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**Recent advances and future directions in the management of knee osteoarthritis: Can biologic joint reconstruction replace joint arthroplasty and when?**

Paschos NK. Can biologic joint reconstruction replace joint arthroplasty?

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**Abstract**

In this article, a concise description of the recent advances in the field of osteoarthritis management is presented. The main focus is to highlight the most promising techniques that emerge in both biologic joint replacement and artificial joint arthroplasty. A critical view of high quality evidence regarding outcome and safety profile of these techniques is presented. The potential role of kinematically aligned total knee replacement, navigation, and robotic-assisted surgery is outlined. A critical description of both primary and stem cell-based therapies, the cell homing theory, the use of biologic factors and recent advancements in tissue engineering and regenerative medicine is provided. Based on the current evidence, some thoughts on a realistic approach towards answering these questions are attempted.

**Key words:** Osteoarthritis; Biologic joint reconstruction; Total joint arthroplasty; Cartilage; Evidence-based

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**Core tip:** In the quest for answers for the future of joint reconstruction, this article explores how feasible is to claim today that biologic joint reconstruction will soon replace artificial joint arthroplasty. Will stem cell-based therapies, biologic factors and tissue engineering and regenerative medicine be able to change orthopedic practice in the near future? What is the current evidence? On the other hand, are kinematically aligned total knee replacement, and robotic-assisted surgery able to further advance joint replacement? Based on the current evidence, some thoughts on a realistic approach for the future of joint reconstruction, biologic or not, are discussed.

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**INTRODUCTION**

Osteoarthritis represents one of the most common disorders in orthopedics. It is believed that it would be one of the main disorders affecting quality of life in the next decades due to the increasing aging of the population[[1](#_ENREF_1)]. Management of osteoarthritis has been improved significantly over the last years with further improvement of the current therapeutic modalities, mainly total joint replacement. In parallel, a new era of biologic joint reconstruction has been initiated with the use of biologic tissue that aims to replace degenerative tissue.

In this editorial, a concise description of the recent advances in the treatment of osteoarthritis will be outlined in an attempt to highlight the emerging techniques in both biologic joint replacement and artificial joint arthroplasty. The question of “how feasible is to claim today that biologic joint reconstruction will soon replace artificial joint arthroplasty?” based on the current evidence will be approached. Finally, some thoughts on “how soon these changes can be constituted in clinical practice?” will be shared.

**ADVANCEMENTS IN ARTIFICIAL JOINT REPLACEMENT**

***Kinematic aligned total knee replacement***

Starting approximately 10 years ago, kinematically aligned knee replacement surprised most of us with the favorable subjective outcomes scores reported[[2](#_ENREF_2),[3](#_ENREF_3)]. The goal in kinematically aligned TKR is to align the femoral and tibial components so that the three axes that describe tibiofemoral and patellofemoral kinematics would be restored according to the normal joint lines. Kinematically aligned knee replacement remains very effective with comparable – if not better- results from those of mechanically aligned total joint arthroplasty[[3-5](#_ENREF_3)]. This led to a rather constructive criticism, and theories that could interpret these data that could be remarkably helpful in guiding further improvement of arthroplasty design and techniques[[6](#_ENREF_6)]. The main advantages of kinematically aligned Total knee arthroplasty (TKA) is that allows proper positioning of TKA implants in order to restore the axis of both patellofemoral and tibiofemoral flexion/extension axes. As a consequence, it is independent of the femoral head and ankle position that outline the mechanical axis of the knee that is used as a reference in mechanically aligned TKA. A randomized control trial confirmed these advantages by demonstrating the superiority of the kinematically aligned TKA compared to mechanical aligned TKA in terms of almost all clinical outcomes, such as Oxford Knee and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, as well as better flexion and reduced pain[[3](#_ENREF_3)]. Also a study with a mean follow up of 6 years demonstrated an implant survivorship of 97.5% with an overall Oxford Knee score of 42.7[[2](#_ENREF_2)]. As always, time will be the judge of whether the principles of kinematically aligned arthroplasty can be expanded and embraced in a way that they will improve outcomes and orthopedic practice.

***Navigation***

Navigation assisted arthroplasty was an innovation that it is clear that improves better alignment and positioning of the arthroplasty implant[[7-9](#_ENREF_7)]. Specifically, in a prospective study, it was shown that computer-assisted TKA was associated with significantly less variability, resulting in a mechanical axis with more than 3 degrees difference only in 4% of the cases, which was significantly lower to the 22% of the conventional technique[[7](#_ENREF_7)]. Another randomized controlled trial suggested that navigation resulted in improvement in varus/valgus axis and rotation of the femoral component[[8](#_ENREF_8)]. However, almost ten years after the first promising reports, computer-assisted arthroplasty still struggles to prove its efficiency and establish its role in joint arthroplasty due to the fact that there is not adequate support that the observed difference in alignment can be indeed translated into better subjective and outcome analysis scores[[10](#_ENREF_10)] – especially when in other subspecialties, *e.g.*, in spine, its beneficial role was earlier and widely accepted[[11](#_ENREF_11),[12](#_ENREF_12)]. However, more recent findings seem to demonstrate a tendency of improved outcome scores as a correlation of better implant positioning[[13](#_ENREF_13),[14](#_ENREF_14)].

***Robotic technology in orthopedics***

Robotic surgery is probably the most common application that can depict the future involvement of technology in clinical orthopedic practice. Even though robotic-assisted surgery started its first steps more than 20 years ago, with orthopedics being one of the first specialties that used a robotic system, it was only at the last 5 years that its use has been remarkably extended. The experience reported so far with unicompartmental knee arthroplasty has shown that robotic systems can improve coronal alignment and show some improvement in clinical outcome compared to conventional unicompartmental knee arthroplasty[[15](#_ENREF_15)]. Several other reports suggest better alignment and accuracy with robotic–assisted surgeries[[16-18](#_ENREF_16)]. For TKA, early findings suggested the potential improvement in accuracy in component placement, but also highlighted the increased cost, prolonged operative time and high complication rate during surgical learning curve[[19-22](#_ENREF_19)]. In a randomized control study where in patients undergoing bilateral TKA, one TKA was performed with robotic-assisted technique while the other was conventional, the statistically better alignment achieved with robotic-assisted technique was not associated with improvement in clinical outcomes[[23](#_ENREF_23)]. Thus, even though literature shows an improved accuracy with robotic-assisted technique, however, long term data are yet to be reported, and additional data from high level studies and registries are necessary[[24](#_ENREF_24),[25](#_ENREF_25)]. One of the major factors that limit their application in the near future is high cost, concerns regarding hardware and software failure, and the learning curve required[[15](#_ENREF_15),[24](#_ENREF_24),[26](#_ENREF_26)].

**ADVANCEMENTS IN BIOLOGICAL JOINT RECONSTRUCTION**

The concept of biological joint reconstruction envisions the replacement of the degenerative articular cartilage with biologic, non-artificial material that can be fully incorporated and integrated with the remaining healthy tissue. Even though the idea is miraculous, unfortunately regeneration of articular cartilage has proven not a simple task so far[[27](#_ENREF_27)]. Articular cartilage represents a tissue composed of thick collagenous extraarticular matrix maintained by chondrocytes, the only cellular component of articular cartilage. As such, articular cartilage lacks vessels and nerves, and it has a poor healing and regeneration potential. Therefore, any attempt to enhance this potential is condemned to fail, especially in an environment that led to degeneration in the first place.

During the evolution and further development of the biological approaches for joint reconstruction over the last years, there are some interesting advancements and that may be proven as important milestones in further evolution in the field.

***Primary and stem cell-based therapies***

Primary chondrocytes remain the golden standard as a cell source for cartilage defect treatments, twenty years after their description of autologous chondrocyte implantation (ACI) that has initiated the concept of biological joint repair[[28](#_ENREF_28)]. Despite the fact that ACI and subsequent modifications have been applied in clinical practice for several years, it was only recently that its superiority over microfracture was evident in meta-analyses[[29](#_ENREF_29),[30](#_ENREF_30)]. Interestingly, microfracture technique still shows favored outcome, that in certain cases seems comparable to chondrocyte implantation[[29](#_ENREF_29)].

Stem cells represent the other part of the dipole in the quest of appropriate cell source for biologic cartilage reconstruction. Again, since the first animal report in 1994[[31](#_ENREF_31)], there are only few recent high-level studies validating the successful effect of mesenchymal stem cells in clinical practice[[32](#_ENREF_32)]. Two main stem cell populations have been widely used in animal and clinical studies with promising results, *i.e.*, bone-marrow derived mesenchymal stem cells and adipose derived stem cells[[32](#_ENREF_32),[33](#_ENREF_33)]. Another important step toward the extensive use of mesenchymal stem cells was the fact that they exhibit a relatively safe profile regarding toxicity, organ system adverse effects, infection, and malignancy in a recently published meta-analysis[[34](#_ENREF_34)]. The advantage of stem cells is the fact that they can potentially override primary cell donor morbidity and limited availability and they can be used in various culture technology systems[[35](#_ENREF_35)]. Unfortunately, only limited clinical data are available for stem cell use in cartilage reconstruction, therefore, these findings are promising but still preliminary[[36](#_ENREF_36)].

***Cell homing***

The recruitment of endogenous cells in an anatomic compartment is due to various stimuli and their contribution in tissue healing and regeneration. Even though the initial hypothesis has been stated for tissue growth and development, it seems that cell homing is a mechanism that takes place in multiple levels and various physiological mechanisms[[37](#_ENREF_37)]. This concept was proven valid in musculoskeletal tissue regeneration as well. The entire articular surface of the proximal humeral was successfully regenerated *via* cell homing only, without any cell transplantation in the joint[[38](#_ENREF_38)].

Cell homing could be the mechanism behind the reported success of several applied techniques in musculoskeletal repair and regeneration. In one of the most widely used techniques in cartilage management, the concept of cell homing explains in part the favorable results seen in microfracture technique, despite its simplicity. The release of progenitor stem cells from the bone marrow into the joint, allow these cells to differentiate into the “cell in need” and to replace the defective area. However, it is important to accept the inherent limitations that “cell-homing” process, such as the inadequacy to differentiate in all different cell types and that cell homing is a delicate process that needs specific requirement in order to act. Further exploration of combining cell-homing with other regeneration strategies, such as biologic growth factors promises to open an entirely new field in biologic cartilage joint reconstruction. It is also of paramount importance to acquire a better understanding of the exact pathways that are activated during cell homing and of the stimuli that are involved in this process.

***Biologic growth factors***

The extensive use of biologic factors that can enhance cartilage repair, or even prevent degeneration is probably the most “hot topic” of the last decade. A simple Web of science search combining the term “osteoarthritis” with the term “platelet rich plasma” returns 199 items within the last 5 years with more than 1780 citations according to web of science; Other terms like “autologous chondrocyte implantation” or “ microfracture” return only 326 and 207 results with 2894 and 1782 citations. That means that the number of studies published about PRP reached the number of studies for microfracture and is approximately half of those dealing with ACI. More interestingly, the average number of citations per article is 8.94 for platelet rich plasma (PRP), 8.88 for ACI, and 8.61 for microfracture. This demonstrates that PRP received more citations per article compared to either ACI or microfracture. This is indicative of the popularity that PRP has received over the last years. Going through these articles you easily realize that PRP is one of those modalities that has sworn enemies and sworn supporters. Despite their popularity, high quality evidence that justifies their use and supports its effectiveness was only recently released. Unfortunately the existing evidence seems contradictory and does not clearly favor PRP use.

***Tissue engineering regenerative medicine applications and clinical biological approaches***

The idea of creating tissues *in vitro* that they can be implanted to replace degenerative tissue is an appealing approach. The field is advancing fast with significant improvement in the biomechanical properties of the engineered tissue. Two of the most appealing clinical applications that demonstrate promising data are the use of particulated juvenile articular cartilage and the use of Neocart, an autologous cartilage tissue implant[[39](#_ENREF_39),[40](#_ENREF_40)]. Both emerging techniques seem to have a favorable safety profile and they show improved clinical outcome[[39](#_ENREF_39),[40](#_ENREF_40)]. Longer term safety and effectiveness studies are required in order to verify their upcoming use in cartilage repair. The use of osteochondral allografts for large defect transplantation represents another technique that worth mentioning. In prospective studies, this technique has shown high efficacy and improved clinical outcome[[41](#_ENREF_41),[42](#_ENREF_42)]. The possibility of combining this technique with meniscus transplantation could provide an additional benefit to those patients[[43](#_ENREF_43)]. Lastly, several biological approaches that include osteotomy, osteochondral and/or meniscal implants can be successfully used to potentially delay osteoarthritis and provide good activity level in young patients[[44](#_ENREF_44),[45](#_ENREF_45)].

**CONCLUSION**

My understanding based on the above information is that the question “how feasible is to claim today that biologic joint reconstruction will soon replace artificial joint arthroplasty?” could be probably misleading. The question should not be about biologic reconstruction replacing arthroplasty but rather how effectively biologic cartilage repair can delay total joint arthroplasty? Based on the current evidence, the answer is that biologic joint reconstruction has shown promising data toward this direction. Data from registries seem to confirm a trend toward delay for primary knee joint replacement over the last decade. However, it is important to acknowledge that joint reconstruction is one of the most successful orthopedic techniques, with an average survival of more than 90% at 15 years for knee replacement and 86% survival at 22 years for hip replacement[[46](#_ENREF_46),[47](#_ENREF_47)].

In conclusion, biologic joint reconstruction can serve as a transitional period prior to joint replacement in the near future. The combination of both techniques and their proper use according to their specific indications and known limitations seem to be the only viable solution for now, as well as for the future. A successful use of biologic reconstruction will delay further conventional primary joint replacement and may eliminate the need of revision surgery. As always, further research and more high level evidence are essential in order to clarify further the advantages and disadvantages of the emerging techniques and to promote validation of their effectiveness and safety.

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