



Systematic review on comparative outcomes in cell-based regeneration techniques vs. traditional techniques in osseointegration of implants in total knee arthroplasty

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Abstract

Background: Total Knee Arthroplasty (TKA), a proven and cost-effective orthopedic surgical technique, consistently reduces preoperative morbidity, enhances functional capacity, and alleviates pain in degenerative knee osteoarthritis.

Objectives: The aim of this study was to compare cell-based and traditional techniques in Osseointegration in Total Knee Arthroplasty.

Methods: The literature search was conducted, across various electronic databases including Google Scholar, PubMed, Web of Science, Scopus, and the Cochrane Library. The search was conducted from 2001 to 2022, aiming to identify studies related to TKA and the various techniques employed in the procedure. Articles were screened based on the relevance to cell-based and traditional Osseointegration techniques, focusing on extracting information related to outcomes and complications.

Results: We included 11 studies in the study, employing the Cochrane 'Risk of Bias tool' to assess bias in randomized trials across five domains. The majority of articles demonstrated low risk (56.36%), signifying reliability, while 'Unclear' studies (32.73%) had some ambiguity without invalidating results. Studies classified as 'High risk' (10.91%) indicated substantial bias and potential errors. Our findings suggest that cell-based techniques are efficient for the treatment of TKA.

Conclusion: Osseointegration presents significant advantages in terms of function and pain relief for patients willing to accept associated risks. Cell-based techniques have proven effective in preventing the need for revision in TKA, demonstrating long-term effects.

Keywords: Knee arthroplasty, Osseointegration, Cell techniques, Metal implants, Osteoarthritis.

Introduction

Bone is a collagenous tissue with the ability to self-heal, but severe damage or large defects may hinder proper repair. Porous metal implants, such as titanium alloys and cobalt-chromium alloys, are commonly used to repair serious bone defects. However, the success of these implants depends on their ability to achieve strong biological fixation to fragile bone substrates. Complications can arise in orthopedic surgery due to major bone abnormalities resulting from acute traumatic damage, chronic disease, tumor removal, infection, or

previous implant failures.^[1]

The study of Vaidya et al., (2020), reported a significant increase in joint replacement surgery.^[2] Based on a market survey, it has been observed that the annual count of joint replacement surgeries in India is consistently on the rise. The projected figures for knee arthroplasty procedures are expected to reach approximately 200,000 by the year 2020.^[3] Knee osteoarthritis has emerged as one of the main causes of disability among individuals over the age of 65. It leads to increased pain, functional difficulties, reduced productivity, and diminished quality of life. Several

therapy options exist for managing mild-to-moderate osteoarthritis, with total knee arthroplasty (TKA) being the recommended treatment for end-stage knee arthritis.^[4] TKA, also known as surgical knee replacement, is a highly effective and cost-efficient procedure that improves function, mobility, discomfort, and overall health-related quality of life.^[5] However, TKA is not without risks and complications. It is a major surgical procedure often performed on elderly patients with comorbidities, making them susceptible to both immediate and delayed problems and failures.^[6]

Aseptic loosening of metallic implants is a common reason for revision procedures, accounting for approximately one-third of cases. Achieving long-term and permanent anchoring of implants is crucial for successful knee arthroplasty. Osseointegration (OI) has shown promise in providing a reliable and durable fixation of implants. OI refers to the direct structural and functional connection between living bone and the surface of an artificial implant. Cementless implants and their integration with bone are key factors in achieving successful knee arthroplasty outcomes.^[7]

In recent years, cell-based regenerative therapy has advanced significantly and has become the standard for treating serious chondral lesions and traumatic osteochondral defects. It holds the potential for addressing degenerative cartilage lesions in early osteoarthritis cases. Ongoing advancements and exploration of alternative cell sources may extend cell-based regeneration therapy to treat all structures around the knee joint.^[8] Mesenchymal stem cells (MSCs) have gained significant attention in various therapeutic procedures due to their high differentiation capacity, proliferation potential, and ability to migrate to injury sites. MSCs have been widely used in the treatment of regenerative changes in joints, bone and cartilage restoration, and other clinical applications.^[9] As the aging population grows and the number of total joint replacements performed on patients under the age of 65 increases, regenerative joint preservation techniques have gained attention. These techniques include autologous chondrocyte transplantation (ACT), matrix-guided autologous chondrocyte transplantation (MACT), mosaicplasty, microfracture, injectable MSCs, and MSC scaffold approaches.^[10]

Objectives

With the increasing demand for total knee joint surgery, there is a need to advance the development of cell-based regenerative techniques and enhance traditional osseointegration methods. Thus, the present systematic

review presents the comparative outcomes in cell-based regeneration techniques versus traditional techniques in osseointegration of implants in TKA.

Methods

The protocol for the study was built on approved reporting articles for systematic review (PRISMA-P) declaration and all the changes were properly reported. The Cochrane Handbook and the PRISMA statement were followed in conducting and reporting this systematic review. This review was not registered. Our literature search included Google Scholar, PubMed, and Scopus among other computerized databases. The articles were taken from 2011 to 2022. The related keywords in the following search terms include: Cell-based regeneration, Total knee arthroplasty, Osseointegration, Mesenchymal cell therapy, and traditional techniques in Osseointegration were used in the limitation to publication in the English language. By starting from 2011, the intention was to include up-to-date and relevant studies, considering that older publications might not reflect the current state of knowledge and practices. Several eligibility factors, including inclusion and exclusion criteria were taken into consideration when doing the study selection.

Inclusion criteria

- RCTs (Randomized clinical trials)
- Most widely used traditional Osseointegration techniques
- Articles that provide information on TKA
- Clinical trials, full-text articles
- Articles written in the English language
- Articles that provide information on cell-based techniques
- Gender: Both (male and female)

Exclusion criteria

- Case reports, Case series
- Conference articles
- Incomplete texts
- Duplicate articles that are excluded from the study
- Patients with psychiatric disorders, pregnant women
- Articles before 2011

Quality assessment of included study

A total of 11 studies were included in this review. The piloted data extraction was performed in Microsoft Office Excel 2013 (Microsoft Corporation, USA), using RevMan software version 5.4. Two review authors independently evaluated the risk of bias in the studies. Risk of Bias Tool for Randomized Controlled Trials was used to assess the

included trials. Studies were classified as high risk (+), unclear risk (?), or low risk (-). The following domains were assessed: random sequence generation, allocation concealment, blinding of outcome assessor, incomplete

outcome data, and other sources of bias. To assess the quality of the included studies, the Cochrane checklist was used as a guide for describing and assessing patient-reported outcomes in clinical trials.

Table 1. Cell-based techniques versus traditional OSSEO integration techniques

Sr. No.	Author, Year	Study Design	Techniques		Outcomes	
			Cell-Based	Traditional (Osseointegration)	Advantage	Disadvantage
1.	Freitag et al. (2016) ^[10]	Randomized clinical trial	Autologous Chondrocyte Transplantation (ACT)	-	-Result in hyaline-like cartilage formation via skin incision. -Improvement in pain and function -Long-term durability	- Risk of transplant failure -Paucity of autograft donor site -Chondrocyte dedifferentiation
2.	Zellner et al. (2015) ^[11]	Randomized clinical trial	Matrix-guided autologous chondrocyte transplantation (MACT)	-	-Used for large, full-thickness articular cartilage defect -Best quality of regenerated tissues	-Failure at long-term follow-up
3.	Inderhaug et al. (2019) ^[12]	Randomized clinical trial	Mosaicplasty	-	-Knee articular cartilage lesions.	-Not recommended for patients with osteoarthritis
4.	Gomoll et al. (2011) ^[13]	Randomized clinical trial	Microfracture	-	-Treatment of small defects in femoral condyles -Low invasiveness	-First line treatment for patients with small lesions -Patellofemoral joint deteriorates after several months
5.	Lopa et al. (2019) ^[14]	Clinical Trial	Injectable MSC	-	-Harvestable with a minimum invasive procedure An easy way to deliver is an intracellular injectable -Selection of homogenous cell population	-Less evidence of efficacy -Inconsistent observation of disease condition
6.	Yamagata et al. (2018) ^[15]	Randomized clinical trial	MSC Scaffold	-	-Use in hyaline-like cartilage, regenerative medicine for articular cartilage -No donor site morbidity	-Long-term effects are inconsistent, potential chondrocyte hypertrophy
7.	Unune et al (2022) ^[16]	Randomized clinical trial	-	Metal based (Titanium and Titanium alloy, tantalum, Cobalt-chromium alloy, Stainless steel)	Corrosion resistance, low density, low electrical and thermal conductance, biocompatible, good mechanical properties	Allergic reactions, oxidational wear, wear debris
8.	Ayatollahi et al. (2019) ^[17]	Randomized clinical trial	-	Ceramics based (Zirconia, alumina)	High wear and fatigue resistance, high resistance, high mechanical strength, scratch resistance, reduced micro motions	No health implications, aging process, bioinert, leaching of toxic metals, or load

					and shielding effect, development of soft tissue between bone and prosthesis	shielding generated due to high Young's modulus
9.	Mishra and Chowdhary (2019) ^[18]	Randomized clinical trial	-	Polymer based (Polyetheretherketone (PEEK))	Cell adhesion, proliferation, biocompatible, reduced chance of peri-implant infection, chemical resistance, mechanical resistance	Bioinert, lacks antibacterial activity
10.	Lei et al (2019) ^[19]	Randomized clinical trial		Allograft bone grafting	Free to use, non-time consuming, effective method to reduce blood loss	Increased risk of infection, transmission of viral diseases and immunological diseases, expensive
11.	Schmidt (2021) ^[20]	Randomized clinical trial		Autograft bone grafting	Histocompatible, no risk of disease transmission, osteogenic	Time-consuming, blood loss

Results

The present systematic review yielded 12,546 articles on initial search; 12 articles of additional records identified from the cross references were found in which the first 8541 duplicate or triplicate publications were removed. In this study, 4017 published studies were screened. On detail screening, additional 1761 articles were excluded because of missing parameters, in addition to that 1542 articles were irrelevant to the present review. Based on inclusion criteria full-text articles were evaluated for the review. Incomplete irrelevant data, case reports/ case studies were removed. After performing a complete screening and analysis of data, a total of 11 studies were included in the present systematic review [Figure 1]. The articles ranged in the date from 2011 to 2022.

In this study, 11 literatures were included of which 6 studies^[10-15] were on cell-based regeneration techniques as well and 5 studies were found with traditional Osseo integration techniques [Table 1].^[16-20]

This researcher's risk of bias was evaluated using the Cochrane "Risk of Bias tool" for randomized trials. In RCT, the following five domains of bias were estimated using the Cochrane Collaboration tool for assessing the risk of bias.

- The randomization technique
- Deviations from intended interventions
- Incomplete outcome data
- Measurement of risk
- Bias in the selection of the reported result

Most of the articles^[10-20] were given a low-risk rating

(56.36%) based on an assessment of the overall bias risk for each chosen work. A "low-risk" research employs a reliable method to assign patients to different courses of therapy, and the findings are regarded as reliable. An "unclear" study may have (32.73%) bias, but likely not enough to make the findings erroneous. It also might not have all the necessary data. A "high risk" (10.91%) denotes a large amount of bias that might make the findings erroneous. In this instance, there are several gaps in knowledge or reporting inconsistencies.

Discussion

The most popular inpatient surgical technique is TKA. Between 2005 and 2030, the frequency of TKA surgeries is going to increase rapidly, resulting in about 3.48 million surgeries yearly. The development and application of a multidisciplinary strategy to improve the TKA have become necessary.^[4] In another study presented by Shafaghi et al., a total of 61,421 TKA procedures were carried out in Canada during 2014–2015, a 20% increase during 2000-2001. Between 2014 and 2015, revision total knee arthroplasties (rTKAs) made up 6.8% of all TKA procedures; by 2025, this percentage is expected to increase by another 12%.^[21] With the potential to prevent disease development, recent findings suggest that the degenerative process can be reverted thus the MSC-based cell treatments present a promising option for the treatment of OA.^[10] According to research by Marlovits et al., approximately 40% of ACTs show chondrocyte adaption. This could be connected to the dysregulation of

chondrocytes during ex vivo culture, ultimately leading towards the synthesis of type 1 collagen instead of type 2 collagen.^[22] With increasing knowledge the ACT has become the frequently used technique with good outcomes and results. Direct injection of MSCs into knee joints was carried out by Centeno et al. who directly injected the mesenchymal stem cells into knee joints which is formulated in PBS to the patients having degenerative OA.

In the second week, the patient received a second injection of 1 mL of 10 ng/mL dexamethasone which stimulates the chondrogenesis when given in small doses. Following up with the patients at three and six months revealed improved cartilage volume up to 28.64% and decreased pain in OA patients. Only one patient was studied and no long-term effects considered were the limitations of the study.^[23,24]

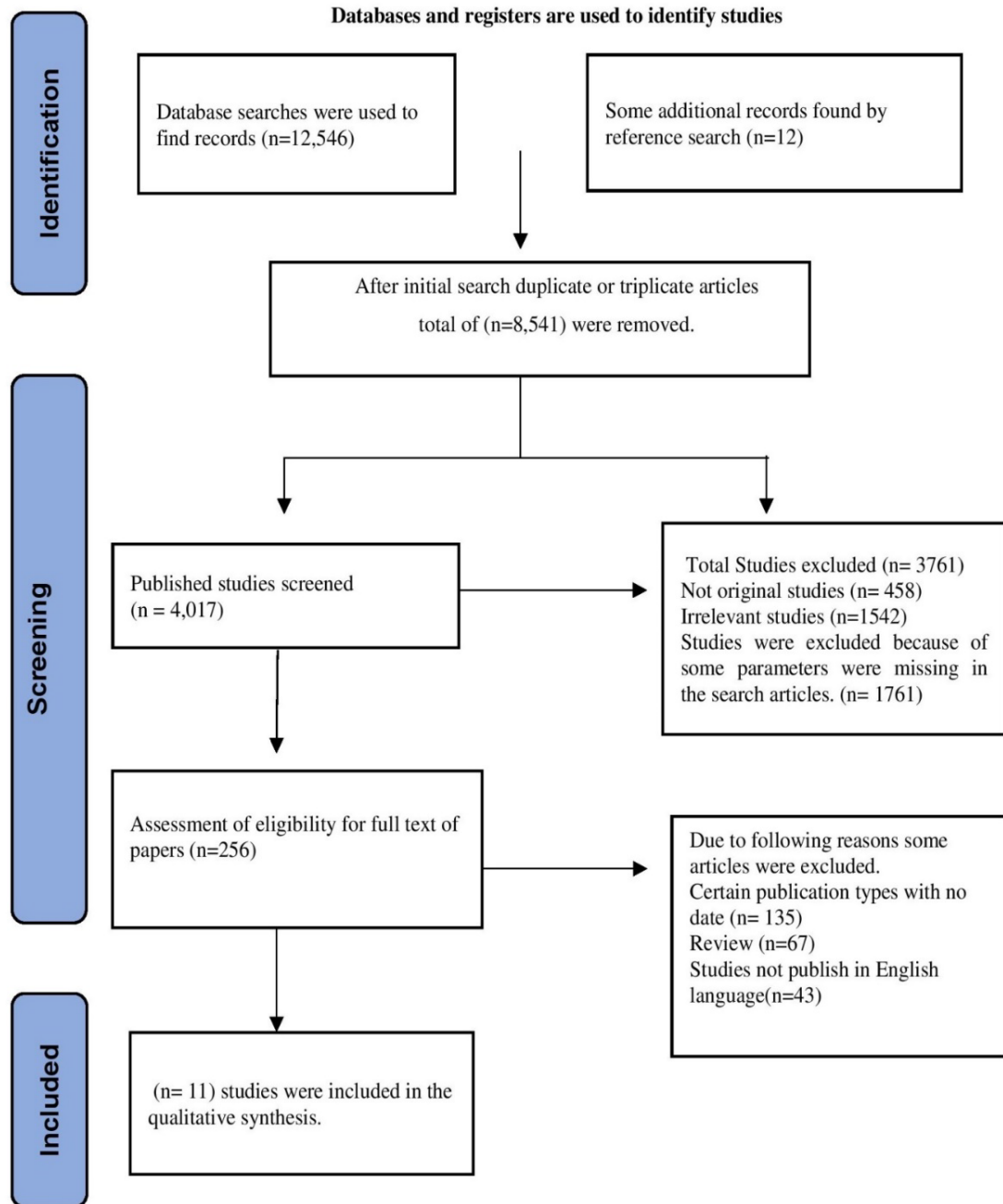


Figure 1. The PRISMA flow diagram as well as the article's specified relevant database

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Other bias
Andreas H et al. (2011)	+	?	?	+	+
Ayatollahi et al. (2019)	+	?	?	+	+
Freitag et al.(2016)	+	+	?	+	+
Inderhaug E et al. (2019)	?	+	+	+	+
Lei P. et al (2019)	?	+	+	+	+
Lopa S. et al.(2019)	+	?	?	+	?
Mishra, S. and Chowdhary, R. (2019)	+	+	+	+	?
Schmidt H. (2021)	+	?	+	?	+
Unune D. et al (2022)	+	+	?	+	?
Yamagata K et al.(2018)	?	+	?	+	+
Zellner J et al. (2015)	+	?	+	+	+

Figure 2. Summary of risk of bias: evaluation of each’s study involved item’s risk of bias

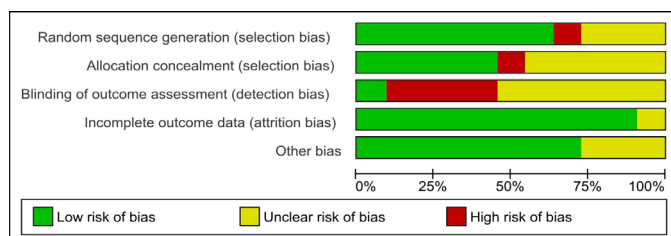


Figure 3. The author's evaluation of each risk of bias item represented as percentages through all involved articles in the risk of bias graph

In the study presented by Ozturk et al., for chondral lesions up to 2.5 cm², mosaicplasty was performed on 19 patients, the oldest of whom was 46 years old. After a median follow-up of 32.4 months, we found 11 outstanding as well as 7 positive performances which are equivalent to those published in the literature. Marcacci et al., similarly concluded that mosaicplasty was a reliable and secure procedure at the short- and medium-term follow-up in research including 37 patients.^[25] By providing a necessary scaffolding component for the utilization of stem cells, research on stem cells in combination with autologous bone may prove to be the

true gold standard of bone regeneration because it delivers optimal attributes for bone growth.^[26,27]

In comparison to the autologous bone grafting technique, the utilization of mesenchymal cells is a method of choice, and Chabord et al., termed it a platinum standard for bone regeneration.^[28] In the study performed by Kahn et al., the majority of patients experience a favorable outcome in TKA surgery. They compared their outcomes with other research studies and showed a favorable correlation between the pre and post-operative outcomes. The study findings regarding the relationship between preoperative and postoperative suggest some risk factors including osteoarthritis and joint pain continually exist.^[29] The success of osseointegrated prostheses in Sweden, as demonstrated by Aschoff et al., inspired the development of implants in Germany in the late 1990s. The German implant design substituted porous-coated alloy intramedullary press-fit devices, which are comparable to those used in joint arthroplasty, for screw-type fixation. To prevent implant fatigue failure, a stabilizing bone bracket attachment was also included in the original design which was designed under the guidance of Ashoff et al., which is termed as exo-endo prosthesis of femur. During their first operation, they implanted a Spongiosa Metal surface which was porous allowing OI without need of cement. About 6 to 8 weeks later, during the second stage of surgery, a stoma was made to expose the implant's distal end and attach a dual cone adaptor for the prosthetic parts' fixation.^[30] In another study concluded by Dibartola et al., a follow-up study of several months MACT was proven to be successful for cartilage regeneration over a wide range of clinical outcomes with a positive outcome of 35.7%.^[31] The microfracture cell-based regeneration technique was proven to be efficient for small bone defects which decrease pain and mobility. In another study conducted by Fortier and Cole, they described the complication risk as 50% because of the formation of cysts or the growth of subchondral sclerosis.^[32] Between 1994 and 2009, Franke et al., employed an allograft bone grafting technique in 27 patients. The patients were monitored for about five years to study the survival rate of revision on TKA. The research showed 63% outstanding results with 14% good outcomes and 6% poor outcomes.^[33] Baldwin P et al. demonstrated that the gold standard for treating postoperative problems such as fracture and delayed union. In some patients, the outcomes of autograft bone grafting were less inadequate due to donor site morbidity or insufficient graft extraction. However, in recent years, advances in allograft and bone graft replacements have led to practical alternatives that

overcome some of the limitations of autograft.^[34] To enhance the overall osseointegration, the surface roughness of implants can be improved at macro, micro, and nano spatial scales. According to previous research studies, there is a trade-off between enhancing osseointegration and preventing bacterial adhesion for an ideal surface roughness for hard tissue osseointegration.^[1] Bade et al., in the study observed the results of patients and compared them with the old, young patients with a follow-up after the first and third week and then 6 months following TKA. After 6 months patients had noticeable defects in their knees while walking and climbing stairs as compared to other adults. Postsurgical, participants in this trial underwent a standardized recovery regimen. Just 26% of patients receive outpatient physical therapy after TKA. The participants in the current study may represent a group of patients who were unable to provide physical treatment after TKA. However, the patients after TKA will fall for the risk in the first year of surgery. This will create the need for research to decrease the risk of falls and problems which is faced by patients after TKA.^[35] Thus, the cell-based techniques have proven to be efficient as compared to traditional osseointegration techniques.

Conclusions

Musculoskeletal disease is becoming more prevalent, which focuses on the preventive need and regenerative therapy instead of frequently applied painful treatment methods. Aseptic loosening and fibrous encapsulation are the major causes leading to the failure of orthopedic implants. The most effective and used surface modification techniques are needed currently. MSC-based cell treatments offer fascinating opportunities in the treatment of OA with the potential to prevent disease development and recent findings of repairing this degenerative process. Thus, the least explored but most exciting areas of research for the next generation are bone-related regenerative medicine devices for physiologically enhancing porous metal implants. TKA is a successful and affordable option for treating end-stage knee arthritis, but there are still certain perioperative risks, problems, and long-term failures that effectively need new clinical trials or techniques for better improvement.

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None.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

Total knee arthroplasty: TKA; Osseointegration: OI; Mesenchymal stem cells: MSCs; Autologous chondrocyte transplantation: ACT; Matrix-guided autologous chondrocyte transplantation: MACT; Randomized clinical trials: RCTs.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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