Clinical Use of Adipose-Derived Stem Cells for Breast Volume Enhancement

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Implantation of artificial prostheses is a standard method of breast augmentation, but complications derived from the foreign body, such as capsular contracture, malposition, implant rupture, and infection, occur at a relatively high rate (10 to 20 percent) and frequently result in removal or replacement of implants.

In addition, hospitals in Japan reject women who have breast implants from undergoing mammography as a part of annual social health examinations because of a potential risk for implant rupture by external pressure. On the other hand, the use of autologous fat tissue for the breasts has not gained acceptance due to a lack of consensus on its safety, as well as concern that the development of micro-calcifications could complicate mammogram evaluation.

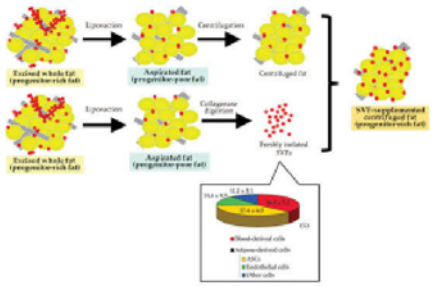

Fig. 1. Concept of cell-assisted lipotransfer (CAL). Relatively progenitor-poor aspirated fat tissue is converted to progenitor-rich fat tissue by supplementation with the stromal vascular fraction (SVF) isolated from one-half of the aspirated fat sample. SVF contains 10 to 35 percent adipose-derived stem/stromal cells (ASCs) and other adipose-derived cells such as vascular endothelial cells as well as blood-derived cells such as leukocytes. SVF cells are attached to the aspirated fat tissue, which acts a scaffold in this strategy.

Advantages

Although unpredictability and a low rate of graft survival due to partial necrosis are issues that remain to be resolved, autologous fat transplantation offers many advantages, such as the lack of scarring and complications associated with foreign materials. It was recently re-evaluated as an alternative to breast implants for augmentation or reconstruction [1], possibly reflecting recent technical advances in autologous fat transfer and the radiological detection of breast cancer [2].

Tissue-specific progenitor cells in adipose tissue can differentiate into various cell lineages. These progenitors, called "adipose-derived stem/stromal cells" (ASCs), are expected to become valuable tools in a wide range of cell-based therapies. ASCs have been used in clinical trials of treatments for bone defects (autologous fresh ASCs), rectovaginal fistula (autologous fresh or cultured ASCs), tracheomediastinal fistula (autologous fresh ASCs in fibrin glue), graft-versus-host disease (non-autologous ASCs), adipo-genesis (autologous cultured ASCs seeded on biomaterial scaffolds), and soft tissue augmentation (our trial; autologous fresh ASCs combined with aspirated fat tissue).

ASCs are believed to act as progenitors of adipocytes and vascular cells, reside between adipocytes or in the extracellular matrix especially around vessels, and are a main contributing cell population to adipose tissue turnover and remodeling such as injury repair (adipose tissue is considered to turn over with a cycle of two to 10 years [3]).

In order to address the problems of lipoinjection above, we designed a new strategy, called cell-assisted lipotransfer (CAL), based on the finding that aspirated fat tissue contains fewer vessels and ASCs than does intact fat tissue and also on our hypothesis that the relative deficiency of tissue-specific progenitors in aspirated fat tissue might contribute to the low survival rate and progressive atrophy of transplanted fat tissue, as was partially confirmed in animal studies [4]. In the CAL strategy, the progenitor deficit was compensated by supplementation with stromal vascular fraction (SVF) isolated from a separate volume of aspirated fat tissue.

Speculated roles of ASCs in CAL are:

1. To differentiate into adipocytes and contribute to adipose regeneration;
2. To differentiate into vascular endothelial cells or mural cells and may promote angiogenesis;
3. To release angiogenic growth factors such as hepatocyte growth factor (HGF); and
4. To survive as original ASCs (e.g. as adipose tissue progenitors).

Cellular and molecular events that occur in the grafted adipose tissue during the early phase (ischemia and subsequent reperfusion phase) after transplantation have not been well studied. However, adipose tissue and vessel remodeling occurs after experimental ischemia-reperfusion injury and, during the repair process, ASCs were a main proliferating cell population and promoted adipose tissue regeneration by releasing HGF [5].

Our experience with the cell-assisted lipotransfer technique showed generally satisfactory clinical results without any major complications.

In a clinical trial of CAL (more than 230 cases since 2003), the SVF comprising 10 to 40 percent ASCs was freshly isolated from half of an aspirated fat sample via collagenase digestion and recombined with the remaining half of the aspirated fat sample, converting relatively progenitor-poor aspirated fat tissue into progenitor-rich tissue.

Our experience with the CAL technique showed that atrophy of transplanted progenitor-enriched fat grafts was minimal, and clinical results were generally satisfactory without any major complications, suggesting that ASC supplementation is effective and safe [6].

Pre- and post-operative evaluations included mammography, magnetic resonance imaging (MRI), echography, photography, videography, and three-dimensional measurements that enabled volumetric evaluation of the breast mound with the patient in a standing position.

Mammography showed micro-calcifications seen at 24 months only in a few cases, and MRI analyses showed that the fatty layers around the mammary glands became substantially thicker at 12 months. Cyst formation (>5mm) was detected by MRI or echogram in several cases at 12 months. For breast augmentation, progenitor-enriched fat tissue with a mean volume of 260ml was transplanted and 100-200ml augmentation was achieved at 12 months. The 3D measurements showed that the transplanted adipose tissue was gradually absorbed during the first two post-operative months but that the breast volume showed change minimally thereafter. The surviving fat volume varied among patients and the graft take ranged from approximately 40 to 80 percent.

The reasons for the variations in enhancement volume remain to be fully understood, and multiple factors are likely to affect the clinical outcomes. Patient factors include skin redundancy of the breast. Technical factors include devices, liposuction techniques, period and temperature of graft fat preservation, and injection techniques. For lipoinjection to breasts, we think that devices such as a long (150mm) 18-gauge needle and a screw-type syringe are very useful and may affect clinical results. Although a large-volume (200-400ml) augmentation cannot be achieved by this method, patients obtained soft and augmented breasts with natural contour without having concerns about future possible complications derived from implants.

Other applications

CAL was applied not only to breast augmentation but also to a variety of other tissue augmentation or reconstruction: breast reconstruction after mastectomy, replacement of breast implants, inborn defects of breasts, facial lipoatrophy [7], facial rejuvenation, hand rejuvenation, and buttock lift (augmentation). It is noted that clinical outcomes of CAL-mediated breast augmentation immediately after implant removal were much better than we had expected; this may be due to redundancy of the breast skin, which was formerly expanded by breast implants.

Similarly, because the breast skin of women with a history of pregnancy and breastfeeding has expanded due to enlargement of the mammary glands, their breasts can more easily accept a larger injection volume than those with no history of pregnancy. It is clear that lean patients such as those with BMI of less than 20 are not good candidates for large-volume liposuction/injection.

Our experience of breast augmentation with CAL is encouraging so far, especially in quality of the

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Africa with cleft lips and palates. Says Miller:

"To be successful, the foundation has to be led by South African medical and non-medical volunteers and sustained by South African corporate partners. Prof. Madaree shares OSSA's vision to provide free medical care to all children and adults suffering with facial deformities and has the experience and passion to lead the foundation and help make this a reality."

Professor Madaree says: "If there are kids out there that require our help, we want to – and must – help them. This world must be enjoyed by all."

In addition to leading missions across South Africa, Swaziland and Madagascar, Prof. Madaree has started and spearheaded Africa's first World Care Program based at Inkosi Albert Luthuli Central Hospital in Durban. This program provides free craniofacial surgery to patients in and around Africa throughout the year while also providing educational opportunities to Southern African medical professionals interested in this type of surgery.

Before and after cleft lip surgery

We wish to target countries where there is little or no care for cleft patients. One of these countries has been the island of Madagascar. This country has a population of just below 20 million with no cleft services. We have performed two missions thus far, in November 2007 and May 2008, and operated on 132 and 211 patients respectively.

It is not unusual to see adults with cleft lips. In May 2008, 46 adult patients were operated on. There is still a huge backlog of patients and another mission is planned for November 2008.

Professor Anil Madaree is the Head of the Plastic and Reconstructive Surgery at Inkosi Albert Luthuli Central Hospital and also the Medical Director of Operation Smile Southern Africa (OSSA). He has been an integral part of the organization since the South African branch was officially registered in 2006. www.operationsmile.org

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breast tissue. Further controlled studies with longer follow-up are required to elucidate more definitively the efficacy and safety of this procedure. Adipocytes are very fragile and easily die in an operating room before injection. Through research seeking more facts about what the adipose tissue is and how it recovers from ischemic injury, we could handle and manipulate adipose tissue more gently and improve clinical outcomes of lipoinjection in the future.

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