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Review Article

Autologous Fat Grafting as a Stand-Alone Procedure for Post-Mastectomy Breast Reconstruction and the Potential for Improvement using Adipose-Derived Stem Cells

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Abstract

Autologous fat grafting is an appealing method for breast reconstruction following mastectomy for breast cancer. Surgeons often perform this technique to optimize the aesthetic results of the more popular implant-based or autologous breast reconstruction by correcting residual defects and contour lines. Autologous fat grafting is less invasive, less costly, and easier than the reconstructive procedures mentioned. These advantages pose the possibility of using this method as a stand-alone procedure for post-mastectomy breast reconstruction. However, the literature is inconsistent when describing harvesting and processing methods and reporting patient outcomes. Graft retention rates are also variable. The use of adipose-derived stem cells can address the issue of unpredictable graft retention due to their angiogenic and adipogenic action. The novelty of using stem cells with autologous fat grafting also raises concerns, especially regarding its oncologic safety. This review aims to present a critical perspective of the literature on autologous fat grafting as a stand-alone procedure for post-mastectomy breast reconstruction and highlight areas for further research that can improve its outcome. Moreover, it discusses the potential use of adipose-derived stem cells in conjunction with autologous fat grafting to improve graft retention and the considerations surrounding the safety of this procedure.

Keywords: Autologous fat; Breast cancer; Centrifugation; Adipose tissue; Cancer cell; Breast reconstruction methods.

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Introduction

Despite the recent advances in diagnosis and treatment, breast malignancy remains the cancer with the highest incidence and mortality rates in females worldwide [1]. Surgical intervention commonly follows the detection of breast cancer, with mastectomy being the primary surgical treatment [2]. Unfortunately, such an operation carries several costs related to the breast's role in femininity. Body image issues, a feeling of losing the female identity, and unsatisfactory sexual life are among the adverse post-mastectomy outcomes reported by patients [3,4]. The introduction of breast reconstruction surgeries addresses a mastectomy's undesirable physical and psychological effects by ameliorating a patient's bodily defect. Patients undergoing a post-mastectomy breast reconstruction report a more remarkable improvement in their overall health than patients who do not opt for this procedure [5,6].

Current breast reconstruction methods

A popular option for post-mastectomy patients is implant-based breast reconstruction (IBR) which utilizes biomaterials like silicone [7]. While autologous breast reconstruction (ABR) requires more recovery time than implant-based reconstruction, it offers a more natural feel as it uses the patients' own tissue to reconstruct the breast, such as flaps from the abdominal wall or the back. Moreover, ABR carries lower re-operation rates and can be an option for patients requiring post-mastectomy radiation where implants can undergo capsular contracture [8]. However, ABR is a large-scale procedure with significant risks such as flap necrosis, donor site morbidity, and aesthetic concerns due to the scarring. ABR also needs a surgeon's microsurgical skills to perform the micro-anastomosis between the vessels responsible for the flap's viability [9]. The limitations of both procedures and the fact that surgery is moving towards a less invasive era [10] are a call toward a novel technique for breast reconstruction such as autologous fat grafting (AFG).

Autologous fat grafting

Several authors [9,11,12] consider AFG as an easy, quick and safe procedure. AFG is the transfer of adipose tissue (fat) from a donor site of the patient's body to the chest to reconstruct the breast in a series of minimally invasive procedures [13]. This entails fat harvesting, processing, and injection [11,12]. It is usually used as an adjunct to IBR and ABR to correct contour and residual deformities after reconstruction and patients report satisfactory outcomes [14].

The literature describes several advantages of AFG over other breast reconstruction techniques. Firstly, it is a minimally invasive technique which does not require large incisions at the donor site like ABR. It is radiologically safe as patients often undergo post-mastectomy radiotherapy. It also offers a natural feel, it is technically easier, with a shorter recovery time and lower complication rates [9,11,13]. Authors also consider AFG as a more cost-effective technique compared to other reconstruction methods [11,15].

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Techniques involved in autologous fat grafting

The Coleman [16] procedure describes a method commonly followed for harvesting adipose tissue. By withdrawing the plunger of a 3mm blunt-edged cannula connected to a 10ml syringe, fat is suctioned manually. A gentle negative pressure is created as the surgeon withdraws the plunger after the cannula is pushed into the harvest site. Small blocks of fat move through the cannula and Luer-Lock aperture into the barrel of the syringe. When filled, the syringe is disconnected from the cannula, which is replaced with a plug that seals the Luer-lock end of the syringe. The plunger is removed from the syringe before the fat is processed. This involved sedimentation, filtering and centrifugation to remove other elements present in the harvested adipose tissue such as, collagen fibres and blood that can cause inflammation at the recipient site.

After centrifugation three layers are created and the middle consists of the lipoaspirate that is used for fat grafting. The lipoaspirate is then injected at multiple areas at the recipient site with small gauge cannulas. This is to reduce the risk of bleeding, hematoma and poor oxygen diffusion [13].

Furthermore, non-invasive tissue expander systems such as BRAVA can aid AFG. BRAVA is a breast enhancement and shaping system that patients wear following a specific protocol before the AFG session. Essentially, it is a bra containing plastic domes that causes a 'reverse' expansion of the skin envelope due to negative pressure; thus, there is more space for the graft. Another benefit of this technique is that its negative pressure induces vascularization and stem cell increase. An extended follow-up multicenter prospective cohort study confirmed its efficacy and cost-effectiveness when used with AFG compared to other reconstruction procedures [15].

Autologous Fat Grafting as a stand-alone procedure

Having discussed the advantages of AFG, it is appropriate to consider whether this can be performed as a stand-alone procedure for breast reconstruction in breast cancer patients. The novelty of the technique means that the evidence of its efficacy and safety is considerably sparser compared to the other reconstruction methods. The latest review [17] on the applications of AFG argues that its use results in high satisfaction rates as it is linked to the patients' psychological well-being and improved sexual function. However, the literature lacks a more critical view of the studies reporting patient outcomes after a stand-alone AFG procedure. For this reason, the following section will discuss four studies [9,12,18,19] published between 2019 to 2022 that base their results on patient-reported outcomes after stand-alone AFG for breast reconstruction. Studies using AFG for full breast augmentation for non-breast cancer patients are not discussed.

Firstly, there are several similarities between the studies. All studies included female breast cancer patients who have undergone total or nipple-sparing mastectomy. Their mean age ranges from 46.1-61, and their mean BMI varies between 23-34.5. Most patients have

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undergone or were planned to undergo radiation [9,12,18,19]. Common donor sites were the abdominal wall and the thighs or legs [9,12,18]. Lam et al. and Kempa et al. used general anesthesia [12,18]. AFG was often performed as an outpatient procedure [9,12,19]. An overall of 3-3.5 procedures were required in a space of 2.8-3 months [9,19].

Moreover, the BRAVA system was used in two of the studies [9,18]. Fitoussi et al. and Lam et al. described fat injection [9,12] from deep to subcutaneous as the sessions progressed. Notably, there needs to be a consensus on which injection plane is the best for avoiding complications. There was a range for the total mean volume injected, and similar volumes were injected per session [9,12,19]. The donor site, number, and frequency of procedures agree with the literature on methodologies for stand-alone AFG [15,20,21,22].

On the other hand, there are several differences between the authors' methods as presented in (table 1) For example, Kempa et al. and Siotos et al. performed a delayed first session [18,19], whereas Fitoussi et al., performed the first session immediately after mastectomy [9]. The implications of the timing of the procedure are yet to be examined. Kempa et al. and Siotos et al. used the Coleman procedure [16] for fat harvesting [18,19]. Although Fitoussi et al. and Lam et al. used similar methods [9, 12] as they employed negative pressures, their values varied, as well as the cannulas and syringes that contained the fat. Centrifugation protocol was also heterogenous apart from the studies following the Coleman method [18,19]. Notably, several steps of the methodology were not specified or described in detail in the studies.

Techniques for autologous fat grafting			
Authors	**Fat harvesting**	**Fat processing**	**Fat injection**
Fitoussi et al.,[9]	Used a 3 or 4mm sterile cannula under low pressure suction (-30 to-50mmHg) connected to a 500ml vacuum standard suction drain bottle in series with the liposuction cannula.	Fat was rinsed once for 15 seconds with 100ml-200ml of sterile Ringer solution at room temperature. It was centrifuged at 2000rounds/minute for 40seconds and kept in 10ml syringes.	Deep to superficial. Under direct visualisation, into the upper part of the breast and pectoral muscle using a sterile 1.5mm-2mm diameter cannula. Subsequent fat transfers were done through 1 or 2 small holes.
Lam et al.,[12]	Used liposuction cannulas at-254mmHg.	Centrifuged 100g of fat at 30 seconds.	Under direct visualisation into the intra-muscular and submuscular planes in the first session. Injected in the subcutaneous plane during subsequent sessions.
Kempa et al.,[18]	Coleman technique.	Not specified.	Not specified.
Siotos et al.,[19]	Coleman technique.	Fat was centrifuged at 3000 rounds/minute.	Not specified.

Table1: Summary of the different techniques for autologous fat grafting that the different authors use [9, 12, 18, 19].

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Regarding study design, the largest sample size belonged to the cohort study by Kempa et al. [18], as they included 93 patients, while the rest had a minimal sample size ranging from 3 to 15, as they were case studies [9,12,19].

The latter can capture the uniqueness of a procedure and provide an excellent in-depth understanding, but they cannot produce generalizable results as they are not replicable and can be affected by observational bias. Only Siotos et al. employed a validated patient outcome scale that is BREAST-Q [19], and Kempa et al. [18] used two independent observers to avoid observer bias. However, the rest of the studies [9, 12] used subjective measures open to the authors' interpretation. Moreover, only Kempa et al. [18] had a long follow-up period of 12 years, whereas Fittousi et al. and Siotos et al. may not have adequately explored any long-term effects of AFG between the 12 and 26 months which was their respective follow-up periods [9,19].

Furthermore, the cohort study [18], which has a higher quality of evidence, had several limitations. For example, its retrospective nature without a control group can result in missing data and a lack of comparison. A telephone follow-up was performed about the patients' satisfaction, which could be inaccurate and subjective, especially regarding the aesthetic outcomes.

While the studies discussed above, present some common points that agree with the available literature [15,20,22], the novelty of the technique leads to the need for more consensus on a standardized method for AFG as well as validated patient outcome results in terms of satisfaction. The small sample sizes included in the studies further diminish the reliability of their results. There is also inconsistency between the surveillance period and follow-up post-procedure. Overall, the current studies [9,12,18,19] using AFG as a stand-alone procedure for breast reconstruction lack a robust design to produce sufficient evidence for this technique.

Some further considerations for a stand-alone AFG procedure for breast reconstruction stem from the evidence for graft retention. Necrosis and resorption can lead to decreased graft retention and the need for repeated procedures [23]. Several studies, including the ones using AFG as an adjunct, report a variable graft retention rate of 30-70% [23,26]. As mentioned above, the need for a standardised methodology for AFG and the multiple steps between fat harvesting and injection can contribute to this. Factors such as inflammation and vascularisation of the recipient site can have implications on the graft's survival, which can be affected by the recommended timing of the procedure on which there is a lack of evidence [24]. Graft retention is essential as AFG already requires multiple sessions, and additional procedures can reduce patient satisfaction and use sparse hospital resources [25]. Consequently, further research can explore the standardization of the AFG method and techniques to maintain the integrity of the graft after transfer.

The use of adipose-derived stem cells in autologous fat grafting

Following the discussion on the benefits of performing AFG for breast reconstruction in breast cancer patients, novel research on the use of stem cell enriched fat grafts can address some of the concerns in terms of using AFG as a stand-alone procedure to improve graft retention. Adipose-derived stem cells (ADSCs) are mesenchymal stem cells isolated from adipose tissue [27]. The use of ADSCs has been introduced in 2001 and they can differentiate into multiple lineages and have a high proliferative capacity [28]. Cell-assisted lipotransfer (CAL) is a surgical technique in which autologous adipose tissue is enriched with ADSCs and is used as a graft for the mastectomy defect. It has the potential to surpass AFG due to its better graft retention results [29]. This is because ADSCs produce growth factors such as VEGF, promoting angiogenesis and adipogenesis. This means that CAL grafts can sustain the hypoxic environment of the recipient site and have better long-term graft retention and lower post-operative complication rates [30]. CAL consists of several stages. Firstly, subcutaneous tissue is obtained from a suitable donor site such as the abdominal wall as seen in figure 1 [27]. Then, adipose tissue is minced and undergoes enzymatic digestion with collagenase type II [28]. It is centrifuged and the resulting pellet is called Stromal Vascular Fraction (SVF). 1 mililitre of lipoaspirate can produce 2-6 million cells in SVF [29]. The other half of the aspirated fat is processed for use as a fat graft. Then the combination of SVF and lipoaspirate is placed at the donor site [28,9].

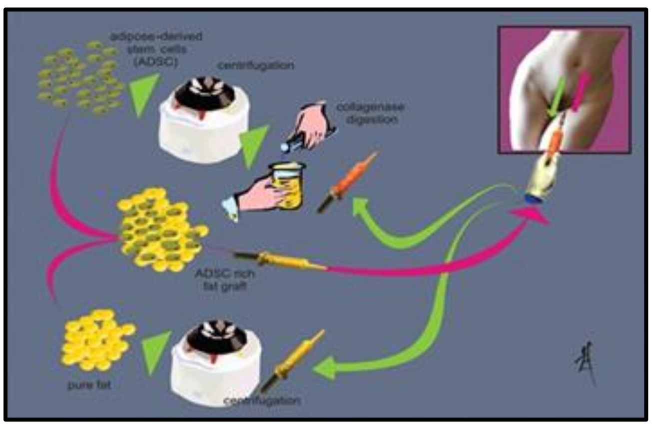

Figure 1: Harvesting and processing of adipose-derived stem cells Adipose tissue is harvested from the lower abdominal wall and the stem-cell rich tissue is processed separately from pure fat. They are then combined and transferred to the donor site [27].

The simplicity of the CAL procedure as well as its benefits in the maintenance of the graft can impress the reconstructive surgery community. However, a systematic review discussing its efficacy, cost effectiveness and oncological safety, highlights the limited literature available [30]. Particularly, its safety profile is mostly based on pre-clinical studies with contrasting results [31,33]. ADSCs can interact with cancer cells and support their growth due to the secretion of inflammatory cytokines and growth factors thus promoting the congregation of cancer cells as well as metastasis [31,32]. It is imperative to further assess the oncologic safety of CAL with respect to adjuvant treatments such as

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chemotherapy as well. Both pre-clinical and clinical studies must explore this topic further and produce long-term safety outcomes.

Conclusion

AFG is a promising method for the future of post-mastectomy breast reconstruction. Its relative ease, natural feel and cost-effectiveness are some desirable features for healthcare teams who are responsible for the treatment of breast cancer. Patients who have suffered the devastating physical and psychological effects of cancer could undergo this minimally invasive procedure that is also radiologically safe. The limited literature supporting its efficacy as well as its variable retention rates indicate the need for more studies to establish a reliable and standardized technique. Moreover, the prospect of using ADSCs and CAL raise new hope for better graft retention rates. However, it is paramount to establish their oncological safety through rigorous research, reviews and meta-analyses. In conclusion, provided that the literature addresses the concerns discussed in this review, AFG complemented by ADSCs has the potential to become an excellent method for post-mastectomy breast reconstruction.

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