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Single Treatment Autologous Chondrocyte Implantation: The Next Generation of ACI

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Open Access **Editorial**

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Introduction

Cartilage defects are known to progress and eventually become generalised osteoarthritis *[1]*, and the pathway of care for osteoarthritis often ends in joint replacement. This can be problematic in younger patients: the likelihood of revision increases with time after the operation and younger patients are unlikely to be outlived by their implant *[2]*. Indeed, in patients aged 50-55, up to a third will require joint revision *[3]*, which is a more complicated procedure with poorer outcomes than the first replacement. Therefore, the longer a joint replacement can be delayed, the lower the chance of revision. But how can one go about delaying joint replacement?

Several procedures to regenerate cartilage lesions to a healthier state, thus reversing progression to osteoarthritis, are utilised. One example is microfracture, where small holes are drilled into a cartilage defect, exposing it to the bone marrow below which contains medicinal signalling cells (MSCs), previously known as mesenchymal stem cells *[4]*. There are believes that these MSCs can regenerate cartilage. While the short-term outcomes of microfracture are reasonable, the mid and long-term outcomes are poor *[5]*. The principle of expecting a 'fracture' to from cartilage is completely illogical, making holes in bone will only leads to haematosis and raise surfaces within the joint and worsen osteoarthritis in long term.

An overview of Autologous Chondrocyte Implantation

So what other options are there for regenerating cartilage? Autologous chondrocyte implantation is a surgical procedure where cartilage is harvested from the patient and enzymatically digested to isolate the chondrocytes. Autologous chondrocytes are used instead of allogeneic chondrocytes to reduce the likelihood of immune rejection. Then, the cells are either re-implanted onto the cartilage lesion and covered with a biological membrane, or seeded onto a scaffold which is implanted onto the lesion *[6]*. The implanted chondrocytes produce healthy cartilage over time, hence repairing the defect. ACI has undergone three significant changes since it was first reported clinically in 1994, and consequently is categorised into three generations. In the first, known as p-ACI, an autologous periosteal flap is utilised as the membrane and chondrocytes are implanted beneath it *[7]*. In the second, known as c-ACI, a bilayer collagen membrane is instead used *[8]*. In the third generation, a scaffold is seeded with chondrocytes and then implanted onto the defect, reducing the likelihood of leakage as the cells are within the scaffold, rather than underneath a membrane *[9]*. This approach is known as MACI: matrix-associated chondrocyte implantation. MACI has been shown to result in better outcomes than older ACI *[10]*, so it can be assumed that seeding chondrocytes onto a scaffold is more effective than injecting them onto a defect and covering it with a membrane. One thing all three previous iterations of ACI have in common is the need for a three-step process: cartilage extraction, culture in a laboratory, and re-implantation of the cultured cartilage onto the defect.

Limitations of ACI

Interestingly, outcomes for newer ACI techniques, like MACI, have been shown to behave better outcomes than microfracture after 5 years *[11,12]*. However, in the multi-step method of ACI, significant cost is incurred due to the necessity of two separate surgeries, transport of the cartilage and culture of the cartilage for up to 6-8 weeks in a laboratory *[6]*. It is unsurprising then, that a recent cost-effectiveness analysis found that microfracture is more cost-effective than ACI *[13]*, with a cost-per-point change of $200.59 for microfracture and $536.59 for early ACI *[12]*. This may be why microfracture is still deemed to be more appropriate than ACI for cartilage defects below 2cm^2 *[14]*. Another limitation of ACI is that after the process of expanding the culture in vitro is complete, the chondrocytes usedare less effective at producing cartilage than uncultured chondrocytes *[15]*. This is due to dedifferentiation, where chondrocytes regress to a fibroblastic form and produce less collagen type 2 and 4 and aggre can and more collagen type 1, thus impairing the quality of cartilage

produced *[16]*. Excitingly, a new generation of ACI has been developed that endeavours to overcome these issues.

Single treatment Autologous Chondrocyte Implantation

STACI (Single Treatment Autologous Chondrocyte Implantation) is a procedure that builds on other ACI procedures, but only requires a single surgery to regenerate the patient's cartilage. In STACI, the laboratory is brought into the surgical environment using the Cartione technique. Cartione is a company providing the skills and equipment to produce an implantable mixture of primary chondrocytes and growth factors in around one hour. Cartilage is taken from the debridement of the defect and non-weight bearing areas of the joint, minced, and enzymatically digested in an incubator to free the primary chondrocytes. The mixture is then centrifuged to isolate the primary chondrocytes, which are then extracted. Meanwhile, the surgeon extracts bone marrow from the patient. Next, the lab technician isolates bone marrow mononuclear cells (BM-MNCs) from the bone marrow, which are added to the chondrocytes with cell medium. This is seeded onto a collagen or hyaluronan scaffold of the surgeon's choice, which is then fixed onto the defect. Finally, platelet rich plasma can be injected into the joint before the surgical incision is closed.

BM-MNCs are a cell group that include haematopoietic lineage cells such as lymphocytes, monocytes, stem cells, and progenitor cells as well as MSCs. BM-MNCs have been shown in to stimulate cartilage regeneration *[17,18]*. Further, they may be as effective as MSCs at encouraging cartilage growth while being more economical and convenient to use *[19]*. A 2-year follow up of 40 STACI patients found a clinically significant improvement in VAS pain scores, IKDC score and KOOS scores in patients with full-thickness cartilage defects of the knee *[20-33]*.

Conclusion

In future, perhaps an arthroscopic approach will be utilised for STACI to minimise complications such as arthrofibrosis, decreased range of movement, pain, and scarring associated with the common approach for ACI: the open arthrotomy. Good results have been achieved using this approach for MACI [20], so it can be inferred that an arthroscopic approach to STACI would also produce good outcomes.

If STACI can exhibit similar patient outcomes to multi-step ACI procedures, the lower cost of the procedure will make it an attractive option for cartilage regeneration. We await more evidence for its efficacy compared to other ACI techniques and microfracture, but the available data is promising. Moreover, the lack of a requirement for two surgeries and culture makes STACI more economical and more convenient, as well as overcoming the problem of dedifferentiation. This may lead to STACI becoming commonplace in the pathway of care for cartilage defects in young patients.

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