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Original Article

Acute and chronic mammary periprosthetic histological changes of the muscle ☆

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ABSTRACT

Background: Augmentation mammoplasty with subpectoral prosthesis implantation is a frequent performed procedure in plastic surgery for reconstructive and aesthetic purposes. Although prosthesis implantation in a pocket under the major pectoralis muscle has been related to volumetric and functional alterations, there is not much information about the associated short- and long-term histological changes. Therefore, the aim of our study was to describe the acute and chronic histological muscle alterations associated with subpectoral prosthesis implantation.

Materials and Method: We collected samples from patients with breast tissue expander (<6 months after implantation) and prosthesis (>1 year after implantation) and from patients without implantation as a control group. The samples were processed for assessing their histological, histochemical and immunohistochemical properties.

☆ This work has not been presented at any meeting. Juan Cámara-Pérez and Ignacio Jimena contributed equally to this study.

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Results: In the control group, no relevant histological findings were identified. Additionally, in the patients with expander, we observed mild augmentation of the internalised nuclei, normal morphology, significant muscle atrophy and fibrosis, whereas in the patients with prosthesis considerable augmentation of internalised nuclei, significant muscle atrophy, fibrosis and alteration of normal muscle morphology were observed.

Conclusion: Prosthesis implantation induces histological changes in the periprosthetic striated muscle. Chronic fibrosis and inflammation play key roles in this process, which should be characterised in more detail from the histological and molecular biological perspective.

Introduction

Augmentation mammoplasty in the submuscular plane is one of the most frequently used plastic surgery procedures. It can be undertaken as an aesthetic procedure or as a part of the breast reconstruction process after mastectomy. The surgical technique consists of pocket creation beneath the *pectoralis major* muscle, where the prosthesis is implanted.[1] In reconstruction surgery, if enough distensibility of surrounding tissue cannot be expected, a temporary expander is placed in the pocket instead of a prosthesis. This expander is sequentially filled, so that the accommodation of the tissues is allowed. After this period, a second surgery is performed to withdraw the expander and place the definitive prosthesis.[2] The histological alterations of the muscle after implantation and their probable role in the associated pathology, especially in capsular contracture, are yet to be elucidated.

Submuscular prosthesis implantation is associated with certain tissue changes in the adjacent anatomical structures. In the case of the mammary gland, it is associated with early volumetric loss during the first months.[3] Although there are radiological studies that indicate volumetric decrease in the *pectoralis major* muscle after prosthesis implantation, isokinetic studies have demonstrated the loss of muscle strength,[4] there is a lack of information about the histological changes induced by prosthesis or expander located in the submuscular plane. The studies carried out to date highlight the presence of microscopic changes after the mammary expander placement within the frame of reconstructive surgery. These changes concerned focal degeneration of muscle fibres with glycogen deposition and mild interstitial fibrosis. Furthermore, some fibres presented disorganisation in the myofilaments of the sarcomeres.[5] However, these findings did not clarify whether these alterations resulted from acute injury, either due to the surgery or volumetric changes associated with the expander placement, corresponding stress/distensibility impact on the muscle or if they were maintained over time.

The surgery itself is an acute traumatic alteration to the muscle. Under normal conditions, striated muscles have high regeneration[6] owing to the ability of the cell to repair itself and processes associated with satellite and other cell types.[7] This regeneration ability of skeletal muscle is limited by fibrosis, which takes place in the injured area and the alterations to the structural architecture of striated muscle.[8] Regarding tissue expansion mechanisms, as observed in other models, the initial muscle atrophy subsequently subsides after the removal of the expander.[9] However, in the case of breast reconstruction, the impact of the breast expander is not reversed, as the expander is not removed, but is exchanged for a breast prosthesis which has a similar effect over time.

An increase in the number of sarcomeres has been observed in other skeletal muscles in which tissue expansion has been used in an experimental manner.[10] This is possibly due to tissue hypoxia related to tissue compression because of the expander placement, which has an initial negative im-

pact on the muscle fibres; however, its maintenance over time might be associated with a stimulus on local angiogenesis and growth factors.[11] In this regard, elucidation of microscopic chronic alterations associated with long-term implanted prosthesis becomes important because of the reported early changes.

Additionally, histological muscle alterations may have an implication on the muscle and play a role in the periprosthetic capsular contracture, because the activity of myofibroblasts implicated in its development is influenced by the tension forces acting over them.[12] Although there is information about the possible origin of the myofibroblasts in other related pathologies, it has yet to be elucidated in the case of the breast, as no studies are available in this regard.

Therefore, the aim of this study was to describe and measure the histological changes in the *major pectoralis* muscle associated with prosthesis or expander placement compared to those in the control group.

Material and Methods

Patient selection

We created 3 groups for this study. In the first expander group (EG), we randomly selected 10 patients who underwent breast surgery to replace mammary expander for definitive prosthesis, with expander placement time <6 months, to observe the acute changes. In the second group, called the prosthesis group (PG), we randomly included 10 patients who underwent surgery to replace mammary prosthesis, with a prosthesis implantation time >1 year, to study the chronic alterations. In the last group, the control group (CG), we randomly selected 10 patients who underwent breast surgery due to a benign pathology without prosthesis or expander implantation. All included patients underwent surgery in the Plastic and Reparative Surgery Department of the Reina Sofía University Hospital, Córdoba, Spain between March 2021 and February 2022.

All patients should be >18 years old. Those with relevant systemic, muscular/neurological pathology or alterations that could disturb the normal morphology of the *pectoralis major* muscle were excluded. Patients with toxic habits or obesity were not included.

Data collection and datasets

Data collection was carried out by accessing the Management Station Application of the software Diraya of the Andalusian Public Health Institution.

Each of the patients was labelled individually for next codification in the new dataset which assured complete anonymisation.

Material

Biopsy samples from the *pectoralis major* muscle were taken during their main surgery. From each patient, 2 samples, with dimensions of 1 cm × 2 cm, were taken.

The samples were prepared for histological, histochemical and immunohistochemical studies. One sample from each patient was fixed in 10% formalin and the other was frozen. The frozen samples were transported in a 4°C ice-box to the lab and were frozen in isopentane (2-methylbutane) cooled in liquid N at -160° C. Serial sections of 6 μm thickness were cut using a Leica CM1860 cryostat model and stored in a freezer at -20° C.

The formalin-fixed samples were transported to the lab in formalin and stored in it, until not <24 h and no more than 72 h, to avoid antigenicity alterations. They were processed and embedded in paraffin. Serial sections of 7 μm thickness were cut on a microtome Leitz 1512 and stored at 40°C for 24 h.

Stains for light microscopy

- Samples embedded in paraffin

Samples embedded in paraffin were stained using haematoxylin and eosin (H&E).

- Samples processed by freezing

Frozen samples were stained using Masson's trichrome and periodic acid Schiff (PAS) techniques.

Immunostaining was performed using the following primary antibodies: desmin (1:100, clone DE-R-11, Leica®), smooth muscle actine (1:50, clone ASM-1, Leica®), MyoD1 (1:50, clone MYOD1/2075R, Abcam®) and myogenin (1:100, clone MYOG/2660, Abcam). After a 5 min acetone fixation, primary antibodies were incubated for 2 h. Visualisation was performed using the LSAB+System-HRP® (K0979, Dako, Denmark) following the manufacturer's instructions. Negative controls were performed in parallel without primary antibodies. Nuclei counterstaining was performed using Mayer's haematoxylin.

Histomorphometric analysis

The images were digitalised with an Aperio GT 450 DX scanner (Leica Biosystems Wetzlar, Germany), with 4x, 20x and 40x magnifications. Five fields (20× objective) from each muscle were analysed. The obtained images were analysed morphometrically using the Image J221® (Fiji 22) software (National Institutes of Health, Bethesda, MD, USA) for measuring the following parameters in the muscle fibres: cross-section area (μm^2), minor diameter (μm), perimeter (μm), shape factor, roundness[1] and fibrosis area (%).

The following changes were evaluated semi quantitatively:

1. Fibres with nuclei internalisations and atrophic fibres
   It was done in sections stained with H&E, NADHtr or anti-desmin under light microscope. For each parameter, points from 1 to 4 were awarded per microscope field (100): grade 1: <25 %, grade 2: 26–50 %, grade 3: 51–75 % and grade 4: >76 %.
2. Anomalies in fibre-type distribution and atrophic pattern

The evaluation of widespread/isolated atrophy, fibres with nuclei clumps, fascicular atrophy and fibre-type grouping was carried out in sections stained with H&E and NADHtr under a light microscope. For each parameter, scores from - to + were assigned per microscope field indicating its presence and severity: grade - (normal or absence), grade + (occasional), grade ++ (moderate), and grade +++ (severe).

Statistical analysis

Data are presented as mean ± standard deviation (SD) for the total analysed areas. Analysis of variance (ANOVA) was used followed by the post-hoc Scheffé or Games–Howell test regarding the homogeneity of the variances. Kruskal–Wallis followed by the pair-comparison of Mann–Whitney U test was used for non-normal data. The analysis of the morphometric parameters was carried out using the statistical software package SPSS 25®. The level of significance was set as $p<0.05$.

Results

The average age of the patients in CG, EG and PG was 52.1 ± 6.4, 52.5 ± 13.1 and 52.8 ± 4 years, respectively.

The average implantation time was 5.1 ± 1 months in EG and 50 ± 31 months in PG.

From the histopathological point of view, no relevant alterations were found in CG. In EG and PG, local changes with focal atrophy and direct signs of denervation and reinnervation were observed. The most relevant histomorphometric data are summarised in Table 1, whereas the nuclear internalisation and atrophic fibres features of the different studied groups are summarised in Table 2.

[1] Shape factor and roundness are descriptors of the shape which range from 0 to 1 and set to how similar a fibre is to a circle. A fibre which scores 0 would be considered as being extremely irregularly shaped with 1 being a perfect circle.

Table 1
Histomorphometric measurements among the different groups. Values are expressed as mean ± SD (standard deviation). The statistical significance was fixed in $p<0.05$. * Significant differences $p<0.05$ vs CG among the groups. Š Significant differences $p<0.05$ vs among the experimental groups (EG vs PG).

	Cross-section area (μm^2)	Perimeter (μm)	Minor diameter (μm)	Roundness	Shape	Fibrosis (%)
CG	3243.22±286,11	226.19±13.41	51.54±1.73	0.71±0.01	0.64±0.05	13.54±3.01
EG	701.32±276.77 Š *	79.26±19.65 Š *	11.66±1.48 Š *	0.43±0.06 Š *	0.58±0.02	81.79±11.98 *
PG	259.13±86.43 Š *	78.88±16.92 Š *	11.21±1.70 Š *	0.38±0.03 Š *	0.48±0.02	81.43±8.87 Š *

Table 2
Percentage of fibres which show histological changes. In brackets: points from 1 to 4 were awarded per microscope field for each parameter, where grade 1: (<25%), grade 2: (26-50%), grade 3: (51-75%) and grade 4: (>76%); -: not detected.

	Nuclear internalisation	Atrophic fibres
CG	-	-
EG	12% (8)	17% (12)
PG	29% (18)	22% (21)

Histological analysis

The muscle fibres of CG, grouped in fascicles, presented polygonal morphology with acidophilic sarcoplasm and outlying nuclei. No changes or abnormal features were observed with the used histochemical staining techniques (Masson's trichrome) and immunohistochemical antibodies.

In EG, the H&E stained muscle fibres were grouped in fascicles with mild and focal atrophy, preserving the polygonal morphology and peripheral nuclei with focal and isolated nuclei clumps. Nuclei internalisation was observed in a proportion that was slightly higher than normal (8-11%; Table 2). With the histochemical techniques (Masson trichrome and PAS) neither fibre-type grouping nor relevant cytoarchitectural changes were found. Immunohistochemistry studies revealed no inflammatory cells. MyoD1 and myogenin expression was inhibited according to the maturity of the muscle. There were no specific findings with respect to desmin and smooth muscle actin (Fig. 1 and 3).

Additionally, atrophic fibres were observed with H&E more often in PG than in CG and EG. This atrophy showed an intrafascicular pattern, with associated inflammatory infiltration. Moreover, there was an increase of peri- and intrafascicular conjunctive tissue, both with routine staining technique and Masson's trichrome staining (Fig. 2). Internalised nuclei were observed, especially in the periprosthetic area in a 10-16% proportion. The histochemical (PAS and NADH) studies revealed no fibre-type grouping or relevant cytoachitectural changes. Immunohistochemically, no isolated inflammatory cells were identified. MyoD1 expression and other immunohistochemical markers were negative. However, with desmin, a spotted pattern in the muscle fibres, especially in the atrophic ones, were observed (Fig. 3).

Histomorphometric analysis

The histomorphometric analysis revealed significant differences ($p<0.05$) in the cross-section area of PG when comparison to that of CG and EG, representing a reduction of 90% and 76% in the muscle cross-section area, respectively (Table 1).

The values obtained with respect to perimeter and roundness followed a pattern similar to the one observed in the cross-section. The shape descriptor had values that were significantly higher in

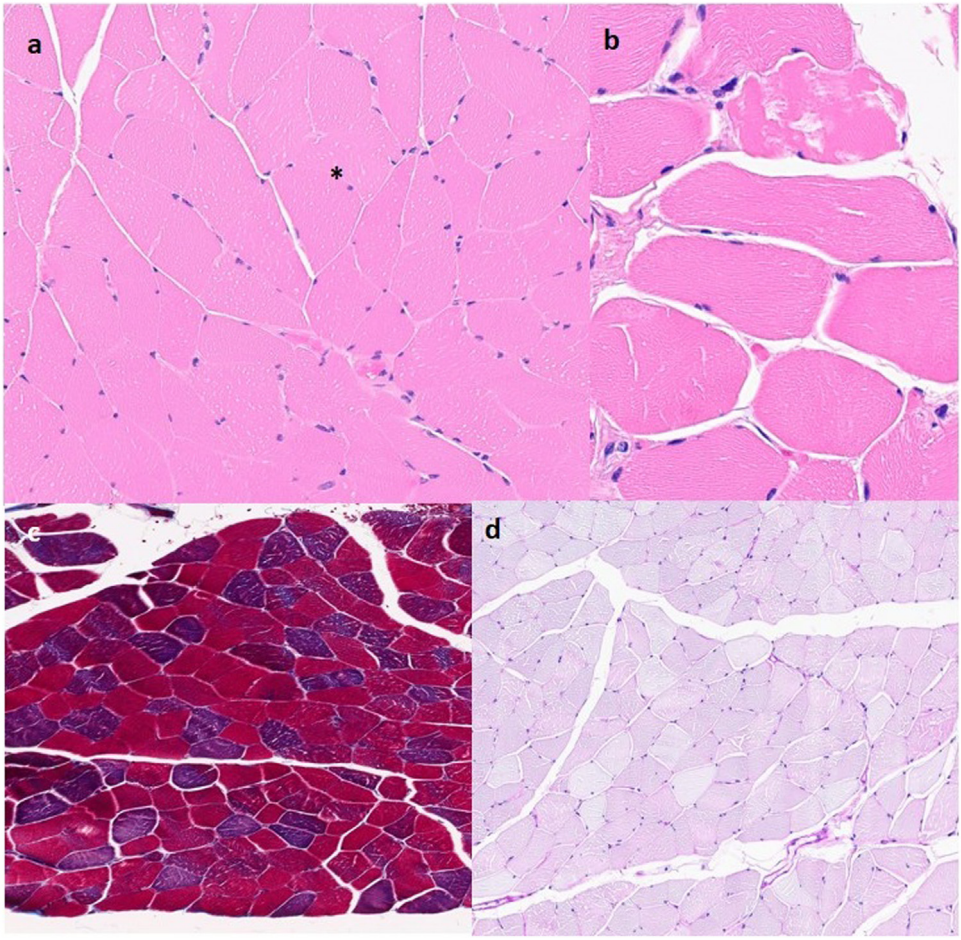

Figure 1. EG group (a) and (b) H&E stained samples at 10x and 40x magnification. Muscle bundles with minimal variability of the fibres and occasional nuclei internalisation (*). (c) Masson's trichrome stained sample at 8x magnification. No increase in epimysial or perimysial conjunctive tissue is observed. (d) PAS stained sample at 8x magnification. Normal preservation of fibre types. No other relevant histological findings.

PG than in the group without prosthesis, which indicated a reduction of 29% in the roundness of the myofibres. No statistically significant differences were found between CG, EG and PG regarding the other parameters (Table 1). Concerning the shape of the cross section of the muscle fibres, variations in PG and EG were observed with respect to CG. No significant increase was found among the different groups in the percentage of conjunctive tissue per field.

The results of the semiquantitative evaluation of the parameters regarding cytoarchitectural changes and abnormalities in fibre-type distribution and atrophic pattern are shown in Table 3.

Discussion

Augmentation mammoplasty is a very frequent aesthetic surgical procedure. It is also used for reconstructive purposes after mastectomy due to breast cancer, subsequent to prophylactic mastectomy by reason of high risk of developing breast cancer or due to malformation pathologies.

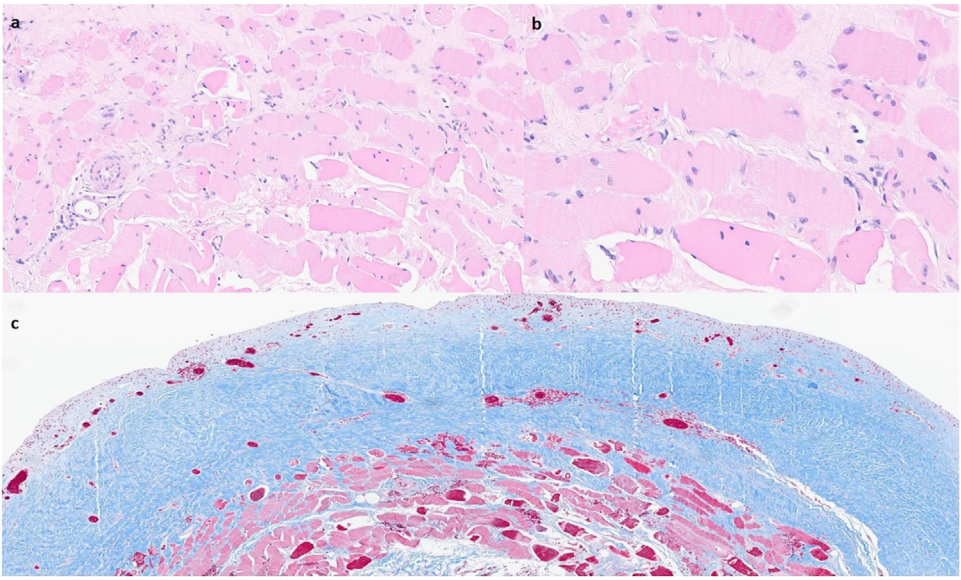

Figure 2. PG group. (a) and (b) H&E stained samples at 10x and 40x magnification. Muscle bundles with severe perifascicular and interfascicular atrophy and focal inflammatory infiltrates. Several small fibres, some of which are basophilic (regenerative) with nuclei internalisation can be observed. (c) Masson's trichrome stained samples at 8x magnification. A notable increase of epimysial and perimysial conjunctive tissue is observed.

Table 3
Abnormalities in fibre-type distribution and atrophic pattern. Rating from - to +++ was used per microscope field for each parameter, correlating their presence and severity: grade – (normal or absent), grade + (occasional), grade ++ (moderate) and grade +++ (severe).

	Disseminated/isolated atrophy	Nuclear internalisation	Nuclear clumps	Fascicular atrophy
CG	-	-	-	-
EG	+	+	-	+
PG	++	+	-	++

Breast augmentation or reconstruction can be achieved using autologous tissue, or with exogenous material for breast prosthesis implantation, for which there are different models, differing in content, morphology and external surface texture.[13]

In breast reconstruction surgery, in selected patients whose tissue distensibility cannot be assured, instead of locating a definitive breast prosthesis directly, a temporal breast tissue expander is implanted. Although its characteristics are similar to a standard breast prosthesis, it has a valve through which sequential filling of the expander can be carried out for a few weeks. Therefore, appropriate progressive expansion of tissues in the breast area can be achieved, and when the optimal size is reached, this expander is exchanged for a definitive breast prosthesis in a second surgery.[14]

Although prosthesis implantation generally achieves morphologic and volumetric restitution or enhancement, with a significant improvement in the self-perception of the patients, this procedure is not completely safe.[15]

Breast implantation has been radiologically related to size reduction of the mammary gland, in the subglandular and submuscular planes, although in the last case this reduction was reversed after one year, while it remained in the subglandular plane.[3] Radiologically significant reduction in the *pectoralis major* muscle size has also been found, in addition to the functional loss of shoulder adduction 12 months after submuscular implantation.[4]

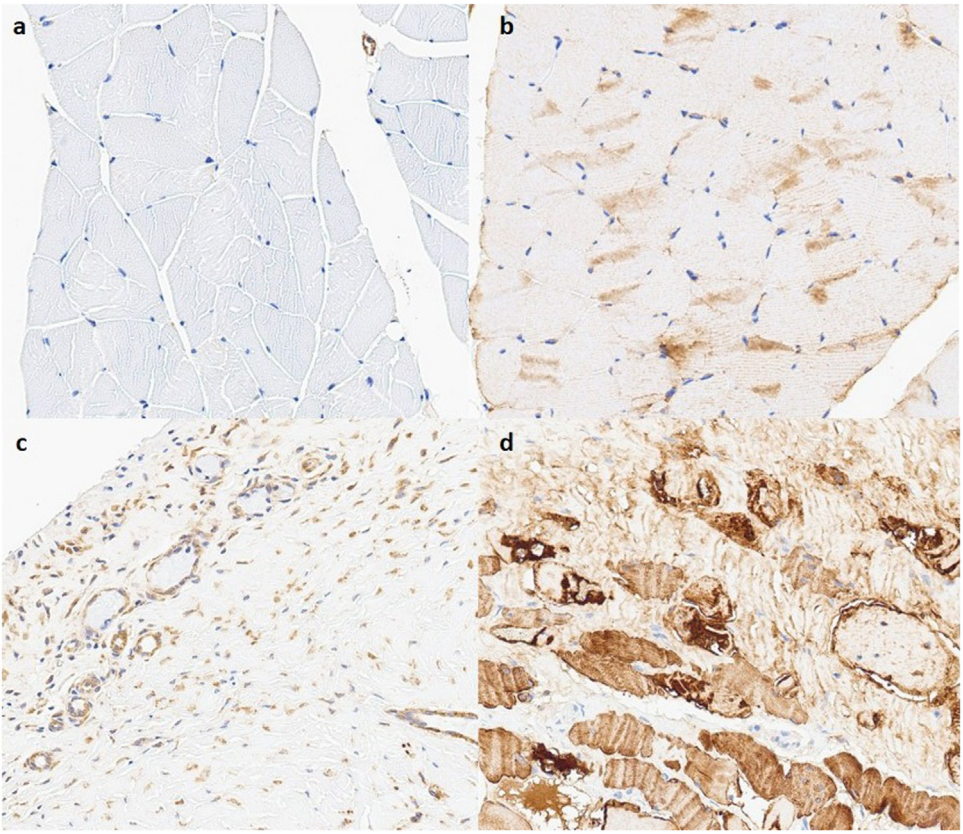

Figure 3. EG group (a) Anti-SMA treated sample at 10x magnification. Immunohistochemistry staining for SMA, negative in the skeletal muscle fibres. (b) Anti-desmin treated sample at 10x magnification. Immunohistochemistry for desmin, positive in perinuclear areas and absent in the central area. PG group (c) Anti-SMA treated sample at 10x magnification. Immunohistochemistry staining for SMA negative in the skeletal muscle fibres. (d) Anti-desmin treated sample at 10x magnification. Immunohistochemistry for desmin positive atrophic muscle fibres.

Beside these morphologic and functional changes, our study revealed the presence of histological alterations of the *pectoralis major* muscle associated with prosthesis implantation in the submuscular plane.

The results showed that the muscles of EG presented less histopathological alterations than those in PG. The most relevant were atrophy, clumps and nuclei internalisation. In addition, we observed that although some changes were different in short- and long-term, several of these alterations were preserved over time to a greater or lesser extent.

The samples from the EG group showed histological and morphometric changes of lower magnitude and relevance when compared to those from PG. This result is probably related to the breast implant pericapsular fibrosis process, which is greater in the muscle fibres that are closer to the breast implant and thereby shows more changes than the muscle fibres that are closer to the expander, and the time of implantation also plays a role.

The changes found in EG could be considered as acute or short-term changes, because the average implantation time was 5.1 months, and in no case the implantation time was >6 months. However, the findings in PG could be considered as chronic or long-term changes, considering that the average implantation time was 50 months, and in no case was the implantation time lesser than 1 year. It is precisely the greater evolution time of the chronic inflammatory process which might condition

the presence of more histopathological findings in the skeletal muscle. Moreover, the reduction in the inflammation time or muscle neurostimulation could be a pathway for the reduction of the fibrotic process.[16] Although muscle injury is related to the injury of the capsular retraction, the contiguity of both tissues (muscle and breast conjunctive tissue) cannot be ignored as an essential target for the decrease in morbidity following this surgical procedure, which is similar to our findings in this study.[17]

Regarding the muscle fibres size in cross-section, there was a significant reduction in perimeter and minor diameter after implantation in EG and PG.

This highlights that breast implantation induces an initial atrophy of muscle fibres which remains over time. Previous studies suggested that tissue hypoxia, due to the pressure exerted by an expander on the muscle tissue, could be a stimulus for subsequent muscle regeneration.[18] Although the expander placement was only temporary in these studies, the prosthesis implantation remained in place for several years. Evidently, in this case, there was significant muscle atrophy which did not reverse afterwards. Notably, during surgery there is partial muscle denervation, although minimal, which may induce changes such as atrophy and nuclei internalisation.[17]

Similarly, there was a pronounced increase of fibrotic tissue after breast implantation which was not reversed over the years. This finding, in addition to nuclei internalisation of muscle fibres, as it is maintained over time, may suggest a degeneration-regeneration process indicating that breast prosthesis placement induces a continuous and maintained injury to contiguous muscle tissue. Under normal conditions, after injury, the skeletal muscle exhibits a high capacity to regenerate. This regeneration is constrained by the extent of injury and development of fibrosis.[19] The fibrosis that was observed in our samples could be proposed as being the leading cause of constraint for muscle regeneration. Nevertheless, nuclei internalisation indicates that muscle fibres continue to take part in long-term regeneration; therefore, fibrosis, which does not vary over years as it is observable, is not the main limiting factor for this regeneration to be effective, but it could be attributed to a concomitant degeneration process that occurs in parallel to the regeneration which is probably the implantation itself.

Its clinical implications still need to be elucidated. The studies that show isokinetic reduction in *pectoralis major* contraction after prosthesis implantation could be the translation of the observed histological changes. Moreover, this persistent aggression could indicate the maintenance of a local proinflammatory status around the breast prosthesis and could play a role in the development of the periprosthesic capsular contracture. In addition, this proinflammatory status and the associated histological alterations might be involved in other pathologies, including malignant ones such as anaplastic large cell lymphoma. However, new studies should be conducted to go deeper into this fact.

Although it was accepted initially that capsular contracture was caused by bacterial contamination,[20] this theory has been partially abandoned in pursuit of others that suggest that a maintained proinflammatory status[21] causes this condition. Similarly, rising tension could also influence the activity of myofibroblasts involved in the capsular contracture.[12] Based on the results of our study, the breast implant induces the development of a chronic aggression on the adjacent muscle, which could explain the capsular contracture development in predisposed patients, although further studies are needed to find the precise causal factor. Furthermore these histological changes could justify some cases of chronic breast pain after prosthesis implantation.[22] In addition, it has been found that these microscopic alterations are statistically significant and differ between implantation times. However, further research with larger sample size should be conducted to find a relation between this variable and the semiology related to breast implants. The main challenge in our current line of research was to find a clinical association between the in vitro findings regarding the fact that mechanical tension promotes myofibroblasts activity[12] and the possibility that a higher prosthesis size/pocket size ratio could correlate with higher risk of capsular contracture.

The main limitation of the study is the sample size, although it was sufficient for statistically significant differences, further studies with larger sample size should be undertaken to figure out the main aetiological factor and a correlation between the results and clinical symptoms. In addition, other variables, such as thorax anthropometric values, should be considered in forthcoming studies to be combined with the implant size to obtain a more realistic interpretation of the hypothetical results.

Conclusions

- Normal morphology and peripheral nuclei were observed in patients without implantation.
- Submuscular prosthesis implantation was associated with histological alterations of the muscle, in short-term (<6 months) and long-term (>1 year) scenario.
- The muscle from patients with tissue expander (short-term) showed mild augmentation of nuclei internalisation, normal morphology, focal muscle atrophy and minimal interstitial fibrosis.
- The muscle from patients with prosthesis (long-term) showed important augmentation of nuclei internalisation, significant muscle atrophy, fibrosis, and alteration of normal muscle morphology in the periprosthetic fibres.
- Further studies are needed to elucidate the aetiology of periprosthetic capsular contracture, both from histopathological and molecular points of views.

Ethical Approval Statement

This study was approved on 30th May 2022 by the clinical research ethics committee of Córdoba, Spain (0802-N-22).

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Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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