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Adipose-derived stem cell enrichment is counter-productive for the majority of women seeking primary aesthetic breast augmentation by autologous fat transfer: A systematic review

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Summary *Background:* Autologous lipotransfer (AL) is a popular method despite unpredictable retention rates. Higher retention rates have been reported when co-administering adipose-derived stem cells (ASCs), a process called cell-assisted lipotransfer (CAL). Our hypothesis is that CAL might indeed limit volume gain in most women seeking aesthetic breast augmentation because it doubles the amount of fat required without consistently improving the outcome.
Methods: Electronic databases were searched for articles published between January 2008 and October 2019 in English and German. All original articles evaluating fat viability following autologous breast augmentation *in vivo* were included. Based on the reported retention rates, potential volume gains were estimated for CAL and AL.
Results: A total of 23 studies were selected. The AL retention rate varied from 39% to 76%, whereas CAL increased this rate at best by 24%. The body mass index (BMI) ranged from 18.8 to 23.4 (20.4±1.6) in the study population, whereas the BMI of women in the same age group is 28.7 (±8.4). We calculated that, starting from 200 ml of harvested fat and after two sessions of AL of 100 ml each, the volume retained would be at most 152 ml. In contrast, after one session of CAL of 100 ml, while the remaining 100 ml are used to isolate ASCs, a maximum of 95 ml of fat would remain.
Conclusion: The volume gain after two sessions of AL is far superior to that after one session of CAL for the same volume of harvested fat. This is an important practical consideration for

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women with low BMI, as the extra fat required to isolate ASCs is not counterbalanced by an increase in the retention rate. Therefore, two sessions of AL may be preferable to maximize the volume gain.

Introduction

Autologous fat grafting is a minimally invasive procedure and its potential for augmenting breasts for aesthetic reasons is nowadays well known and accepted. It is a more than 100 years history that began in 1893 when Neuber reimplanted upper-arm fat tissue to restore a depression in the face.[1] After the technique of harvesting the fat was improved by Illouz,[2] who invented the blunt cannula, Coleman in the 1990s successfully began grafting fat to the face and body with lipoaspirate, defining Coleman's technique, which became an eminent procedure in the plastic surgery community.[1] In 2007 the American Society of Plastic Surgery (ASPS) founded a task force on fat grafting which stated that, if properly performed, the procedure is effective and poses no additional risks, thus underlining the volume limitation caused by the likelihood of necrosis and cyst formation if fat is not properly transferred.[3] Although fat grafting is actually performed worldwide, varying outcomes of fat retention rate have been observed, even when using similar techniques.[4] Authors want to emphasize that the use of the term "retention rate" in this paper is synonymous to the terms "survival rate" and "take rate", as these terms are frequently used in the literature defining the amount of fat finally remaining in the recipient area after lipotransfer. In 2001, Zuk first described the presence of human stem cells as part of the stromal vascular fraction (SVF) of the aspirated adipose tissue. These cells are now recognized as adipose-derived stem cells (ASCs).[5] Similar to mesenchymal stem cells (MSCs) found within the bone marrow, stromal adipose tissue is derived from the embryonic mesenchyme. ASCs have a similar capacity to differentiate to adipogenic, myogenic, chondrogenic, and osteogenic lineages.[5] Subsequently, it was observed that the separation of the SVF and its addition to autologous fat grafts, as well as the addition of ex-vivo expanded autologous stem cells to fat grafts, enhanced the retention rate of the transferred fat.[6,7] Stem cells are thought to exert their effects by differentiating into endothelial cells and increasing neovascularization (6, 7), as well as by releasing hormones, cytokines, or growth factors that promote graft. Soon the industry invented numerous devices to separate ASCs from fat tissue.[8]

Enriching fat with ASCs, however, presents several disadvantages. The machines are very expensive and prolong the operation by 2–2.5 h.[9] Especially, it requires an extra amount of fat, which has to be separately processed and cannot be used for subsequent volume gain. In most cases of breast augmentation, either through silicone implants or through autologous lipotransfer (AL), a decent volume gain of 200–400 ml per side is sought.[10,11,12] To achieve this volume by AL, 400–800 ml of fat needs to be harvested in total for both sides assuming that the retention rate of the fat is 100%. If ASCs are added to enhance the retention rate after AL, then the necessary amount of fat may double to 800–1600 ml.

However, patients considering breast augmentation for aesthetic reasons show a mean BMI of 21.9 (±1.6), which is distinctly lower than the average BMI (28.7 (±8.4)) of women in the age group of 25–34.[18,19,30-32]

It is of utmost importance to define precisely the medical indication of cell-assisted lipotransfer (CAL), since it doubles the amount of harvested fat, prolongs the duration of the intervention, and last but not least, considerably raises the overall costs. This study tests the hypothesis that CAL reduces the overall potential of volume gain in the majority of women considering primary aesthetic breast augmentation.

No systematic review provides so far, to the best of our knowledge, a comparative and critical analysis of potential volume gain following AL and CAL for breast augmentation. Our goal is to evaluate how the lipotransfer strategy determines volume gain. We purposely take into account practical considerations such as woman's BMI, duration, and costs of the intervention when advising on the best strategy to maximize volume gain.

Methods

A comprehensive review and critical evaluation of the literature on volume maintenance after AL or CAL for aesthetic breast augmentation was performed according to PRISMA guidelines. The literature was also screened for the BMI of patients seeking aesthetic breast augmentation. Based on the results of this review, a hypothetical assessment is presented comparing the volume gain of one session of CAL to two sessions of AL using the same amount of harvested fat, given that one session of CAL requires as much fat as two sessions of AL.

Search methods

A systematic literature search for relevant articles published between January 2008 and October 2019 was performed on Ovid, MEDLINE, and Google Scholar databases. Both "free-text terms" and "MeSH terms" searches were run sequentially to capture all papers in which ASCs were co-administered with autologous fat grafts. Variations of the following keywords were combined using the matrix of Boolean operators detailed in Supplemental Digital Content 1: ("Mesenchymal Stem Cells"[Majr]) AND "Stem Cells"[Mesh] OR ASC OR adipose derived stem cell (s) OR CAL OR adsc OR SVF AND fat graft (s) OR fat injection (s)

OR free fat graft (s) OR fat grafting OR fat transplant OR fat transfer OR lipofilling OR lipomodeling AND enriched OR enrichment OR cell enhanced OR autologous AND breast AND augmentation. All studies in English and German were included regardless of the country of origin. The study selection was based on an initial review of the titles and abstracts and a further review of the full texts. The reference lists of selected articles, other related studies, and review articles were checked for eligible studies. The authors agreed upon the final list of included studies.

Study selection criteria

A full set of inclusion and exclusion criteria were prespecified and agreed upon by all authors in advance. This study protocol was not eligible for registration on the PROSPERO database, as it constitutes a review of hypothetical calculations for aesthetic reasons. Only clinical breast fat grafting *in vivo* studies, with or without the addition of stem cells, were eligible for inclusion. All methods of fat grafting (such as lipofilling, contouring, and solid tissue transplant) were deemed eligible. No distinction was made with regard to the isolation and preparation methods of stem cells. *In vitro* fat grafting studies were excluded. Studies in which CAL was used for areas other than the breast were read and cited, but excluded from our calculation, as were case reports, letters, editorials, book chapters, reviews, and studies without methods.

Data collection and analysis

All data were collected by a single author (DL) and recorded on a predesigned electronic form before being independently verified by the second author (ET). The primary endpoint for this review is retention rate based on volume assessments 6–12 months after breast augmentation surgery. In addition, the following information was extracted from the selected studies:

1. general study information (title, author(s), year, journal, country, *in vivo* model)
2. experimental details (study design, number of fat graft procedures, follow-up timepoint, and volume assessment technique)
3. stem cell isolation method
4. fat extraction (method of fat harvest, fat processing methods, preoperative vacuum therapy of recipient area)
5. demographic data of the subjects (BMI and age).

No assumptions have been made about missing data, where these have not been explicitly reported. If authors referred to supplemental materials, appendices, or other articles in their methods, these were reviewed to extract relevant data.

The reported retention rates were used to estimate maximal volume gains following AL and CAL using 200 ml of harvested fat. For CAL, the best-case scenario (enhancement of the AL retention rate by 25%) was considered. Additionally, the mean BMI in the study population of all included studies was calculated.

Statistical analysis

Due to the high clinical and methodological heterogeneity among the selected studies (patient characteristics, study design, assessment of primary outcome), we do not report a pooled estimate for retention rates. Instead, narrative synthesis with tabulation of studies was used to summarize data. Results of mean BMI were taken from two different findings: 1. all 346 patients of studies using CAL (Table 1) as well as results from nearly 130,000 patients as shown in (Table 6).

Quality assessment

This systematic review provides a critical overview of the published literature. All studies fulfilling the inclusion criteria were added to the review, and low-quality studies lacking a clearly stated methodology were discarded. Formal evaluation of experimental and clinical outcomes was beyond the scope of the current research objective.

Results

Study selection

The electronic database search strategy returned 335 results. After screening titles and abstracts for the predefined research objectives, we excluded 228 articles and read the 107 remaining papers in full to assess their eligibility for inclusion. We found a total of 37 studies that met the selection criteria. In the next step, 14 manuscripts were eliminated for the following reasons: vacuum pre-expansion, breast cancer, different recipient area, reviews, letters, no reporting of methods, *in vitro* experimental studies only. In total, data was extracted from a final shortlist of 23 articles included in the qualitative synthesis. A comprehensive study attrition diagram is provided in Figure 1.

Overview of studies

Among all studies concerning breast lipofilling for aesthetic breast augmentation, only 8 studies (316 patients in total) evaluated the outcome of CAL on grafted fat viability. Of those, only 2 controlled studies (Peltoniemi et al. 2013 and Chui et al. 2018) provide a comparison between CAL and AL for aesthetic breast augmentation. Furthermore, to complement the discussion, we included other 17 studies in the discussion examining: 1. mean amount of transferred fat for breast augmentation, 2. retention rate of sole fat grafting, and 3. different recipient areas of CAL.

Fat retention rate in the presence or absence of ASCs

A summary of the studies on graft survival and enhancement by the use of CAL is provided in Table 1, including the method of measurement and the mean amount of transferred fat for each study. According to the literature, the

Table 1 Legend: Overview of studies reporting primary breast augmentation with autologous fat using CAL. n: number of patients in the study and (n) number of patients in the control group, if performed. * clinical improvement observed without indicating the amount. **Kamakura indicated the volume gain by measuring the circumference of the chest.

CAL	*n* (control group)	Retention rate CAL (%)	Retention rate control group (%)	Measurement method	SVF isolation method	Volume injected (ml) (left/right)	Follow-up (month)	BMI
Yoshimura et al., 2008	40	4-8 cm*	no control group	Chest Circumference	laboratory	268,1/ 277,3	6 ($n=19$)	19,1
Yoshimura et al., 2010	15	58,2	no control group	MRI	Celution system	259/268	6 ($n=10$)	19,5
Kamakura et al., 2011	20	3,3 cm **	no control group	Chest Circumference	Celution system	235,1/244,9	9	Not indicated
Peltoniemi et al., 2013[9]	10 (8)	50 (SD 10)	54 (SD 7)	MRI	Celution system	292	6	23,4
Wang et al., 2015	12	48,16	no control group	MRI	Lipokit Medikhan System	289/277,3	6	22,1
Jung et al., 2015	5	47,3 (SD 14)	no control group	MRI	not indicated	196,2/246,2	18	20,18
Chiu et al., 2019[29]	105 (101)	68,7	67,9	3D laser scanning	laboratory	334 310	12	20,3 18,8
Gentile et al., 2012[15]	50 (10)	74	51	MRI, ultrasound and self-evaluation	Celution, Lipokit Medikhan System, Fatstem and Mystem system	93,54	6	not indicated

Table 2 Different SR of AL for breast augmentation.

Author(s)	SR (%) (N)	Area	Follow-up time (months)
Zocchi Zuliani, 2008[21]	55 (181)	Breast	12
Choi, 2013 [13]	39 (90)	Breast	6
Groen et al., 2016[33]	62.4 (3565)	Breast	12
Ueberreiter, 2010[14]	76 ± 11 (85)	Breast	6

boost in retention rate that can be achieved by ASC enrichment for aesthetic breast augmentation ranges from 0 to 1%, differences being not statistically significant (Peltoniemi et al. 2013 and Chui et al. 2018). The other listed authors showed retention rate ranging from 40 to 80% for CAL, which is comparable to the rate ranging from 39% to 76% for AL, as listed in Table 2. All these studies, however, were performed without a control group. Only Gentile et al. documented the highest possible enhancement of the retention rate by ASCs up to 24% (CAL 63%, control group 39%) in female patients who were treated with CAL but had breast cancer surgery prior to treatment and therefore different prerequisites for survival of the fat in the recipient area. Enhancements of retention rate up to 64.6% as documented by Kolle et al. are unique in the literature (Table 3), and may be restricted to recipient areas other than the breast. Due to fat necrosis in the control group of this study and the small number of participants, these results are inadequate to be set as a benchmark and can by no means be applied to aesthetic breast augmentation by lipofilling.

Average BMI of the study population

The mean BMI of women seeking breast augmentation for the first time was 21.9 (±1.6).[30-32] The average age of women seeking breast augmentation is around 30,[12] while the mean BMI of women in this age group (25-34) lies at 28.7 (8.4).[18,19,30-32]

Literature overview regarding the number of interventions

Most studies describe that lipofilling for breast augmentation is performed in multiple sessions of lipofilling while the amount of transferred fat can vary considerably (Table 4).

Estimation of volume gain using 200 ml of harvested fat

To estimate the outcome of CAL *vs* AL, two main factors were taken into account: the retention rate and the amount of fat used for the procedure. Table 5 shows the calculated volume gains resulting from one session of CAL compared to one and two sessions of AL. Because the literature review displayed a variety of different retention rates following fat grafting, we calculated volume gains based on retention rates ranging from 10% to 80%. Likewise, there is

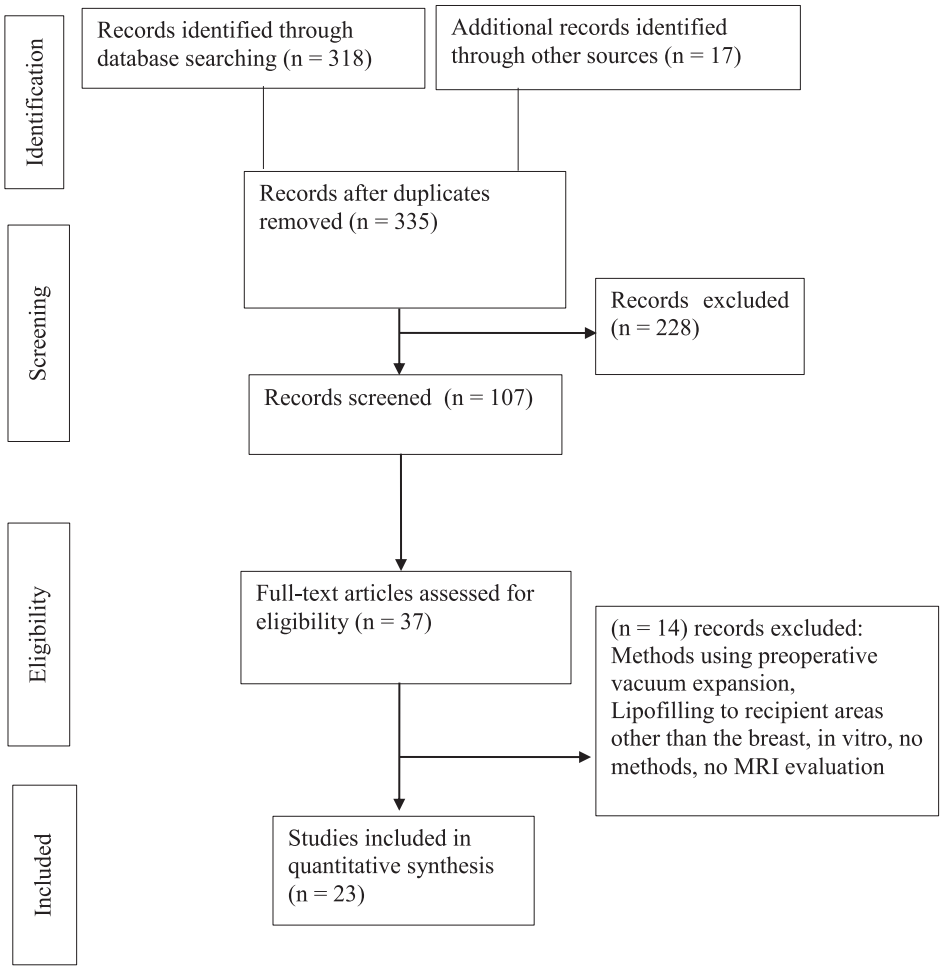

Figure 1 Overview of literature search.

Table 3 Studies performed with a control group showing enhancement of retention rate with CAL in recipient areas different from the breast.

Author	Retention rate with CAL (%)	Retention rate with AL (%)	Enhancement (%)	Area
Li et al., 2013	64,8	46,4	**18,4**	Face
Kolle et al., 2013[6]	80,9	16,3	**64,6**	Arm
Tanikawa, 2013[28]	88	54	**34**	Face
Koh et al., 2012	79,4 (20,59 resorption rate)	53,9 (46.10 resorption rate)	**25,5**	Face

Table 4 Volume of transferred fat and number of sessions performed.

Author	Volume of transferred fat (ml)	Sessions	BMI
Münch[20]	170 (100-280)	2-3	22.7
Zocchi et al.[21]	325 (160-685)	2-3	not indicated
Del Vecchio et al.[22]	430 (220-550)	1-2	not indicated
Coleman et al.[23]	278 (50-450)	1-3	not indicated

no unanimous assent found in the literature concerning the ASC-mediated enhancement of the retention rate for breast augmentation, and the results are spread poorly between 0 and 1% for aesthetic breast augmentation and widely 0-24% when considering also breast reconstruction. For convenience, we used 25% as the mean enhancement rate in Table 5. We calculated that, starting from 200 ml of extracted fat in total used in two sessions of 100 ml each for AL, the volume retained would be 20 ml, 40 ml, 60 ml, 80 ml, 100 ml, 120 ml, 140 ml, or 160 ml, assuming a retention rate of 10%, 20%, 30%, 40%, 50%, 60%, 70% and 80% respectively. In contrast, after extracting 200 ml of fat for one session of CAL with 100 ml of transferred fat, while the remaining 100 ml are used to isolate ASCs, only 12,5 ml, 25 ml, 37,5 ml,

Table 5 The retention rate and the resulting volume gain after two sessions of AL are far superior to those after one session of CAL for the same volume of harvested fat. Hypothetical volume gains were calculated based on AL retention rates ranging from 10 to 80%. We assumed that CAL enhanced this rate by 25% (the highest enhancement reported in the literature for breast augmentation is 24%). In AL, all the harvested fat is transferred to the breast. In CAL, half of the harvested fat is transferred to the breast, while the other half is used in the process of ASC isolation. With admitted enhancement of retention rates with CAL below 25%, the prior listed numbers would naturally pivot even more in favor to the final retention rate after two sessions of AL. In slim patients—which present the majority patients seeking primary breast augmentation—with restricted fat deposits it is preferable to perform two sessions of AL than one session of CAL.

Method	Volume of harvested fat (ml)	Volume of transferred fat (ml)	Volume gain (ml) based on different retention rates (%)							
			10%	20%	30%	40%	50%	60%	70%	80%
AL one session	**100**	100	10	20	30	40	50	60	70	80
CAL one session	**200**	100	12.5	25	37.5	50	62.5	75	87.5	100
AL two sessions	**200**	200	20	40	60	80	100	120	140	160

Table 6 Mean BMI of patients seeking breast augmentation.

Author	BMI	n = number of patients
Maher, 2010[30]	20.8 ± 2.0	100
	21.6 ± 2.7	
	22.6 ± 3.3	
Gupta, 2017[31]	24.3 ± 4.4	129,007
Shi, 2015[32]	20.19	144

50 ml, 62.5 ml, 75 ml, 87,5 ml, and 100 ml of fat volume would remain respectively. With admitted enhancement of retention rates with CAL below 25%, the prior listed numbers would naturally pivot even more in favor to the final retention rate after two sessions of AL.

Discussion

The results presented here show that CAL may in fact limit the volume gain in the majority of women getting aesthetic breast augmentation with autologous fat. It is mandatory to discuss practical considerations when using autologous fat in breast augmentation, which should be factored in, as clinical guidelines further explore the added benefit of using ASCs in breast augmentation.

Physicians constantly search for new methods to improve fat survival and reduce the number of necessary sessions when performing autologous fat transfer. Among the many approaches including different fat harvesting techniques, the use of ASCs has been reported to enhance volume retention by up to 64%.[6,7,8,27,28] However, before blindly adopting the highest enhancement rate reported in the literature, and independently of how the fat is harvested and ASC isolated, one has to take into account three other factors that seem to have a major impact on ASC function: recipient area, amount of transferred fat, and cohort characteristics. The highest enhancement rate of 64% was observed when 30 ml of fat was injected subcutaneously in the upper arm of healthy participants.[6] In this study, 20 million cells/ml of fat were used, representing 2000 times the physiological ASC density. The literature further shows remarkable improvements in the retention rate by ASCs for graft volumes under 100 ml.[6,15,28] Additional studies are needed to establish whether the amount of enriched fat or the recipient area influence the fat retention ability of ASCs.

As for aesthetic breast augmentation, we found no evidence in the literature that CAL ensures a higher volume retention rate.[9,29] As demonstrated in two controlled studies of breast augmentation (200–300 cc of grafted fat) in healthy subjects[9,29], the differences in retention rates following AL *vs* CAL were not statistically significant. Gentile et al. documented the highest enhancement rate in lipofilling to the breast (up to 24%).[15] However, the study cohort was rather heterogenous, including patients who underwent breast cancer surgery, radiation therapy, or implant removal before lipofilling; furthermore, small amounts of enriched fat (less than 100 ml) were used.[15] Interestingly, they tested four different automated systems for SVF cell isolation and found a correlation between stem cell yield and fat retention rate. Other studies, showing a promising retention rate after CAL (40–80%) in either aesthetic breast augmentation or breast reconstruction, lacked an AL control group.[4,7,16] Since the literature on AL to the breast shows similar retention rates (39–76%), it cannot be stated that CAL enhances the retention rate significantly.[14,17,21] Altogether, it is our opinion that the added benefit of CAL in aesthetic breast augmentation is very questionable.

An important practical consideration in autologous fat transfer is the need to harvest double the amount of fat for ASC isolation[6,7,8,27,28], which could otherwise be used for additional fat grafting. Notably, the average BMI of women seeking breast augmentation is quite low.[18,19,30-32] If harvesting the desired volume of fat from a woman with a BMI of 20.4 ($\pm$1.6) already poses a challenge, then opting for CAL will only reduce the overall potential of volume gain.

The vast majority of breast augmentation procedures require repeated surgeries, in general between two and four sessions, to achieve the desired result.[3,15,24,25,26] Owing to the anatomical boundaries of the soft tissue surrounding the breast, large volumes can rarely be transferred during primary breast augmentation—particularly if the breast of the specific age group is small and firm. The soft tissue should not be stretched too much because the resulting mechanical force on the transferred adipocytes would considerably

reduce their retention rate. The findings of this study imply that it is preferable to perform two sessions of AL instead of one session of CAL to maximize volume gain in a population characterized by their low BMI. The fact that this approach requires two procedures to achieve the best possible outcome can be discussed, as two procedures can be regarded as a disadvantage for the patients. Nevertheless, given that these procedures can be done in an outpatient setting under local anesthesia or sedation, it is the authors' opinion that this represents an acceptable harm for the patients for the benefit of a distinct better result. Moreover, the advantages of this approach are that two single sessions of AL are faster, cheaper, and have a lower risk of contamination than one session of CAL. All this has to be taken into consideration prior to deciding whether to perform CAL, especially because for women seeking primary breast augmentation, CAL does not ensure a (sufficiently) higher retention rate, making additional costs and longer operation time difficult to justify.

Study limitations

The major limitation of this study is the heterogeneity in reporting autologous fat transfer efficacy across the different studies. We cannot rule out that the different timepoints and volume assessment methods may be associated with biases in data synthesis. Some studies were of sub-optimal quality and only three compared CAL directly with AL.

Conclusion

There is strong evidence that the added benefit of ASCs in lipotransfer described by multiple authors is not applicable to aesthetic breast augmentation. Starting from the same volume of harvested fat, the best possible volume gain after two sessions of AL is always distinctly superior to one session of CAL admitting 25% as the best published increase of RT. Since the average BMI of patients seeking aesthetic breast augmentation is low, their fat deposits are rather limited. Hence, ASC enrichment is counter-productive in the majority of patients seeking primary aesthetic breast augmentation with autologous fat. Further studies in this patient group are warranted to confirm these findings.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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Ethical approval

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