Adipose-Derived Stem Cells in Autologous Fat Grafting to the Breast

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Effective Date June 1, 2016
Revision Date(s) 05/10/16; 12/08/15
Replaces N/A

Policy

The use of adipose-derived stem cells in autologous fat grafting to the breast is considered investigational.

Note: Autologous fat grafting to the breast without the use of adipose-derived stem cells is not subject to medical review.

Related Policies

None

Policy Guidelines

Coding

<table>
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<tr>
<th>CPT</th>
<th>Description</th>
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<tr>
<td>19366</td>
<td>Breast reconstruction with other technique</td>
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<tr>
<td>19380</td>
<td>Revision of reconstructed breast</td>
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<td>20926</td>
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Description

Autologous fat grafting to the breast has been used as an adjunct to reconstructive breast surgery, for post mastectomy pain and in irradiated skin. Adipose-derived stem cells (ADSCs) have been proposed as a supplement to the fat graft in an attempt to improve graft survival, although, a complete understanding of the mechanisms of any possible role ADSCs may have in tumorigenesis remains unknown.
Autologous Fat Grafting to the Breast

Autologous fat grafting to the breast has been proposed for indications that include breast augmentation and following oncologic surgery. Proposed indications after oncologic surgery include as an adjunct to reconstruction post mastectomy or lumpectomy for contour deformities and improved shape and volume of the breast, for post mastectomy pain syndrome (neuropathic pain), and for irradiated skin to soften the skin and restore it to nonirradiated appearance and consistency which may reduce complication and failure rates of implant reconstruction. Variability in long-term results and oncologic concerns have limited its application in the breast.

Note: This evidence review does not address the use of autologous fat tissue in aesthetic breast augmentation (i.e., cosmesis).

Adipose-Derived Stem Cells

Stem cell biology, and the related field of regenerative medicine, involves multipotent stem cells that exist within a variety of tissues, including bone marrow and adipose tissue. Studies have shown that 1 gram of adipose tissue yields approximately $5 \times 10^3$ stem cells, which is up to 500 times greater than the number of mesenchymal stem cells in 1 gram of bone marrow.1 Stem cells, because of their pluripotentiality and unlimited capacity for self-renewal, offer promise for tissue engineering and advances in reconstructive procedures. Adipose tissue in particular represents an abundant and easily accessible source of adipose-derived stem cells (ADSCs), which can differentiate along multiple mesodermal lineages. ADSCs may allow for improved graft survival and generation of new fat tissue after transfer from another site. (1)

This identification of several potentially beneficial therapeutic properties of ADSC has led to proposed novel techniques of fat grafting in conjunction with ADSC therapy for breast fat grafting, including the differentiation of ADSC into adipocytes as a reservoir for adipose tissue turnover; the differentiation of ADSC into endothelial cells and the subsequent increase in blood supply to the grafted fat tissue, thereby decreasing the rate of graft resorption, the release of angiogenic growth factors by ADSC; and the induction of angiogenesis, protection of the graft from ischemic reperfusion injury by ADSC and acceleration of wound healing at the recipient site. (1)

Current methods for isolating ADSCs can involve various processes, which may include centrifugation and enzymatic techniques that rely on collagenase digestion followed by centrifugal separation to isolate the stem cells from primary adipocytes. Isolated ADSCs can be expanded in monolayer on standard tissue culture plastic with a basal medium containing 10% fetal bovine serum, (2) and newly developed culture conditions provide an environment within which the study of ADSCs can be done without the interference of animal serum. They also allow rapid expansion of autologous ADSCs in culture for use in human clinical trials. A standard expansion method has not yet been established.

Yoshimura et al., in an effort to address the problems of unpredictability and low rates of fat graft survival, developed a technique known as cell-assisted lipotransfer (CAL), which produces autogenous fat rich in ADSCs. (3) In CAL, half of the lipoaspirate is centrifuged to obtain a fraction of concentrated ADSCs, while the other half is washed, enzymatically digested, filtered, and spun down to an ADSC-rich pellet. The latter is then mixed with the former, converting a relatively ADSC-poor aspirated fat to ADSC-rich fat.

A point-of-care system is available for concentrating ADSC from mature fat. The Celution™ System (Cytori Therapeutics) is designed to transfer a patient’s own adipose tissue from 1 part of the body to another in the same surgical procedure.

Regulatory Status

In September 2006, Celution™ Cell Concentration System (Cytori Therapeutics) was cleared for marketing by the U.S. Food and Drug Administration’s (FDA) Center for Devices and Radiological Health through the 510(k) process as a cell saver device. The system is cleared for the collection, concentration, washing, and reinfusion of a patient’s own cells for applications that may include, but are not limited to, cardiovascular, plastic and reconstructive, orthopedic, vascular, and urologic surgeries and procedures. FDA product code: CAC.
Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

Benefit Application

N/A

Rationale

This evidence review was created in October 2015, with the most recent literature search performed through April 21, 2016.

The literature on the use of fat grafting to the breast with the use of adipose-derived stem cells (ADSCs) consists of retrospective cohort studies, case series, and case reports. Following is a summary of the key literature to date, including systematic reviews of the studies using fat grafting to the breast and all identified case series using fat grafting to the breast with the supportive use of ADSCs.

Several review articles summarize autologous fat grafting and ADSCs. (1-4)

Pérez-Cano et al. conducted a single-arm, prospective, multicenter clinical trial of 71 women who underwent breast-conserving surgery for breast cancer and autologous adipose-derived regenerative cell (ADRC)—enriched fat grafting for reconstruction of defects 150 mL or less (the RESTORE-2 trial). (5) Trial end points included patient and investigator satisfaction with functional and cosmetic results and improvement in overall breast deformity at 12 months after procedure. Female patients (age range, 18-75 years) presenting with partial mastectomy defects and without breast prosthesis were eligible. The RESTORE-2 protocol allowed for up to 2 treatment sessions, and 24 patients elected to undergo a second procedure following the 6-month follow-up visit. Of the 67 patients treated, 50 reported satisfaction with treatment results through 12 months. Sixty-one patients underwent radiotherapy as part of their treatment; 2 patients did not receive radiation, and the status of radiation treatment was not known for the other 4 patients. Using the same metric, investigators reported satisfaction with 57 of 67 patients. There were no serious adverse events associated with the ADRC-enriched fat graft injection procedure. There were no reported local cancer recurrences. The LENT-SOMA scale included investigator and patient assessment of post-radiation signs and symptoms. (LENT-SOMA is one of the most common systems to assess the late effects of radiotherapy.) The investigators found the LENT-SOMA insufficiently sensitive to adequately reflect the clinical improvements seen in the trial population. Patients with LENT-SOMA grade 3 and 4 scores (most severe symptoms) were excluded during screening, which may have contributed to the subtle LENT-SOMA score changes observed in the trial. The investigators reported improvement from baseline through 12 months in the degree of retraction or atrophy in 29 of 67 patients, while 34 patients had no change and 4 patients reported worse symptoms. Post-radiation fibrosis at 12 months was reported as improved in 29 patients, while 35 patients had no change and 3 patients had worse symptoms. Management of atrophy was reported as improved in 17 patients, with 48 patients having no change and 2 patients reporting worse symptoms. Improvement in these measures was statistically significant. The authors concluded that future comparative studies are needed to determine the incremental benefit of ADRC-enriched fat grafting compared with traditional fat grafting in various clinical circumstances. The follow-up of the study was inadequate to draw conclusions on long-term risk of cancer recurrence.
In 2008, Yoshimura et al. reported on the development of a novel strategy known as cell-assisted lipotransfer (CAL), in which autologous ADSCs are used in combination with lipoinjection. (3) From 2003 to 2007, the group performed CAL in 70 patients (in the breast in 60 patients, including 8 who had breast reconstruction after mastectomy). They reported outcomes for 40 patients with healthy thoraces and breasts who underwent CAL for purely cosmetic breast augmentation; patients undergoing breast reconstruction for an inborn anomaly or after mastectomy were not included. Nineteen of the 40 patients had been followed for more than 6 months, with a maximum follow-up of 42 months. The authors observed that the transplanted adipose tissue was gradually absorbed during the first 2 post-operative months, and the breast volume showed a minimal change thereafter. Final breast volume showed augmentation by 100 to 200 mL after a mean fat amount of 270 mL was injected. The difference in breast circumference (defined as the chest circumference at the nipple minus the chest circumference at the inframammary fold) had increased in all cases by 4 to 8 cm at 6 months. Cyst formation or microcalcification was detected in 4 patients. The authors concluded that their preliminary results suggested CAL is effective and safe for soft tissue augmentation and superior to conventional lipoinjection, but that additional study was necessary to further evaluate the efficacy of this technique.

In 2007, Rigotti et al. reported the results of a pilot study on the presence and effectiveness of ADSCs in 20 consecutive patients undergoing therapy for adverse effects of radiation treatment to the breast, chest wall or supraclavicular region, with severe symptoms or irreversible function damage (LENT-SOMA scale grades 3 and 4). (6) Mean patient age was 51 years (range, 37-71 years). The rationale behind the study was that the ADSCs, which have been shown to secrete angiogenic and antiapoptotic factors and to differentiate into endothelial cells, could promote neovascularization in ischemic tissue such as irradiated tissue. Targeted areas included the supraclavicular region, the anterior chest wall after mastectomy with or without breast prosthesis, and breast after quadrantectomy. A lipoaspirate purification procedure was performed by centrifugation to remove a large part of the triglyceride portion of the tissue and to disrupt the cytoplasm of the mature adipocytes to favor their rapid clearance after injection. A stromal-vascular fraction was isolated by enzymatic digestion of extracellular matrix, centrifugation, and filtration, and the fractions were cultured for 2 to 3 weeks to obtain a homogenous cell population. To assess the presence of mesenchymal stem cells, the stromal-vascular fraction derived from the adipose tissue was cultured and characterized by flow cytometry. The number of procedures was 1 in 5 patients, 2 in 8, 3 in 6, and 6 in 1 patient. Clinical follow-up varied between 18 and 33 months (mean, 30 months). Clinical results after treatment with lipoaspirates were assessed by LENT-SOMA scoring. The 11 patients initially classified as LENT-SOMA grade 4 (irreversible functional damage) progressed to grade 0 (no symptoms), grade 1 and grade 2 in 4, 5 and 1 cases, respectively. In 1 case, no improvements were observed. In the 4 patients who had undergone mastectomy and had breast prostheses and areas of skin necrosis, the necrosis showed complete remission. In the group of 9 patients classified as LENT-SOMA grade 3, fibrosis, atrophy, and retraction progressed to grade 0 and 1 in 5 and 4 cases, respectively.

In 2015, Schweizer and colleagues published a review of the influence of ADSCs on breast cancer cells (BCC). They found that the majority of preclinical studies trend to support the propensity of mesenchymal stromal cells and ADSCs in promoting growth, progression, and metastatic spread of residual or de novo breast cancer after resection. In contrast, only a few clinical case series and trials are reflective of similar findings. They cited two possible scenarios: 1) Any residual unresected microscopic tumor foci persisting after mastectomy could be activated by ADSCs used in postsurgical restoration or 2) Occult dormant cancer cells in patients with no diagnosed breast cancer but undergoing ADSC therapies for breast augmentation may undergo a malignant transformation. They concluded that the concerns of safety and the debate on efficacy versus such unresolved risk remain ongoing until larger randomized and controlled clinical trials shed light on the scenario. Overall, most of these studies do not support using autologous stem cell-enhancement at the present, whereas whole fat grafting appears to be safe in many circumstances.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in April 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

**Summary of Evidence**
The evidence for the use of adipose-derived stem cells (ADSCs) in patients who have breast cancer and are undergoing autologous fat grafting to the breast includes small single-arm studies, some of which are prospective. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease severity, morbidity events, functional outcomes, quality of life, resource utilization, and treatment-related morbidity. Studies have
mainly reported patient and investigator satisfaction and functional and cosmetic results. Limitations of the data are small numbers of patients, short-term follow-up, and lack of understanding of the possible oncologic influence ADSC may have on the fat grafting procedure. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Society for Aesthetic Plastic Surgery and American Society of Plastic Surgeons

A joint task force of the American Society for Aesthetic Plastic Surgery (ASAPS) and the American Society of Plastic Surgeons released a position statement on the use of stem cells in aesthetic surgery during the 2011 annual meeting of ASAPS. (7) Based on a systematic review of the peer-reviewed literature, the task force concluded that while there is potential for the future use of stem cells in aesthetic surgical procedures, the scientific evidence and other data are very limited in terms of assessing the safety or efficacy of stem cell therapies in aesthetic medicine.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References


Appendix

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<td>12/08/15</td>
<td>New Policy. Policy created with literature review through September 13, 2015; the use of adipose-derived stem cells (ADSC) in autologous fat grafting to the breast is considered investigational. (Note: The former policy addressing both autologous fat grafting and ADSC has been archived. This policy only addresses ADSC. Policy statement regarding ADSC remains investigational.)</td>
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<tr>
<td>05/10/16</td>
<td>Annual Review. Policy updated with literature search. Reference added. No change to the policy statement.</td>
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