | 1 | HTO + microfracture + sIA injection of MSC | HTO + microfracture + placebo injection | MRI assessment, HSS knee rating scale |
| Tran *et al*[36], 2019 | AD | Auto | SVF | NA | Arthroscopic micro fracture + sIA injection of MSC | Arthroscopic micro fracture | WOMAC, MRI assessment |
| Lee *et al*[37], 2019 | AD | Auto | CE-ADMSC | 10 | sIA injection of MSC | Placebo injection with normal saline | WOMAC, MRI assessment |
| Koh *et al*[38], 2012 | AD | Auto | SVF | 0.189 | Arthroscopic debridement + sIA injection of MSC + PRP | Arthroscopic debridement + PRP | VAS, Tegner Score, Lysholm Score |
| Koh *et al*[39], 2014 | AD | Auto | CE-ADMSC | 0.411 | HTO + sIA injection of MSC + PRP | HTO + PRP | VAS, Lysholm Score |
| Hong *et al*[40], 2019 | AD | Auto | SVF | 0.745 | sIA injection of MSC | sIA injection of 40 mg HA | VAS, WOMAC, MRI assessment |

AD: Adipose derived; Allo: Allogenic; Auto: Autologous; BM: Bone marrow; BMC: Bone marrow concentrate; CE-ADMSC: Culture expanded adipose

derived mesenchymal stem cell; CE-BMMSC: Culture expanded bone marrow mesenchymal stem cell; HA: Hyaluronic acid; HSS: Hospital for special surgeries; HTO: High tibial osteotomy; IA: Intra-articular; IKDC: International Knee Documentation Committee; KOOS: Knee Osteoarthritis Outcome Score; PRP: Platelet rich plasma; MRI: Magnetic resonance imaging; MSC: Mesenchymal stem cell; sIA: Single intra-articular; SVF: Stromal vascular fraction; VAS: Visual analog score; WOMAC: Western Ontario Mc-Master Universities Osteoarthritis index.

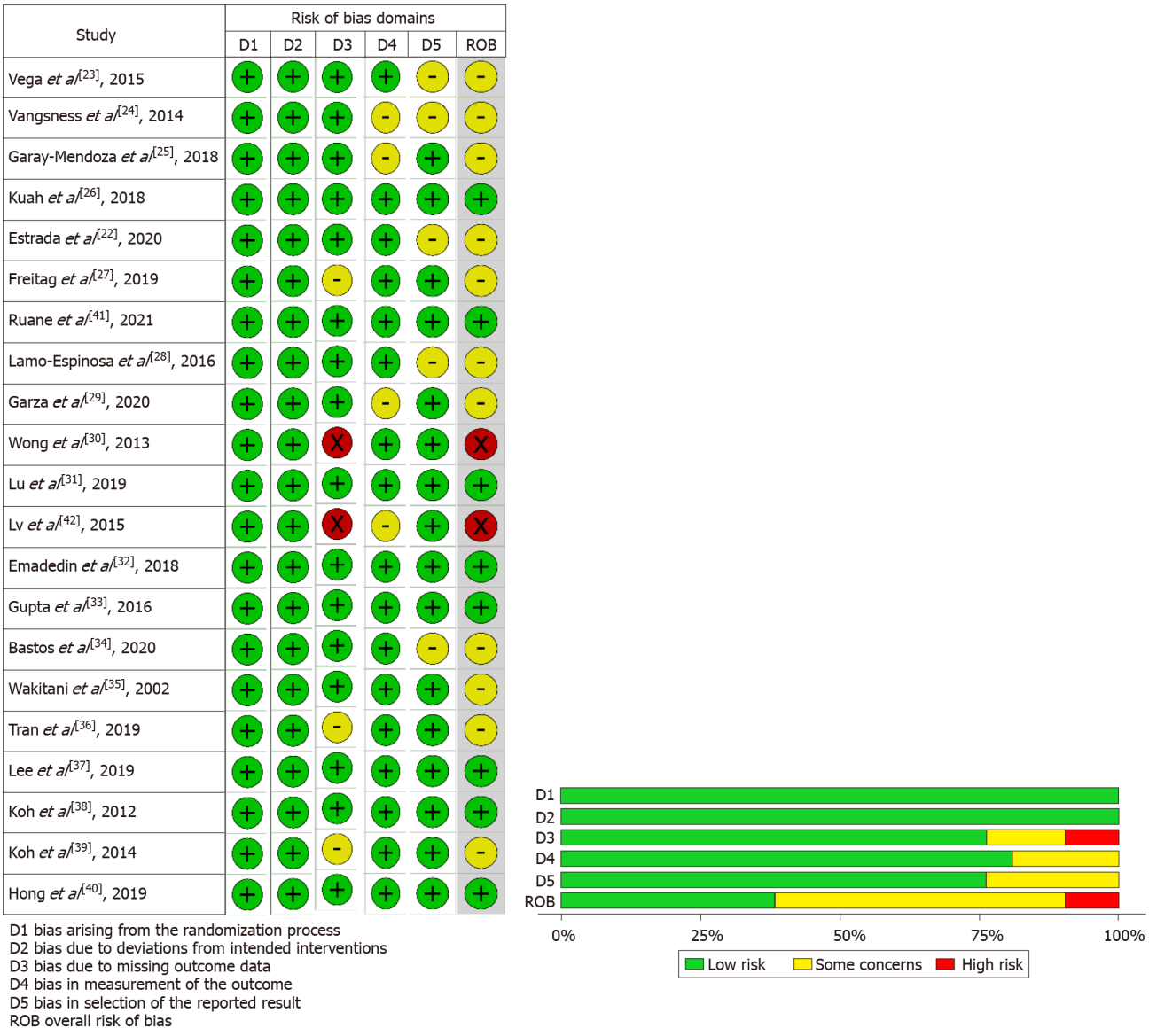


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**Figure 2 Methodological quality and risk of bias assessment of all the included studies.**

### *Safety*

Seven studies involving 141 patients reported adverse effects with low heterogeneity among the included studies using adipose tissue as the source of MSC for knee OA. ($I^2$ = 0.0%, $P$ = 0.968). Hence, a fixed-effects model was used for analysis. There was no significant increase in the adverse events compared to the controls (RR = 1.081, 95%CI: 0.754-1.549, $P$ = 0.673; Figure 5).

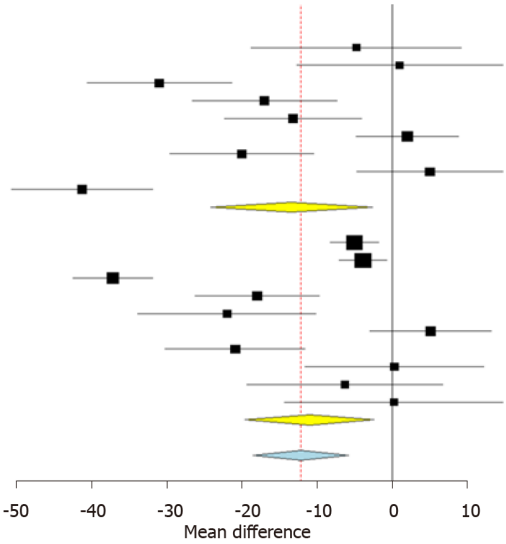
Seven studies involving 180 patients reported adverse effects with low heterogeneity among the included studies with AD-MSC ($I^2$ = 0.0%, $P$ = 0.996). Hence, a fixed-effects model was used for analysis. There was no significant increase in the adverse events compared to the controls (RR = 1.072, 95%CI: 0.440-2.612, $P$ = 0.876; Figure 5). No major serious adverse events with permanent effects such as death, tumor, or immune reaction to the intervention were noted during follow-up in either of the sources of MSCs.

### *Sensitivity analysis*

We conducted sensitivity analysis whenever heterogeneity was noted in the outcomes analysed. The

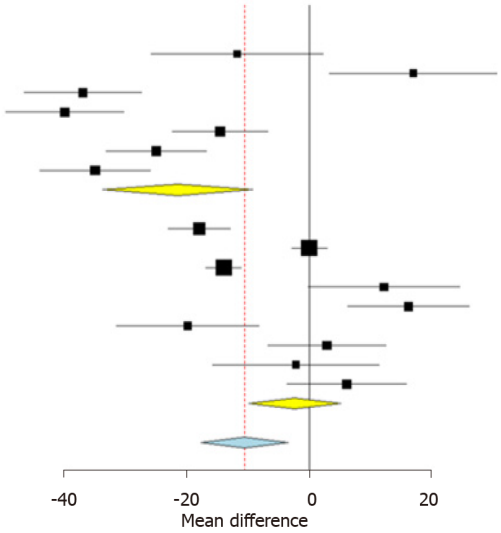
**A**

| Study | Estimate (95%CI) |
|---|---|
| Kuah *et al*[26], 2018 | -4.800 (-18.822, 9.222) |
| Kuah *et al*[26], 2018 | 1.000 (-12.696, 14.696) |
| Freitag *et al*[27], 2019 | -31.000 (-40.642, -21.358) |
| Freitag *et al*[27], 2019 | -17.000 (-40.642, -21.358) |
| Lu *et al*[31], 2019 | -13.200 (-22.361, -4.039) |
| Tran *et al*[36], 2019 | 2.000 (-4.852, 8.852) |
| Lee *et al*[37], 2019 | -20.000 (-29.602, -10.398) |
| Koh *et al*[38], 2012 | 5.000 (-4.705, 14.705) |
| Hong *et al*[40], 2019 | -41.300 (-50.712, -31.888) |
| Subgroup adipose ($I^2$ = 90.89 %, $P$ = 0.000) | -13.414 (-24.175, -2.653) |
| Vangsness *et al*[24], 2014 | -5.000 (-8.223, -1.777) |
| Vangsness *et al*[24], 2014 | -3.900 (-7.123, -0.677) |
| Garay-Mendoza *et al*[25], 2018 | -37.200 (-42.518, -31.882) |
| Lamo-Espinosa *et al*[28], 2016 | -18.000 (-26.269, -9.731) |
| Lamo-Espinosa *et al*[28], 2016 | -22.000 (-33.841, -10.159) |
| Emadedin *et al*[32], 2018 | 5.100 (-2.996, 13.196) |
| Gupta *et al*[33], 2016 | -20.900 (-30.218, -11.582) |
| Gupta *et al*[33], 2016 | 0.300 (-11.606, 12.206) |
| Gupta *et al*[33], 2016 | -6.300 (-19.316, 6.716) |
| Gupta *et al*[33], 2016 | 0.200 (-14.309, 14. 709) |
| Subgroup bone marrow ($I^2$ = 94.17%, $P$ = 0.000) | -11.028 (-19.605, -2.450) |
| Overall ($I^2$ = 92.68%, $P$ = 0.000) | -12.160 (-18.539, -5.780) |



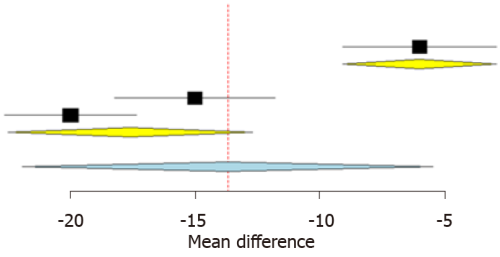

**B**

| Study | Estimate (95%CI) |
|---|---|
| Kuah *et al*[26], 2018 | -11.800 (-25.822, 2.222) |
| Kuah *et al*[26], 2018 | 17.000 (3.304, 30.696) |
| Freitag *et al*[27], 2019 | -37.000 (-46.642, -27.358) |
| Freitag *et al*[27], 2019 | -40.000 (-49.642, -30.358) |
| Lu *et al*[31], 2019 | -14.600 (-22.419, -6.781) |
| Tran *et al*[36], 2019 | -25.000 (-33.223, -16.777) |
| Hong *et al*[40], 2019 | -35.300 (-44.035, -25.965) |
| Subgroup adipose ($I^2$ = 90.93 %, $P$ = 0.000) | -21.498 (-33.819, -9.177) |
| Vega *et al*[23], 2015 | -18.000 (-23.061, -12.939) |
| Vangsness *et al*[24], 2014 | -0.000 (-2.910, 2.910) |
| Vangsness *et al*[24], 2014 | -14.000 (-16.910, -11.090) |
| Lamo-Espinosa *et al*[28], 2016 | -12.200 (-0.218, -24.618) |
| Lamo-Espinosa *et al*[28], 2016 | 16.200 (6.255, 26.145) |
| Gupta *et al*[33], 2016 | -19.900 (-31.528, -8.272) |
| Gupta *et al*[33], 2016 | 2.900 (-6.762, 12.562) |
| Gupta *et al*[33], 2016 | -2.200 (-15.807, 11.407) |
| Gupta *et al*[33], 2016 | 6.100 (-3.680, 15.880) |
| Subgroup bone marrow ($I^2$ = 92.64%, $P$ = 0.000) | -2.366 (-9.912, 5.180) |
| Overall ($I^2$ = 93.96%, $P$ = 0.000) | -10.556 (-17.690, -3.422) |



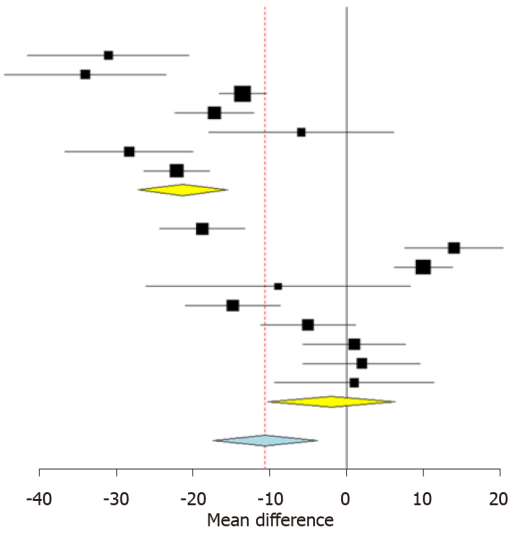

**C**

| Study | Estimate (95%CI) |
|---|---|
| Koh *et al*[39], 2014 | -6.000 (-9.079, -2.921) |
| Subgroup adipose ($I^2$ = NA, $P$ = NA) | -6.000 (-9.079, -2.921) |
| Vangsness *et al*[24], 2014 | -15.000 (-18.223, -11.777) |
| Vangsness *et al*[24], 2014 | -20.000 (-22.641, 17.359) |
| Subgroup bone marrow ($I^2$ = 81.92%, $P$ = 0.019) | -17.589 (-22.486, -12.692) |
| Overall ($I^2$ = 95.65%, $P$ = 0.000) | -13.691 (-21.921, -5.461) |




**D**

| Study | Estimate (95%CI) |
|---|---|
| Freitag *et al*[27], 2019 | -31.000 (-41.518, -20.482) |
| Freitag *et al*[27], 2019 | -34.000 (-44.518, -23.482) |
| Lu *et al*[31], 2019 | -13.500 (-16.555, -10.445) |
| Tran *et al*[36], 2019 | -17.200 (-22.319, -12.081) |
| Lee *et al*[37], 2019 | -5.880 (-17.909, 6.149) |
| Koh *et al*[38], 2012 | -28.300 (-36.615, -19.985) |
| Hong *et al*[40], 2019 | -22.100 (-26.356, -17.844) |
| Subgroup adipose ($I^2$ = 83.57 %, $P$ = 0.000) | -21.317 (-27.146, -15.488) |
| Lv *et al*[42], 2015 | -18.770 (-24.275, -13.265) |
| Vangsness *et al*[24], 2014 | 14.000 (7.625, 20.375) |
| Garay-Mendoza *et al*[25], 2018 | 10.000 (6.223, 13.777) |
| Lamo-Espinosa *et al*[28], 2016 | -8.900 (-26.155, 8.355) |
| Emadedin *et al*[32], 2018 | -14.800 (-20.974, -8.626) |
| Bastos *et al*[34], 2020 | -5.000 (-11.161, 1.161) |
| Bastos *et al*[34], 2020 | 1.000 (-5.695, 7.695) |
| Wakitani *et al*[35], 2002 | 2.000 (-5.612, 9.612) |
| Gupta *et al*[33], 2016 | 1.000 (-9.390, 11.390) |
| Subgroup bone marrow ($I^2$ = 93.11%, $P$ = 0.019) | -1.958 (-10.273, 6.357) |
| Overall ($I^2$ = 94.97%, $P$ = 0.000) | -10.577 (-17.392, -3.763) |



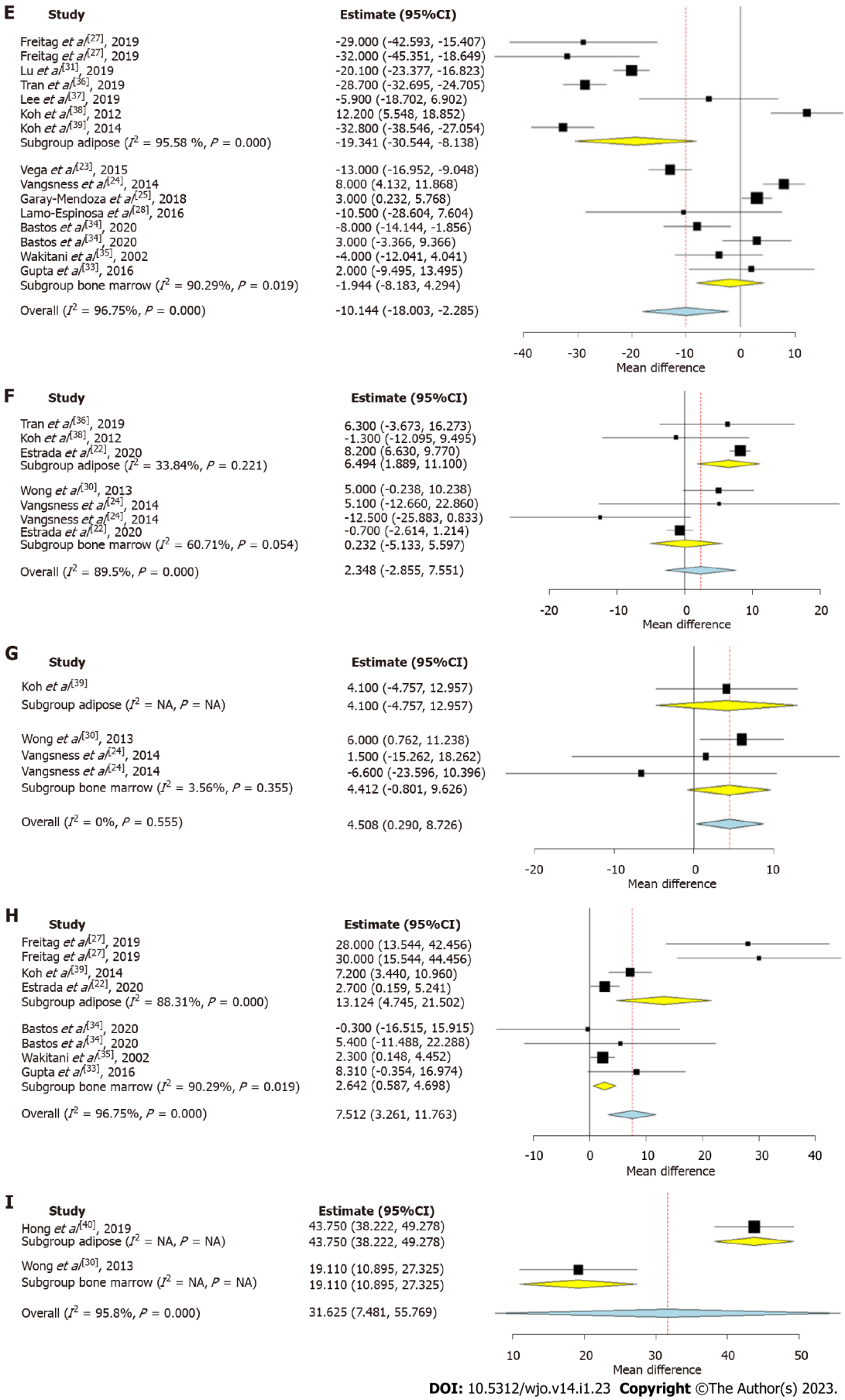



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**Figure 3 Forest plot of the included studies comparing adipose tissue and bone marrow as a source of mesenchymal stromal cell therapy compared to their controls.** A: Visual analog scale (VAS) at 6 mo; B: VAS at 12 mo; C: VAS at 24 mo; D: Western Ontario McMaster Universities

Osteoarthritis Index (WOMAC) at 6 mo; E: WOMAC at 12 mo; F: Lysholm at 12 mo; G: Lysholm at 24 mo; H: Knee osteoarthritis outcome score at 12 mo; I: Magnetic resonance observation of cartilage repair tissue score at 12 mo. CI: Confidence interval; NA: Not available.

results of the outcomes analysed such as VAS for pain, WOMAC, Lysholm, KOOS, MOCART, and adverse events were not significantly altered by sequentially omitting each study in the meta-analysis. We also did not note a change in the consistency of the results for the outcomes analysed upon changing the analysis to the random-effects model.

### Publications bias

Publication bias was analyzed utilizing the funnel plot, normal quantile plot, and Egger's regression test for the meta-analysis performed. There was no evidence of publication bias by funnel plot and normal quantile plot as shown in Figure 6 or by Egger's regression test ($P$ = 0.519). We noted symmetrical distribution of studies in the funnel plot and studies were found to lie close to the 95%CI and no significant heterogeneity was noted in the distribution of the studies about the axes, suggestive of minimal publication bias.

## DISCUSSION

In the era of regenerative medicine, MSCs serve the ideal cell-based resort for treating cartilage disorders and provide a platform for regeneration. Various animal models have demonstrated the safety and efficacy of MSCs in cartilage regeneration. MSCs bridge a gap between pharmacological and surgical management of OA of the knee. MSCs offer a balanced equilibrium between pro-and anti-apoptotic, pro-and anti-inflammatory cytokines, and pro-and anti-angiogenic factors to maintain joint homeostasis which is required for cartilage regeneration. Though the reliability of cellular therapy for OA knee has been tested in various preclinical and clinical trials, they provide the readers with conflicting results in the source of MSCs to be used for cartilage regeneration. In literature, the ideal source of MSCs for cartilage regeneration is still under debate. The chondrogenesis among the available sources of MSCs is demonstrated in all the sources of MSCs. The most ideal chondrogenic MSC is still under question.

The efficacy of MSC in cartilage regeneration should withstand the biomechanical stress which has to be evaluated according to regulatory guidelines to demonstrate the role of cellular therapy for adoption across an expanding patient population. The reasons behind the less exploration of other sources of MSCs for chondrogenesis are inadequate standardization of isolation protocols to retrieve MSC from that particular source and the strict regulatory guidelines laid by the governing bodies. In this analysis, we tried to analyze whether BM-MSCs or AD-MSCs are the ideal sources for chondrogenesis. Among all the available sources of MSCs, extraction of MSCs from BM and adipose tissue pose minimal morbidity to the donor site while compared with other sources of MSCs. BM-MSC is the most popular source and widely used MSC for osseous and cartilage regeneration. The MSC count in BM appears to be less when compared with the MSC count in adipose tissue. Hence the source of MSC from where it is retrieved plays a major role in cartilage regeneration.

Although Estrada *et al*[22] in their study compared the two sources, they did not randomize the study participants to the interventions analyzed. Instead, they categorized the patients with severe disease to be allotted to adipose-based therapy while mild and moderate diseases to platelet- and BM-based therapy respectively. Hence one cannot objectively compare the efficacy of the two different sources, which necessitated us to undergo a pooled analysis of the studies using adipose tissue and BM as the source of MSCs in the management of knee OA and compared their results using minimum clinical importance difference (MCID) for the parameter concerned.

### Main finding

We comprehensively and critically reviewed all available literature to identify the ideal source of MSCs for knee OA and found that: AD-MSCs showed a statistically significant and consistent improvement in all functional outcome measures, such as the VAS score for pain, WOMAC, Lysholm, KOOS, and radiological outcome parameters such as MOCART at varied time intervals compared to their corresponding controls. In contrast, despite better improvement in the VAS score for pain in the long term (24 mo), BM, as a source of MSCs, did not show functional benefits when evaluated using the WOMAC and Lysholm. However, objective measures of quality of life using KOOS and radiological outcome parameters, such as MOCART, showed significant benefits compared to their corresponding controls.

On comparing the relative improvement in various analyzed parameters, such as the VAS score, WOMAC, Lysholm, KOOS, and MOCART, between the two sources adipose tissue outperformed BM, with the difference in their outcome parameters more than the MCID for the concerned parameter. The MCID used were 15 for VAS score, 10 for WOMAC, 25 for Lysholm, 15 for KOOS[43,44]. There were no significant adverse events with either MSC compared to their controls.

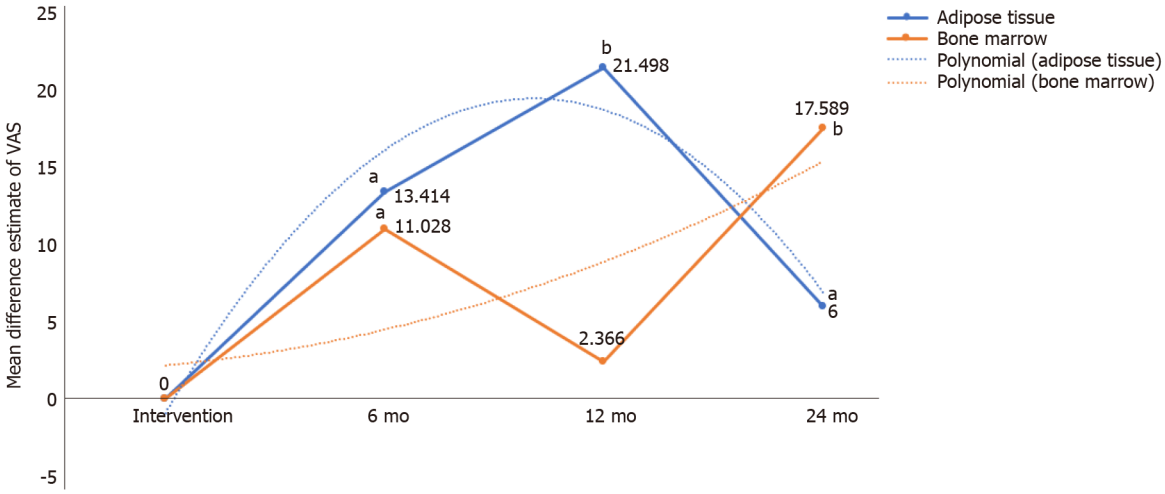


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**Figure 4 Pain reduction potential of adipose tissue and bone marrow at various timepoints based on visual analog scale score.** [a]*P* < 0.05; [b]*P* < 0.001. VAS: Visual analog scale.

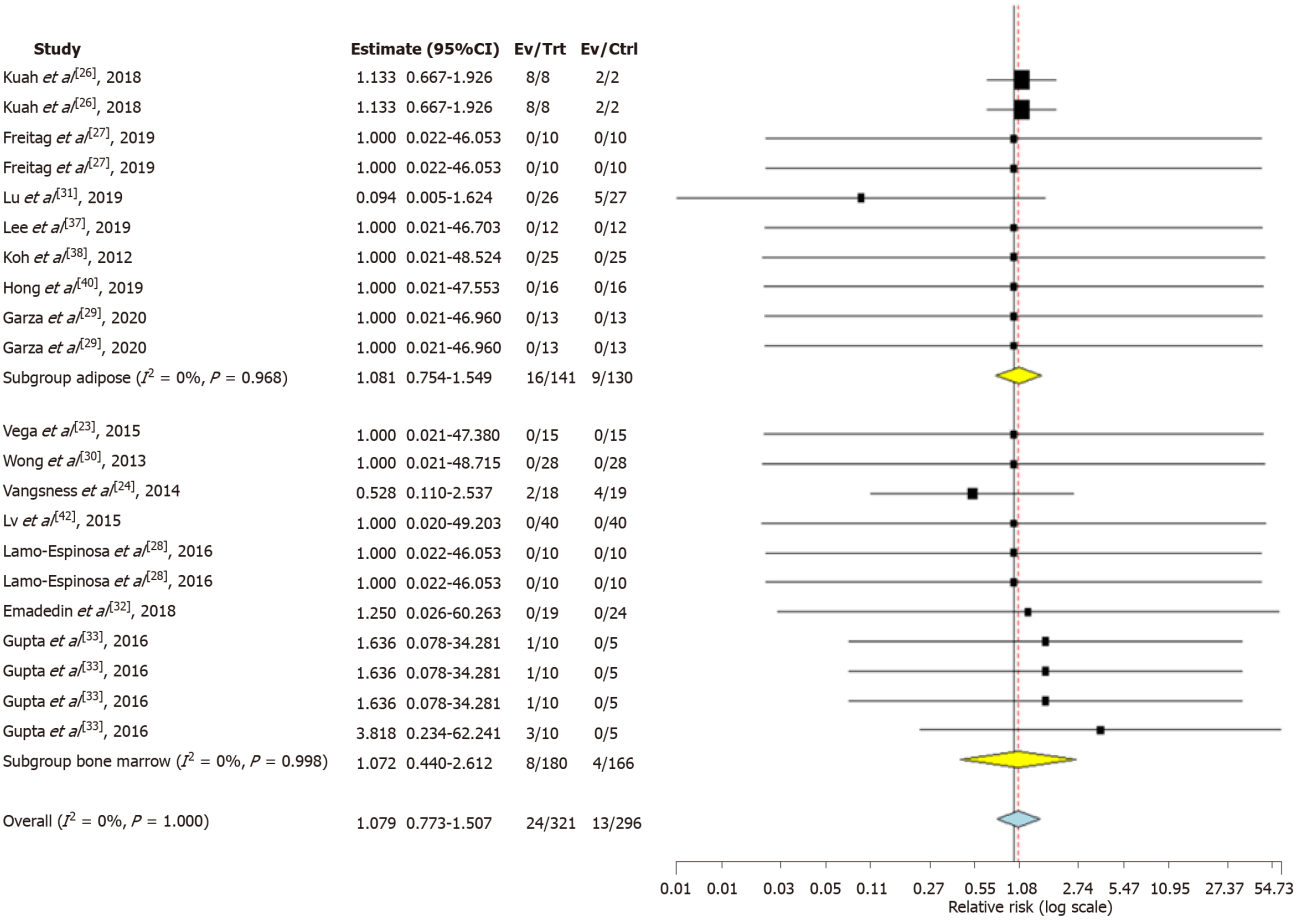


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**Figure 5 Forest plot of the included studies comparing adverse events upon using adipose tissue and bone marrow as a source of mesenchymal stromal cell therapy compared to their controls.** CI: Confidence interval.

### *MSC harvest*

The source of MSC harvesting is an important factor in stem cell research. Although the BM-MSC harvesting method has been the most commonly used method of MSC harvesting, recent studies have pointed towards AD-MSC owing to their ease of extraction and lack of procedure-related morbidity [45]. Isolation of AD-MSCs from adipose tissue blocks is superior to liposuction[11]. There is a well-

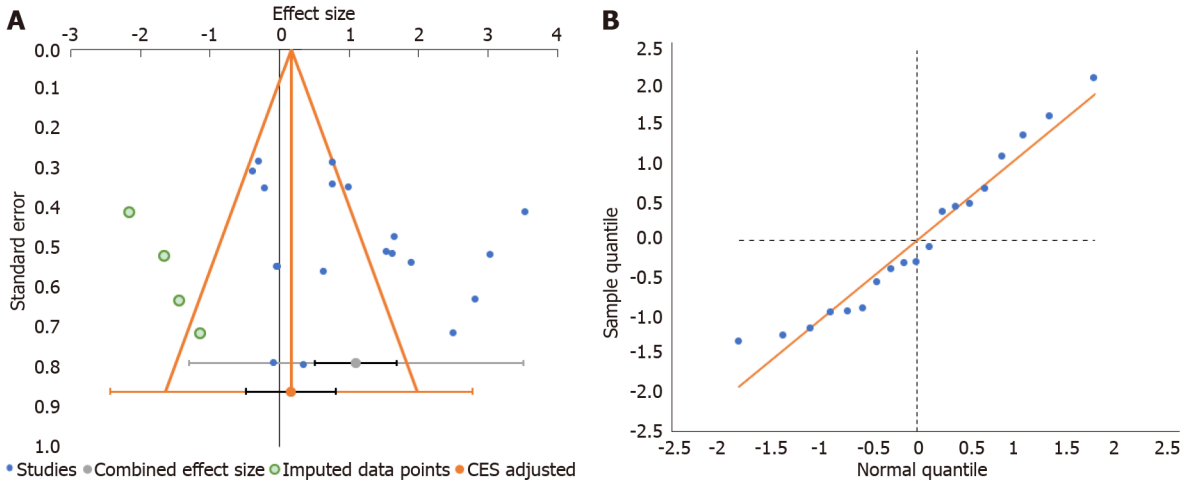


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**Figure 6 Publication bias assessment.** A: Funnel plot; B: Quantile plot for the visual analog score outcome at 6 mo in the included studies. CES: Combined effect size.

documented procedure for harvesting a larger number of AD-MSCs under local anesthesia with minimal procedure-related patient morbidity[46]. Although there have been reports of fat embolism during AD-MSC harvesting, its incidence is very low. With appropriate techniques and skill, the incidence can be further reduced. The ease of access to fat sources and its minimally invasive approach, unlike access to BM, is sufficient to compel researchers to further explore AD-MSC harvesting techniques.

### *MSC yield*

Pendleton *et al*[46] reported that AD-MSCs had a higher yield than BM-MSCs. Furthermore, a higher seeding density is necessary for the successful growth and expansion of BM-MSCs. Luna *et al*[47] recovered $1 \times 10^6$ adipocytes, $1 \times 10^6$ ASCs, $1 \times 10^6$ vascular endothelial cells, and $1 \times 10^6$ other cells from 1 g of adipose tissue. Adipose tissue contains up to 3% stem and progenitor cells in the uncultured SVF, containing 2500 times more stem cells than the BM source[48,49]. SVF mixture, a derivative of adipose tissue, contains 30% MSCs, 3% endothelial cells, and 14% endothelial precursor cells[50], whereas BM-MSCs contain 0.001% MSCs, 0.1% endothelial cells, and 2% endothelial precursor cells[51].

AD-MSCs demonstrate a consistently faster proliferation rate across multiple passages[46]. While the proliferation rate of MSCs from both sources was comparable on days 3 and 7, AD-MSCs continued to proliferate significantly up to day 21, and BM-MSCs attained a plateau from day 14. Similarly, significantly higher cellular metabolic activity was noted in AD-MSCs than in BM-MSCs on days 14 and 21, indicating a higher cellular yield of MSCs[46].

### *MSC differentiation potential*

Although AD-MSCs are harvested with minimal morbidity and provide a better yield than BM-MSCs, the ultimate target of these MSCs in orthopedic research is their differentiation potential in chondrogenic and osteogenic lineages. Chondrogenic differentiation at the gene level, determined by real-time quantitative polymerase chain reaction, showed that the expression of the chondrogenic gene aggrecan varied in AD-MSCs and BM-MSCs from different donors. However, overall, the expression was significantly higher in BM-MSCs than in AD-MSCs. There was no remarkable difference in cartilaginous proteoglycan matrix formation between AD-MSCs and BM-MSCs[11]. The expression of Runx2, collagen type I, and alkaline phosphatase increases from day 7 to day 14 in both AD-MSCs and BM-MSCs, with significantly higher expression in BM-MSCs than in AD-MSCs[11].

Despite easier harvest and superior yield from adipose tissue, AD-MSCs fall short in terms of differentiation potential in chondrogenesis or osteogenesis compared to BM-MSCs. Therefore, research to enhance the necessary lineage differentiation characteristics of AD-MSCs is ongoing to reap the full benefits of its abundant availability and ease of harvesting because AD-MSCs have a more grounded immunomodulatory impact than BM-MSCs in altering the pathological milieu of the target site[52-54].

### *MSC storage*

Short- and long-term storage of AD-MSCs was investigated. The storage of AD-MSCs decreases their cellular proliferative capacity over time[55]. Hence, it must be supplemented with 10% human serum or PRP in 0.9% saline solution at 4 °C for the first 2 h and not more than 4 h[56,57]. For long-term storage, AD-MSCs can be stored at -80 °C in liquid nitrogen for up to 6 mo[58,59]. In contrast, BM-MSCs have been stored for more than 10 years without losing their multipotency[60].

### Future directives

With the evolution in the understanding of the biology of MSCs, there is a corresponding expanding horizon of their therapeutic possibilities with their properties towards induction of angiogenesis; regulation of immune response and inflammation; modulation of cell differentiation and proliferation; extracellular matrix formation; neuroprotective and neurotrophic effects; and anti-apoptotic, anti-tumor, and anti-microbial activities[61]. Apart from identifying the ideal source of MSCs for a particular scenario, the development of methods to identify their potency is needed for objective assessment of the individual MSCs concerned to account for individual variability, which might affect the therapeutic response[62]. The future of MSC-based therapies is driving towards a cell-free secretome-based therapy using MSC-derived exosomal vesicles that exert the necessary functional activities of MSCs, where the ideal required cellular characteristics of MSCs from multiple sources could be combined to obtain the maximum benefits of the individual MSC source[63].

### Limitations

Our study had certain limitations. First, we could not find data on the blinding of the intervention to the participants in most of the included studies, which could invite room for bias on the part of patients or observers. Second, we noted heterogeneity among the majority of the analyzed outcomes, which could be due to the variability in the protocols followed for intervention in the included studies, as shown in Table 2. The heterogeneity could also be attributed to the inclusion of patients with a different spectrum of disease processes or difference in the control interventions utilized across the included studies. Therefore, we recommend a large multicenter trial with a standardized dosage and intervention protocol, evaluated using established outcome measures both in the short and long term, without any adjuvant procedures to further confirm our analysis results.

## CONCLUSION

Our critical analysis of the literature showed that adipose tissue is superior to BM as a source of MSC because of its safety and consistent efficacy concerning improvement in pain and functional outcomes in managing knee OA. However, future trials of sufficient quality are warranted to validate our findings to arrive at a consensus on the ideal source of MSC for use in cellular therapy for knee OA.

## ARTICLE HIGHLIGHTS

### Research background

Mesenchymal stromal cell (MSC)-based therapies are being commonly utilized in the context of knee osteoarthritis (OA) with promising results. The commonly used sources of the MSC remain in the bone marrow (BM) and the adipose derived (AD).

### Research motivation

Despite the prevalence of the use of MSCs of varying origins in the management of knee OA, the literature is not clear on the ideal source to focus on for future research.

### Research objectives

In this study, we aim to compare the efficacy and safety of the two commonly used sources of MSCs namely BM and adipose tissue in the management of knee OA.

### Research methods

We conducted a systematic review and meta-analysis of the randomized controlled trials (RCTs) in the literature identified from databases such as PubMed, EMBASE, Web of Science, and Cochrane Library until August 2021 that analyzed the efficacy and safety of AD and BM-MSCs in the management of knee OA. we used outcome parameters such as the visual analog scale (VAS) score for pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, Tegner score, magnetic resonance observation of cartilage repair tissue (MOCART) score, knee osteoarthritis outcome score (KOOS), and adverse events.

### Research results

We identified twenty-one studies including 936 patients. Of all the studies included, only one study compared the two MSC sources without patient randomization; hence, the results of all included studies from both sources were pooled, and a comparative critical analysis was performed. At six months, both AD-MSCs and BM-MSCs showed significant VAS improvement ($P$ = 0.015, $P$ = 0.012); this was inconsistent at 1 year for BM-MSCs ($P$ < 0.001, $P$ = 0.539), and AD-MSCs outperformed BM-MSCs

compared to controls in measures such as WOMAC ($P < 0.001$, $P = 0.541$), Lysholm scores ($P = 0.006$; $P = 0.933$), and KOOS ($P = 0.002$; $P = 0.012$). BM-MSC-related procedures caused significant adverse events ( $P = 0.003$) compared to AD-MSCs ($P = 0.673$).

### *Research conclusions*

Our study identified adipose tissue to be superior to BM in terms of its safety and consistent efficacy in improving the pain and functional outcome parameters analyzed.

### *Research perspectives*

We suggest for future RCTs be conducted to make a direct comparison of the two sources considering the paucity of the literature identified in this study and also to validate the findings arrived in the study.

## FOOTNOTES

**Author contributions:** Muthu S, Patil SC, Jeyaraman N, and Jeyaraman M involved in the conception and design of the manuscript; Gangadaran P, Rajendran RL, Oh EJ, Khanna M, Chung HY, and Ahn BC contributed to the administrative support; Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, and Khanna M participated in the provision of study materials or patients; Muthu S, Patil SC and Jeyaraman N involved in the collection and assembly of data; Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, Gangadaran P, Chung HY, and Ahn BC analysied and interpreted data; Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, Gangadaran P, Rajendran RL, Oh EJ, Khanna M, Chung HY, and Ahn BC wrote the manuscript writing; Muthu S, Chung HY and Ahn BC are co-corresponding authors of this manuscript; Gangadaran P, Rajendran RL and Chung HY contributed to the funding acquisition; and all authors have read and agreed to the published version of the manuscript.

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