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Breast

How Porcine Acellular Dermal Matrix Influences the Development of the Breast Capsule 1 Year after Implantation: A Histopathological Analysis

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Background: In prepectoral breast reconstruction (PPBR) the acellular dermal matrix (ADM)'s integration capacity into the tissue is known. The aim of this study was to analyze the effect of the ADM on development and composition of the peri-implant breast capsule in a dynamic setting of breast tissue expansion during two-stage prepectoral breast reconstruction.

Methods: This is a prospective single-center study in which 50 patients who underwent mastectomy and breast reconstruction with prepectoral tissue expander and Braxon ADM (group A) and submuscular tissue expander (group B) were enrolled. One-year post implantation hematoxylin & eosin (H&E) staining and immunohistochemistry analyses were done on capsule tissue samples.

Results: The analysis conducted on H&E-stained samples showed a significant reduction of cellular density and a decrease of the cellular infiltration in capsules of ADM-covered expanders compared with naked expander capsules ($P < 0.05$). The immunohistochemical analyses showed that group A capsules presented significantly less M1 CD68+ macrophages ($P < 0.05$), lower alfa-SMA expression levels, and a lower number of myofibroblasts ($P < 0.05$) compared with group B capsules. Presence of lymphatic vessels was minimally detected in both groups.

Conclusions: The ADM presence around the prepectoral tissue expander influences the development of the peri-implant capsule, causing a significant reduction of the number of cells and inflammatory infiltrate, especially M1 macrophages and myofibroblasts. The ADM Braxon is therefore effective in creating a noninflamed capsule around the implant and in dynamic tissue conditions, and such an environment is maintained in time. *(Plast Reconstr Surg Glob Open 2023; 11:e5400; doi: 10.1097/GOX.0000000000005400; Published online 17 November 2023.)*

INTRODUCTION

Thus far, more than 50% of breast reconstructions involve a two-stage approach, in which a tissue expander (TE) is positioned under the pectoralis major muscle first and then it is replaced by a definitive implant when an adequate expansion is achieved (6 months on average).[1] In the last decade, prepectoral breast reconstruction has gained more and more popularity.

Prepectoral breast reconstruction (PPBR) is usually regarded as the placement of an implant above the pectoralis major muscle in association with an acellular dermal matrix (ADM) that covers it completely.[2] The presence of an ADM is essential, given its protective effect against capsular contracture onset.[3–8] Moreover, this technique counts many advantages, among which the best known and recognized are that the reconstructed breast appears more natural, the operative time is slightly reduced, patients feel less postoperative pain and discomfort, and there are no animation deformities or pectoralis major

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muscle spasms.[9–12] In recent times, attempts have been made to extend the benefits of PPBR to patients who could not undergo a direct-to-implant (DTI) surgery offering them a two-stage immediate breast reconstruction. The principle of creating a biological interface between the mastectomy flap and the synthetic implant remains; hence, prepectorally placed TEs also must be wrapped in ADM. This two-stage technique leads to a reduction of outpatient TE inflating, prevents high riding of the expander, eases lower pole expansion,[13] and improves aesthetic results.[14,15] However, there is still more to know about the ADM integration mechanism and about its role in peri-implant capsule dynamics and evolution. The ADM is a graft of deantigenized connective tissue obtained from a decellularization process of human or animal dermis, which has the extracellular matrix component preserved intact.[16] As a graft, it requires complete adhesion to the recipient site so that dead spaces are obliterated and intimate contact with vital tissue allow its integration and revascularization. Unlike synthetic materials, the ADM acts as a scaffold for implantation site cells, allowing their growth and proliferation through collagen remodeling while supporting neoangiogenesis, progressively forming a new tissue and reducing the risk of developing a contractile capsule.[7,17] This process has been widely examined and reported in animal model studies.[15,18–21] In breast reconstruction, there is evidence of reduced rates of capsular contracture when an ADM is used[4,5,7,22]; however, the rates can vary depending on the ADM used.[14–16,19,23] In fact, in the plethora of the commercially available ADMs, different characteristics (such as thickness, presence of fenestration, cross-linking, presence of preservatives, deantigenation method) can influence the ADM's integration and, therefore, capsule quality.[24] Clinical studies that examine the effect on surrounding tissues and the integration mechanism of the ADM Braxon in implant-based breast reconstruction are limited and regard definitive implants.[25,26] The aim of this study was to histologically define the influence that ADM has on peri-implant capsule formation and stabilization after breast tissue expansion and to analyze in the long-term potential differences between a capsule formed by a TE in the presence of an ADM and without the ADM. More in detail, we will investigate the ADM's role in affecting the peri-implant capsular microenvironment through its influence on the physiologic processes of inflammation, neoangiogenesis, and lymphangiogenesis, which can develop once the breast implant is placed.

MATERIALS AND METHODS

This comparative single-center prospective study was conducted at the plastic surgery and pathology departments of Ospedale di Cattinara (ASUGI Azienda Sanitaria Universitaria Giuliano-Isontina), Trieste, Italy. The study was done in full accordance with the Declaration of Helsinki, and an informed consent for an additional procedure was obtained from each patient enrolled in the study.

Takeaways

Question: How does porcine acellular dermal matrix (ADM) influence breast implant capsule development?

Findings: The ADM positively interacts with the normal healing process and leads to the development of a periprosthetic capsule that bears a lower number of cells and inflammatory infiltrate, especially M1 macrophages and myofibroblasts, compared with capsules formed around uncovered tissue expanders.

Meaning: After 1 year from implantation, there is a biological significant difference between the breast implant capsules formed around ADM and the capsules formed around the naked tissue expander.

Patients

The study involves a total of 50 patients subdivided as such: a cohort of 20 female patients (study group named group A) who underwent immediate prepectoral breast reconstruction with TEs totally covered with Braxon (Decomed S.r.l., Marcon-Venezia, Italy), a 30 cm × 20 cm 0.6mm thick noncross-linked porcine ADM, and a cohort of 30 female patients (control group named group B) who underwent submuscular breast reconstruction with TEs. Procedures were performed between January 2021 and January 2023.

Patients excluded from the analysis were those who received pre- or postoperative radiotherapy, who had undergone previous breast surgery or had a history of autoimmune diseases. For the purpose of this prospective study, patients who developed complications such as infections, hematoma, seroma, wound dehiscence, and skin necrosis were also excluded from the collection.

Statistical analysis with Fisher exact test was performed to evaluate the homogeneity of the two groups in terms of demographic characteristics (age, body mass index), permanence of TE, comorbidities (diabetes, vasculopathies), smoking status, and final TE fill volume.

Surgical Technique

Patients underwent mastectomy with transverse incision performed by a single accredited breast cancer specialist; the reconstruction phase was performed by a single senior plastic surgeon.

During the first stage of surgery (that is, TE placement), group A patients underwent immediate prepectoral breast reconstruction with low- or medium-height MENTOR CPX4 Breast Tissue Expander with SILTEX Shell Surface (Mentor, Santa Barbara, Calif.) totally covered by Braxon ADM. The ADM-TE complex is prepared with the "ravioli" technique.[27] Briefly, after rehydration in sterile saline solution for 5 minutes, the matrix is adapted to the partially inflated TE and its anterior and posterior flaps are sutured together with single stitches for complete TE coverage. Then, the so-wrapped TE is placed in the subcutaneous pocket and fixed to the pectoralis major muscle fascia and along the inframammary fold with interrupted sutures.

Group B patients had the low- or medium-height Mentor CPX4 Breast Tissue Expander with Siltex Shell

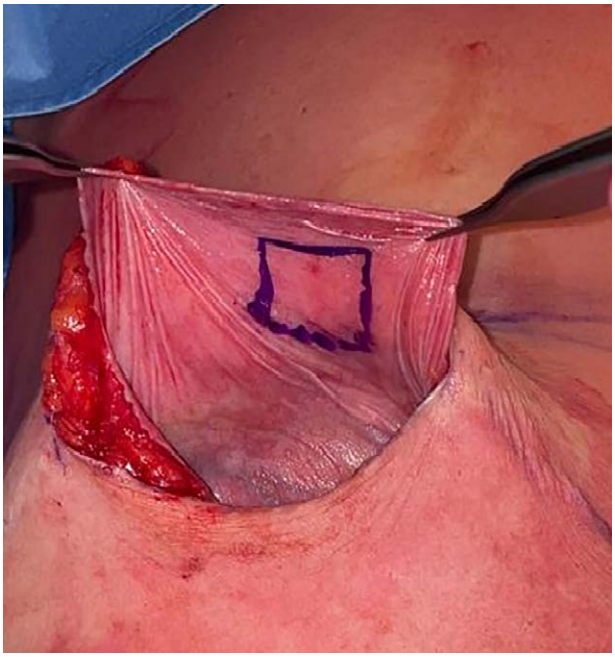

Fig. 1. Intraoperative tissue sampling technique.

Surface (Mentor, Santa Barbara, Calif.) positioned in a submuscular-subfascial pocket.[28] In particular, the pocket was created by lifting the pectoralis major muscle from the underlying chest wall, starting from its lateral border, and once arrived at the muscle's inferior border, the fascia was raised along with the pectoralis major itself, till the inframammary fold. Once arrived at this point, the fascia was interrupted to free and reduce the tension.

Expansion started 1 month after TE implantation, with a 50-mL expansion every 3 weeks, and was terminated when the final desired volume was reached. This was followed by expander removal and positioning of a definitive implant. For this second stage, the same surgical access as for mastectomy was used in all patients. During this second surgery, a full-thickness sample of anterior peri-implant capsule (2×2cm) was collected (Fig. 1), stored in 10% formalin, and processed by the pathology laboratory.

Histopathological Analysis

Hematoxylin and eosin (H&E) staining and immunohistochemistry analyses were performed on the formalin-fixed paraffin-embedded tissue samples. The tissue sections were analyzed semiquantitatively for cell density, vessel proliferation and cell infiltration by H&E staining, whereas immunohistochemical staining was performed to examine a variety of cell populations and anatomical structures such as myofibroblasts (α-smooth muscle actin antibodies, Clone 1A4 Roche), endothelial cells (CD 31 antibodies, Clone JC70 Roche), T-helper cells (CD4 antibodies, Clone SP35 Roche), natural killer T cells (CD56 antibodies, Clone MRQ-40 Roche), cytotoxic T cells (CD8 antibodies, Clone SP-57 Roche), M1 (CD68 PGM1 antibodies, Clone PG-M1 DBS) and M2 macrophages (CD163 antibodies, Clone MRQ-26 Roche), and lymphatic vessels (podoplanin D2-40, antibodies Clone D2-40 Roche).

A single senior pathologist performed a blind analysis on the tissue sections belonging to groups A and B. The following semiquantitative scoring system (SSS) was used: 0 = no response; 1 = minimal/barely detectable; 2 = mild/slightly detectable; 3 = moderate/easily detectable; and 4 = marked/very detectable. A statistical analysis on the scores was completed for both sample cohorts using the Mann-Whitney *U* test (SPSS statistics, v. 25 software IBM Corp, New York, N.Y.).

RESULTS

From January 2021 to January 2023, a total of 50 patients were enrolled in the study. All patients underwent mastectomy for breast cancer and contextual reconstruction with prepectoral ADM-covered TE (20 patients, study group— group A) or subpectoral TE (30 patients, control group— group B). Mean follow-up time was 19.2 months (range 10–24 months). The average time for implant exchange (and so for biopsy sampling) was 12.6 months (range 5–27 months) for group A and 11 months (5–26 months) for group B. All patient's data are listed in Table 1.

No statistically significant differences have been noticed between the two groups in terms of demographic characteristics, time of TE permanence, comorbidities,

Table 1. Patients' Variables Examined

	Experimental Group (A)	Control Group (B)	*P**
No. patients	20	30	/
Age at surgery	57	54.5	0.79
BMI	25	26.2	0.14
Smoke	1	8	0.36
Diabetes	4	0	0.02
Vasculopathy	3	3	0.67
Tissue expander permanence (mo)	12.6	11	0.86
Volume of tissue expander (ml)	430	450.8	0.31
Fill volume of tissue expander (ml)	369.2	412	0.05
Type of mastectomy			
Skin-sparing	12	18	/
Nipple-sparing	8	21	/

*Significance for $P < 0.05$.

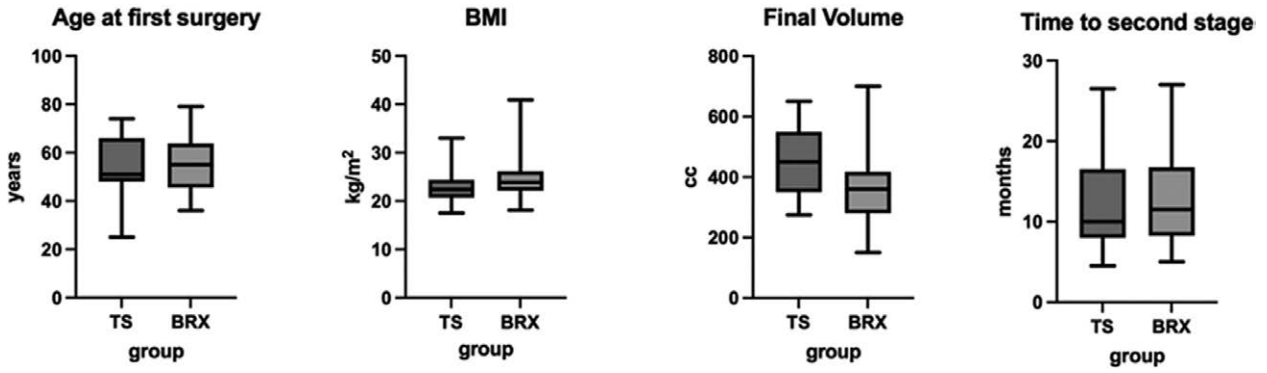

Fig. 2. Graphs demonstrate the homogeneity of the two groups (TS, control group; BRX, experimental group) for demographic characteristics.

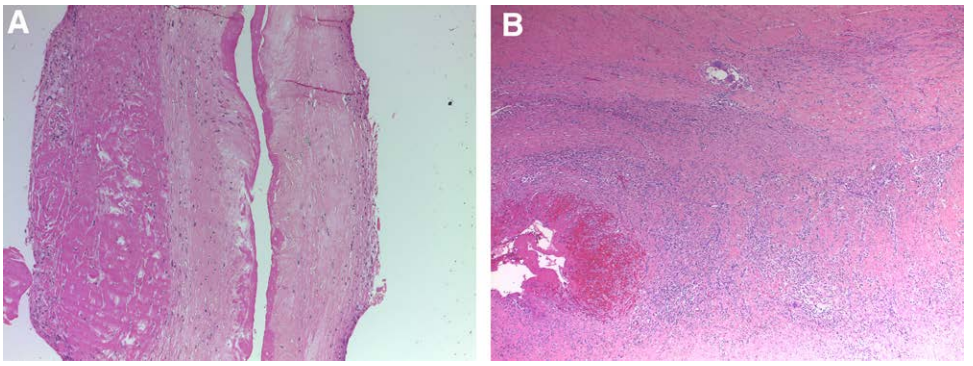

Fig. 3. Histopathologic evaluation of specimens. ADM (A) and native breast capsule (B) specimens (hematoxylin and eosin staining; original magnification, ×100). The H&E staining on the samples showed a significantly lower amount of cellular density and a reduced cellular infiltration in the ADM capsule compared with native capsule.

smoking status, body mass index, and final TE volume, as shown in Figure 2. Diabetes was the only variable significantly more represented in group A (4 versus 0).

Histopathologic Evaluation

The H&E staining on the samples showed a significantly lower amount of cellular density and a reduced cellular infiltration in the capsule's samples belonging to group A compared with those from group B (SSS average value 1.6 versus 2.5; $P < 0.05$ for cellular density and SSS average value 1.7 versus 2.5; $P < 0.05$ for cellular infiltration) (Fig. 3). Vessel proliferation/HPF resulted similarly between the two examined groups. Moreover, only in the native capsule (group B), a qualitative morphological analysis showed the presence of calcifications, foci of foreign body-type giant cell reaction with inflammation, and cholesterin fine needle-shaped crystals.

The immunohistochemical analysis showed that in the capsules formed by ADM integration in the surrounding tissues, there are significantly less CD68+ M1 macrophages compared with the capsules formed around the naked submuscular TE (SSS average value 1.7 versus 2.6; $P < 0.05$) (Fig. 4). Moreover, a reduction of the number of cells positive for alfa-SMA and, therefore, of the number of myofibroblasts could also be appreciated. (SSS average value 1.3 versus 2.3; $P < 0.05$) (Fig. 5).

In both groups, the presence of lymphatic vessels (podoplanin D2-40$^+$) was minimally detectable; in group A, the presence of new endothelium (CD31-expressing cells) was minimally detectable, whereas in group B, it was mildly detectable. T-helper cells (CD4$^+$) and T-cytotoxic cells (CD8$^+$) were minimally detectable; regarding the presence of natural killer T cells (CD56$^+$), the score was zero for both groups. M2 macrophages (CD163$^+$) were mildly detectable in both groups (Table 2) [**See figure, Supplemental Digital Content 1,** which displays the Mann-Whitney *U* test results. A significant reduction of cellular density, cellular infiltration, number of myofibroblasts and number of CD68$^+$ M1 macrophages was found in the experimental group (BRX) compared with the control group (TS). **http://links.lww.com/PRSGO/C856**]

DISCUSSION

Prepectoral breast reconstruction performed with ADM-covered implants provides the patients some well-known clinical and psycho-social advantages, such as more natural appearance of reconstructed breast, a reduction of postoperative pain and discomfort because of pectoralis

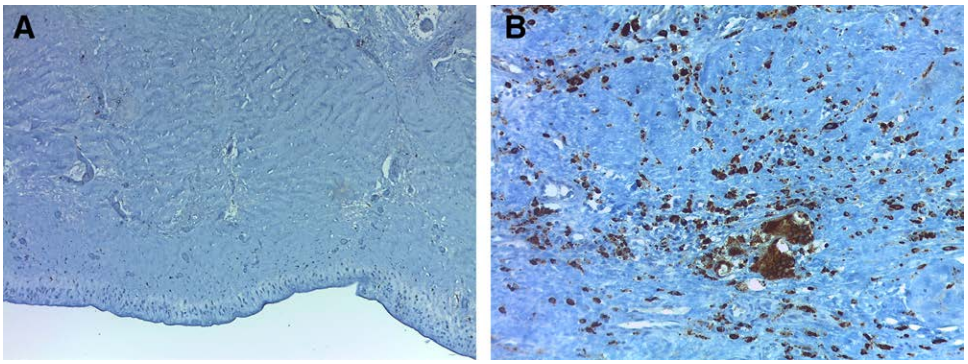

Fig. 4. Histopathologic evaluation of specimens. ADM (A) and native breast capsule (B) specimens. Immunohistochemical identification of $CD68^+$ M1 macrophages.

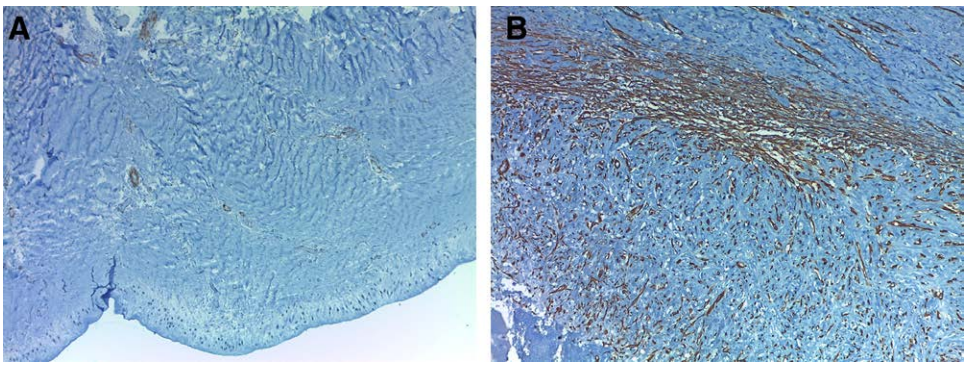

Fig. 5. Histopathologic evaluation of specimens. ADM (A) and native breast capsule (B) specimens. Immunohistochemical identification of cells positive for α-SMA (myofibroblasts).

major muscle sparing, no risk of animation deformity, a better inframammary fold definition, and the possibility to position the implant immediately after mastectomy (one-stage breast reconstruction).

Multiple published papers report the ADM's ability to modulate inflammation and therefore positively influence the peri-implant capsule formation, with modification of the capsular microenvironment compared with naked implants.[4,7,14,16,17,29–31] However, the majority of the studies focusing on the histological aspect of the ADM-formed peri-implant capsules report short-term investigations and consider ADM wrapped around definitive implants that are fixed in volume over time. In addition, their small sample of patients and the lack of a control group bring limited evidence.[29,30]

Our study aims at filling this gap, analyzing at 1 year after reconstructive surgery peri-implant capsule tissues in patients who received prepectoral TE wrapped in ADM; hence, long-term investigations are performed on tissue samples that underwent dynamic changes (expansion) over time (group A). Notably, tissue samples taken from an additional group of patients who received submuscular TE were used as a control (group B). Our results show that 1 year after ADM implantation, the peri-implant capsules present a significant reduction of cell density and a reduced cellular infiltrate compared with control group capsules; in addition, by means of histochemical analysis, it was noticed that the pro-inflammatory M1 macrophages, well known for their role in boosting the inflammation process and the reaction of the organism towards foreign bodies, are significantly less in the group A. This result is also supported by Basu et al,[14] but in a work with biopsies taken at a shorter follow-up (4.38 months), thus confirming that the antiinflammatory role of ADM is maintained over time. The study by Basu and colleagues hypothesizes that, thanks to the biocompatible nature of the acellular cadaveric matrix used, a tidy colonization of the matrix from host cells is allowed, obtaining an appropriate host tissue incorporation and integration. This accelerates the healing process and avoids a prolonged inflammatory phase of the wound. Similarly, from our data, we can assume that the presence of the matrix, by reducing the inflammatory infiltrate and the number of M1 macrophages, leads to a capsular environment with less inflammation and with a decreased reaction of the organism toward the foreign body.

The mild inflammation itself can also explain the significantly lower amount of myofibroblasts found in group A capsules compared with those from group B. The proliferation and differentiation of these cells is physiologically stimulated by macrophages during the inflammatory process. Our results suggest that the presence of ADM may be able to decrease the inflammation process and the proliferation of myofibroblasts in the capsular environment.

Table 2. Results of Histopathological Analysis

	ADM Capsula (SSS Average Value))	Native Capsula (SSS Average Value))	*P*
Cell density	1.6	2.5	<0.05
Vessels/Hpf	2.2	2.1	>0.05
Cells infiltration	1.7	2.5	<0.05
Myofibroblast (α-SMA)	1.3	2.3	<0.05
Linfatic vessels (podoplanina D2-40)	1.1	1.5	>0.05
New endothelium (CD 31)	1.7	2.1	>0.05
T-helper cell (CD4)	1.2	1.5	>0.05
Natural killer T cell (CD56)	0.3	0.5	>0.05
T-cytotoxic cell (CD8)	1.1	1.2	>0.05
M1 macrophage (CD 68 PM)	1.7	2.6	<0.05
M2 macrophage (CD 163)	2	2.5	>0.05

In agreement with our results, Tevlin et al[29] in their study found a significant reduction of myofibroblasts in ADM-derived capsules. Their study was conducted on a small cohort (five patients) and had an internal control group; again, the follow-up was short (5.2 months). Kim et al[30] found an analogue result in 30 patients with a 10-month follow-up and an internal control.

From the clinical point of view, myofibroblast reduction is linked to a reduced risk of capsular contracture: in fact, myofibroblasts are actively involved in the process of fibrosis.[32,33] Despite studies supporting the association between the use of ADM and a clinical decrease of capsular contracture are numerous,[4,7,14,16,17,29–31] the anatomopathological mechanisms underlying such clinical outcome are still to be completely understood.

Interestingly, a lymphatic element was found in the capsule samples, even if at a minimal entity. It is notable that in all previous works conduced on patients, and probably due to the short follow-up of the studies, it was not possible to isolate this component, likely because of the long time that lymphangiogenesis requires.[16,19]

To our knowledge this is the first study that examines the peri-implant capsule that underwent dynamic tissue changes from a histological and immunohistochemical point of view with specimens collected at 12.6 months after TE implantation (in fact, during the COVID-19 pandemic, our National Health Authority delayed expander replacement surgeries). In addition, the study design included comparable patient cohorts receiving prepectoral TEs covered with ADM or submuscular naked TEs. From our results, we can assert that in the 1 year during the formation of the peri-implant capsule, thanks to ADM presence and integration, the inflammation process decreases, thereby preventing the formation of capsule contracture. Capsule samples from subpectorally placed TEs, instead, retained higher levels of inflammation. Lastly, this study demonstrated that ADM integration can effectively occur during tissue expansion.

There are no studies in the literature with an external control group such as ours. For this reason we chose to use as a reference (control group) the most widespread technique of immediate breast reconstruction (ie, two-stage-reconstruction with a submuscular expander). In this way, we also guaranteed the gold standard of reconstruction to the patients in the control group. Despite this, it would be interesting to place a prepectoral expander without ADM as a control group.

Our study presents some limitations: the histopathological analyses are semiquantitative, and there is a different number of diabetic patients in the study group compared with control group. Moreover, this analysis focused on only one type of matrix, and these results should also be investigated with other devices; a single type of implant surface (Mentor Siltex Shell Surface) was analyzed, this aspect can influence the formation of the periprosthetic capsule. Nevertheless, the inclusion of a different and comparable control group, the good sample size, the long time between surgery and peri-implant capsule sampling, and the blind analyses of the samples are strengths.

Our study shows a detailed picture of the biological events taking place in the peri-implant capsule 1 year after the temporary implant placement with and without ADM. Future investigations should concentrate on deepening the knowledge on the molecular mechanisms and paracrine signaling related to the capsule formation process. In addition, a larger sample and a longer follow-up could allow us to recognize potential associations between histopathological characteristics and clinical elements.

CONCLUSIONS

This study investigates the long-term cellular events related to capsule formation during breast tissue expansion with and without ADM. After 1 year from TE implantation, there is a significant biological difference between the breast implant capsules formed around Braxon ADM and the capsules formed around the naked TE. The ADM positively interacts with the normal healing process and leads to the development of a periprosthetic capsule that bears a lower number of cells and inflammatory infiltrate, especially M1 macrophages and myofibroblasts, compared with capsules formed around uncovered TEs. Further investigations are required to understand if and how the ADM's biological activity can be clinically confirmed by preventing the development of capsule contracture in a longer timeframe in the settings of prepectoral two-stage reconstruction.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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