Which is better for articular cartilage regeneration, cultured stem cells or concentrated stromal cells?

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Introduction

Articular cartilage has poor regeneration ability after damage. Consequently, research on cartilage regeneration for treatment of early or moderate stage OA (osteoarthritis) patients has been regarded as a ‘never ending story’ (1,2). There are two major factors dictating this poor regeneration: First, cartilage regeneration is limited because the half-life of cartilage tissue is much longer than that of other tissues, resulting in secondary damage or degeneration during regeneration and remodeling. Second, cellular migration is limited by the cartilage tissue structure, and the chondrocytes in the damaged lesion cannot participate fully in regeneration. Thus, cartilage regeneration is restricted by the limited number of participating surrounding tissue cells (3).

ACI (autologous chondrocyte implantation) was developed for treatment of cartilage defects by utilizing chondrocytes (4). However, harvest of normal cartilage tissue from the knee joint and implantation of the cultivated cells requires two surgical processes, which increases time and cost burdens for both surgeon and patient (5).

Arthritis treatment studies using stem cells from various sites such as bone marrow, adipose tissue, umbilical cord, menstrual blood, and amniotic fluid have been conducted (6-8). Use of ADSVF (adipose derived stromal vascular fraction) and BMAC (bone marrow aspirate concentrate) for cartilage repair have been studied and clinically applied (9-12).

BMAC has been in clinical application since the early 2000s and recently, long-term results have been reported (13-15). Bone marrow-derived stem cells have shown equivalent effects to ACI in short and ten-year long-term data, supporting the use of various sources for cartilage regeneration (16,17).

ADSVF production involves the harvest of adipose tissue and requires centrifugation following enzyme treatment to yield a substantial number of stromal cells. Although treatments using ADSVF have shown favorable outcomes, the relative efficacy of cultivated adipose-derived stem cell (ADSC) versus ADSVF for cartilage regeneration is unclear.

ADSC for cartilage regeneration

Homogenous stem cells can be used for cartilage regeneration following cultivation of stem cells from adipose tissue. However, the relationship between the number of stem cells and clinical results remains unclear.

Jo et al. studied the safety and efficacy of intra-articular injection of ASDC on 18 OA patients of Kellgren-Lawrence...
grade 3 or 4, dividing them into low-dose (1.0×10^7 cells, n=3), mid-dose (5.0×10^7, n=3), and high-dose (1.0×10^8, n=12) groups (18). There were no treatment-related adverse events, and the high-dose group showed the most favorable results concerning pain and function. Furthermore, the high-dose group showed a decrease in cartilage defects and qualitative improvement after six months in serial MRI evaluations and second-look arthroscopy. A two-year follow-up study reported high efficacy and safety in the high-dose group compared to the low and mid-dose groups, supporting use of the high-dose ADSC injection (19).

However, research by Pers et al. presented the opposite results. In their study, 18 OA patients of Kellgren-Lawrence grade 3 or 4 were divided into three equal groups of low-dose (2×10^6 cells), mid-dose (10×10^6), and high-dose (50×10^6). After six months, the low-dose group showed the most significant improvement in pain and function, and there were no adverse effects in any of the three groups. Pers et al. suggested that the reason for this outcome was the immunomodulatory function of paracrine effects that followed ADSC injection to the group with the highest baseline pain (20).

The two studies mentioned above consisted of only 18 patients each, and because the two studies showed opposite results, the optimum dosage of ASDC is still uncertain. Further and larger studies on the efficacy and safety of dosage of injected stem cells are required.

**ADSVF for cartilage regeneration**

ADSC-based treatment has shown favorable outcomes, but the stem cell culture and expansion require substantial time, cost, and the inconvenience of two stage treatment. ADSVF-based treatment has been drawing attention as an alternative, and many studies are in progress (21). Centrifugation or the micro-fragmentation of the adipose tissue is used for ADSVF production. ADSVF that has been obtained through the aforementioned process comprises heterogenous cell populations, including mesenchymal progenitor/stem cells, preadipocytes, endothelial cells, pericytes, T-cells, and M2 macrophages (17,22).

A double-blinded RCT (randomized controlled trial) study on ADSVF treatment was recently held on 16 bilateral knee OA patients (23). One knee underwent intra-articular injection of 4 mL of ADSVF, the other knee was injected with 4 mL of HA (hyaluronic acid), and the results were compared. At a 12-month follow-up, the ADSVF injection group showed significant improvement in VAS (visual analogue scale), WOMAC (Western Ontario and McMaster Universities Arthritis Index), and ROM (range of motion), whereas the HA group did not show such improvement. Additionally, the ADSVF group showed significant improvement in radiologic review of WORMS (Whole-Organ Magnetic Resonance Imaging Score) and MOCART (MR observations of cartilage repair tissue) measurement compared with the HA group (23). Although the study supported use of the ADSVF treatment, the research also consisted of only 16 patients and lacks arthroscopic measurements. Therefore, more ADSVF studies are required because previous research involved a small number of patients, and insufficient follow-up studies.

**The relationship between stromal cells and stem cells**

The initial stage of adipose tissue-derived stem cell culture involves cytolizing the adipose tissue and plating the derived cells on culture flasks. Then following the stem cell culture protocol, the culture-derived cells are utilized as the adipose tissue-derived stem cells. Various differentiation stages of stromal cells are used in the culture. Under a specific culture condition, stromal cells are transformed into cells with stem cell characteristics. Thus, cells derived from adipose tissue show a quantitative relationship as described in Figure 1.

An increased number of stem cells participating in cartilage regeneration can result in a better outcome.
However, not all stem cells applied in surgery or treatment directly regenerate into cartilage, and most contribute to cartilage regeneration by their paracrine effect. Therefore, we can estimate an efficacy limit at a certain stem cell number. Meanwhile, there are a variety of stages of differentiated cells concentrated in the ADSVF, and more effective cartilage regeneration can be achieved by the growth factors, cytokines, etc. secreted from each cell. Therefore, basic research on the differences between ADSVF and ADSC is necessary.

**Comparison of ADSVF and ADSC**

A study by Yokota et al. directly compared ADSC and ADSVF treatment methods. In the study, 59 knees of 49 patients underwent intra-articular injection of $12.75 \times 10^6$ cells of ADSC, and 69 knees of 38 patients underwent intra-articular injection with 5 mL prepared ADSVF and the two groups were compared. VAS and Knee injury and Osteoarthritis Outcome Score (KOOS) were assessed at baseline and at 1, 3, and 6 months, and the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) criteria were used to determine a positive response. Neither group showed major adverse effects, although the ADSVF group showed more minor adverse effects. The ADSC group showed an earlier recovery than the ADSVF group in the KOOS symptom, but the two groups showed no difference in response after six months. There was also no significant difference in OMERACT-OARSI Responder Rate. The only difference was that the ADSC group showed greater improvement in VAS score than the ADSVF group (24).

The study by Yokota et al. is important because it is the first attempt to compare directly the ADSC and ADSVF treatment methods. However, the study lacks relevance in selecting the patient group because it is a retrospective study. Also, even though it is the first attempt to compare the two treatments, it lacks any comparison of radiologic and arthroscopic data. It is also difficult to conclude which treatment is superior because the number of patients was small, and the result showed no significant difference between the two groups; although the ADSC group showed a better response in the study, indicators other than VAS score showed similar results. Thus, if the VAS score alone is considered the clinical differentiator, we question whether it is appropriate to use the ADSC method, which requires significant time and cost compared to ADSVF.

**Conclusions**

There have been various developments and studies on treatments for articular cartilage regeneration. Past studies were focused primarily on cartilage regeneration, whereas current studies are focused on various methods and objectives including comparison of surgical and non-surgical cartilage regeneration treatment, safety, cost-effectiveness, and methods to reduce discomfort of patients and increase recovery (25,26). It is inconclusive, based on the available evidence, whether the stem cell or stromal cell concentration method is more effective for cartilage regeneration. If the two methods show similar clinical outcomes, we expect that the one-step, stromal cell concentration-based cartilage regeneration method will be employed more actively in the future.

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**Footnote**

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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