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Reducing Capsular Contracture Formation in Breast Augmentation with Silicone Implants: Experimental Study on Rats

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Abstract: Silicone implants are frequently used for breast augmentation and reconstruction. However, late complication, such as capsular contracture, remain the most important side effect. In this study we compare different methods for reducing the inflammatory reaction around the silicone implant by introducing one microtextured breast implant in wistar rats. The rats were dividing in 4 groups: the first one was the control group that received untreated implant; in the second we used silicone implants impregnated with rifampin solution, the third one had implant combined with intramuscular dexamethasone injection and the last one had silicone implant associated with autologous centrifuged fat introduced in the implant pocket. The implants and the capsular tissue surrounding were removed after eight weeks. Capsule samples were submitted to histological evaluations. The present study demonstrated that fat grafting may have a role in reducing and preventing capsular contractures after breast augmentation with silicone implants by decreasing the inflammatory process.

Keywords: capsular contracture; breast augmentation; silicone implants; rats

1. Introduction

The capsular contracture is the most common long-term complication of breast augmentation and reconstruction with silicone implants, as it is the result of an exaggerated healing response to the foreign body (the silicone implant) forming a fibrous capsule which wraps the implant. The incidence of capsular contracture is approximately 10.6%. Clinically, the capsular contracture is manifested by: pain, discomfort of varying degrees casused by distortion and displacement of the implant, determining the change in consistency, volume and appearance of the operated breast [1,2]. There are two main theories that can cause capsular contracture [2,3]: Infectious process theory describing a chronic subclinical infection located immediately adjacent to the implant sheath in a microscopic biofilm that is relatively inaccessible to cells and immune humoral function; this apparent process is determined by contamination. The theory of hypertrophic scarring in which the mechanism involved is to stimulate the activity of myofibroblasts that are present in the capsular tissue,

which determines in the future formation of a contractile periprosthetic hypertrophic scar due to a series of phenomena similar to those of the inflammatory reaction towards a foreign body. The stimulus that can trigger the inflammatory reaction can be even the silicone particles on the implant coating but also the hematomas and seroma or the presence of foreign bodies. The diagnosis in case of suspected capsular contracture is establish by clinical and imaging examinations: ultrasonography (USG) and magnetic resonance imaging (MRI). Capsular contracture was clinically classified by Baker (1975) into four degrees: Baker I-non-palpable capsule (normal augmented breast consistency), Baker II—minimum firmness (firm consistency, the implant is not visible, but palpable), Baker III—moderate firmness (breast is harder, implant visible, easy to feel), Baker IV—severe contracture (breast is hard, tender, painful and sometimes distorted) [1–3]. Depending on the degree of Baker's capsular contracture, it is indicated surgery.

Histologically the capsular membrane has three layers: the inner layer—consisting of fascicular collagen fibers, fibrocytes, and histocytes; the middle layer—consisting of dense collagen bundles with fibers arranged parallel to each other; the outer layer—consisting of loose connective tissue. In 50% of cases, synovial metaplasia may appear with a starting point in the middle layer of the capsule [3,4].

The following methods were used to prevent and reduce the risk of capsular contracture formation: placing the implant in the retro muscular plane, dissection of a larger pocket, performing rigorous hemostasis, using implants with a textured surface, minimizing the exposure, contact, and handling time of the implant, irrigation of the pocket with antiseptic solutions or with a broad-spectrum antibiotic solution to prevent the infectious process, use of talc-free gloves, use of corticosteroids, immunomodulatory and anti-inflammatory drugs. An additional method of prevention is wrapping the implant in a layer of acellular dermal matrix, Thus, the proliferation rate of myofibroblasts and the inflammatory process are reduced, which decreases the risk of developing long-term capsular contracture formation [5–7].

Autologous fat transfer is generally used by plastic surgeon for both reconstructive and aesthetic purposes [8]. It's like a natural filler that commonly used in face, breast and buttocks volumetry and rejuvenation [9–13]. Some of these procedures require minimum anesthesia [14,15]. Fat grafting can also improve cicatrization process in patients who have undergone radiation therapy for breast cancer. The effects of radiation cause damage to fibroblasts, scars and reduce microcirculation in the targeted areas [16], causing poor aesthetic results and increased risk of capsular contracture. The pluripotent stem cells from grafted fat are supposed to improve angiogenesis by paracrine signaling and endothelial cell recruitment [17].

2. Materials and Methods

In this study, we used forty-eight Wister rats, adults, with a similar weight, between 300–440 g, which were kept in the same conditions of light and humidity. Water and standard laboratory food for rats were freely provided to the animals, room temperature and alternating 12 h cycles of light and dark. At the end of our study the rats used were euthanized. The study received the Ethics opinion of "Grigore T. Popa" University of Medicine and Pharmacy of Iasi. The tissue fragments taken were processed by the usual paraffin-embedded histopathological technique and stained with hematoxylin-eosin. We implanted with one microtextured breast implant, according to an approved institutional animal care protocol. The implants were each 2 ccs (2 cm diameter).

Before surgical procedures, the rats were anesthetized with intramuscular administration of Ketamine 50 mg/mL, 0.3 mL/kg and Xylazine 2% 0.2 mL/kg. After the animals had been shaved and prepared prior to surgery, the skin of each rat was washed with 4 % Chlorhexidine surgical scrub and their skin was disinfected with Betadine solution that contained 10% povidone-iodine, according to the instructions for performing rodens surgery new drape and a new sterile gloves was used for each animal The animal was positioned in supine position that does not influence the surgical technique and the results

either. The surgical procedure was performed in an animal operating theater following aseptic rules. Talc-free gloves were used at all times during the procedure. Implant pockets were developed throw an abdominal paramedian incision next to the mammary gland, in a retroglandular pocket with atraumatic dissection. Under direct vision, particular attention was paid to hemostasis, avoiding blunt instrumentation; there was no obvious bleeding. A new pair of talc-free gloves were worn when inserting the implants. 8 rats received an untreated implant (control), 17 rats an implant impregnated with rifampicin solution, 12 rats had implant combined with intramuscular dexamethasone injection for ten days and 11 rats had silicone implant associated with autologous centrifuged fat introduced in the implant pocket. The skin incisions were closed using 4-0 nylon sutures.

Rats were sacrificed at eight weeks. Prior to sacrifice, each animal was anesthetized, and a 5-mm incision was made directly over the previous incision, through the skin, we identify the capsular tissue surrounding the silicone implant and we removed it after dissection through the skin incision. Capsule samples were immersed in 10% formalin and were submitted to histological evaluations.

Histological Assessment: Capsule specimens were fixed with 10% buffered formalin and after 24 h were embedded in paraffin. The transversal sections were made in order to evaluate the capsular architecture. Afterwards were performed the hematoxylin and eosin staining and histological assessment for tissue inflammation and capsular thickness. Lympocytes, granulocytes, macrophages, eosinophils, and mastocytes were the types of inflammatory cells evaluated in the capsule. The giant cellular reaction and the signs of acute and chronic inflammation were quantificated. Inflammatory infiltrate was categorized as mild, moderate, or severe, according to the intensity.

Statistical Analysis: Statistical analysis was performed using the statistical software package IBM SPSS Statistics Version 20.0 (International Business Machines Corp., Armonk, New York, USA). The confidence interval (CI) was invariably calculated using the confidence interval analysis (CIA) software (3).

Prior to the statistical analysis, the presumption of normality was performed using the Shapiro-Wilk test. Descriptive data were expressed as mean ± standard deviation (SD), median with interquartile range (IQR), or relative frequency with 95% CI.

The study applied specific tests to various types of data analysed, including tests for comparing the mean values of a parameter corresponding to several data sets, including the ANOVA test and the Student's t-test, specific correlation for quantitative variables and variables. qualitative of which we can mention Pearson Chi-square (χ^2). We considered that there is an association between the tested variables only when the calculated significance level p is lower than the accepted level, $p < 0.05$ (the accepted error is for less than 5% of cases).

3. Results

In the control, none of the 8 implants was ulcerated; 2 of the subjects had developed clinical Baker grade III/IV capsular contracture (Figure 1).

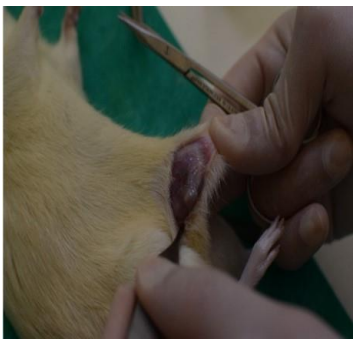


Figure 1. Silicon implant non treated–moment of extraction of the implant with the view of the remaining thick capsule.

The rifampicin group had 1 ulcerated implant, and 2 implants had developed Baker grade II/III capsular contracture (Figure 2).

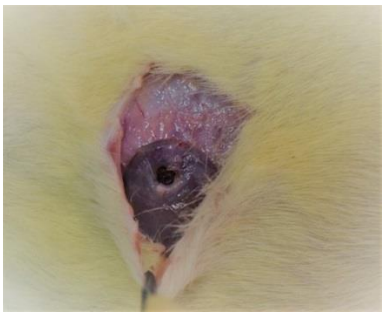


Figure 2. Silicon implant treated with rifampicin–moment of extraction of the implant and a remaining capsule thinner.

In the dexamethasone group, 2 of the 12 implants were ulcerated, and no cases of capsular contracture were observed (Figure 3).

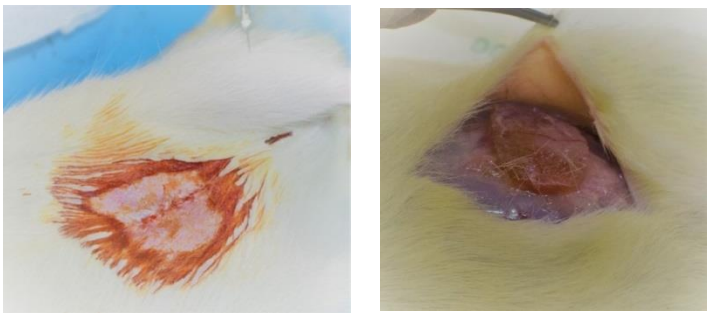
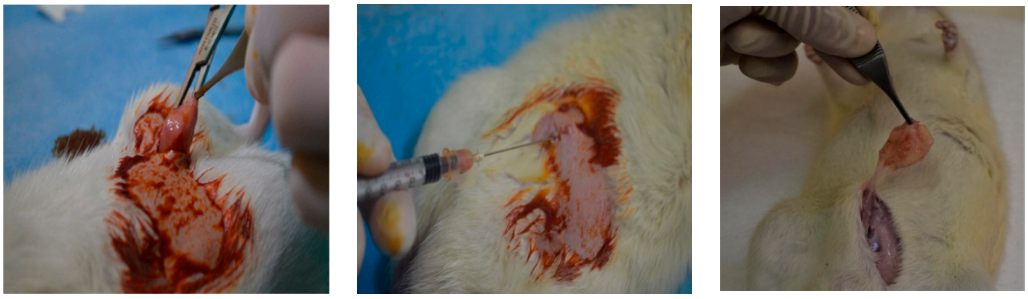


Figure 3. Silicon implant treated with dexamethasone–moment of extraction of the implant with no capsular contracture.

The autologous centrifuged fat group had no ulcerated implants and no clinical capsular contracture has been found. The capsules with contracture were adherent to the adjacent tissue, dense and stiff (Figure 4).



(**a**) (**b**) (**c**)

Figure 4. Silicon implant treated with autologous centrifugated fat (**a**) moment of insertion and fat harvesting; (**b**) fat injection in the implant pocket; (**c**) moment of extraction of the implant with no capsular contracture.

Histology assessment: in the control group was observed an active chronic inflammation associated with giant foreign body cell reaction. More specifically lymphocytes and plasma (Ly-PL) cells were associated with neutrophil *Polymorphonuclear* leukocytes (PMN) in 10% and giant foreign cell reaction in the proportion of 30% (Figures 5 and 6).

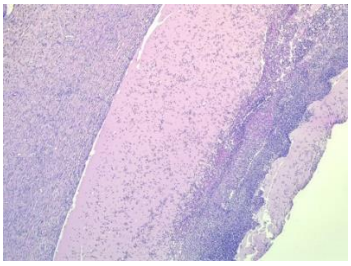


Figure 5. High level of inflammatory infiltrate at six weeks after surgery.

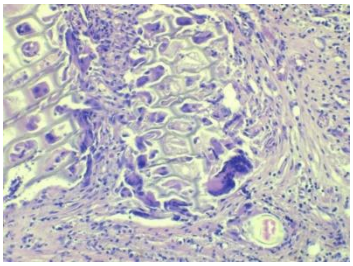


Figure 6. Giant foreign cell reaction at six weeks after surgery.

In the rifampicin group, microtextured breast implant induced an inflammatory chronic reaction with low inflammatory infiltrate consisting mostly of Ly-PL cells (90%), associated with a giant foreign body cell reaction in the proportion of 10% and chronic inflammation with moderate inflammatory infiltrates consisting mostly of lymphocytes and plasma cells (80%), associated with a giant foreign cell reaction in the proportion of 20%.

In dexamethasone group has been identified acute inflammation with abundant inflammatory infiltrate with PMN (70%), the giant cellular reaction of foreign body in the proportion of (15%), macrophages (10%) and Ly-PL cells about (5%) and chronic active inflammation with abundant inflammatory infiltrate in which Ly-PL cells (30%) were associated with neutrophilic PMN in (10%), macrophages (2%) and giant foreign body reaction in the proportion of (58%).

Fat cell group had chronic inflammation to the implants with low inflammatory infiltrate consisting mostly of Ly-PL cells (95%), associated with a giant foreign body reaction in a proportion of 5% and in one case chronic active inflammation with reduced Ly-PL inflammatory infiltrate (90%), associated with PMN (10%) (Figures 7 and 8) (Table 1).

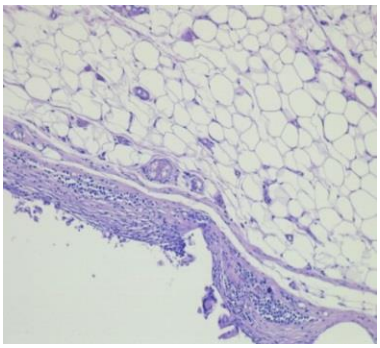


Figure 7. Low inflammatory infiltrate at six weeks after surgery.

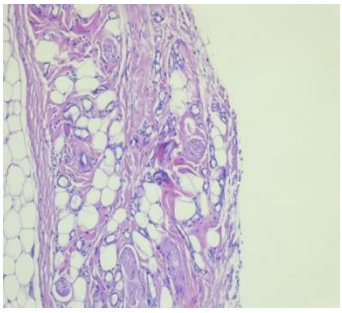


Figure 8. Reduced PMN level at six weeks after surgery.

Table 1. Complications and histological results of the studied groups.

Group	Particularities Group	Number of Animals in Group	Ulceration	Capsular Contracture	Histological Aspects
I	Untreated implant	8	0	2	active chronic inflammation associated with giant foreign body cell reaction (30%)
II	Implant impregnate with rifampicin	17	1	2	inflammatory chronic reaction with low inflammatory infiltrate and giant foreign body cell reaction (20%)
III	Implant associate with dexamethasone injection	12	2	0	acute inflammation with abundant inflammatory infiltrate and giant foreign body cell reaction (58%)
IV	Implant associate with autologous fat	11	0	0	chronic inflammation to the implants with low inflammatory infiltrate and giant foreign body cell reaction (5%)

Statistical analyses revealed low levels of acute and chronic inflammation in the group study treated with autologous centrifugated fat compared to the other three groups. The rifampicin group had a higher rate of acute and chronic inflammation. In the control group, acute inflammation was encountered in half of the study subjects and the rate of chronic inflammation was slightly increased. Dexamethasone intramuscular administration reduced the chronic inflammatory process (Figure 9).

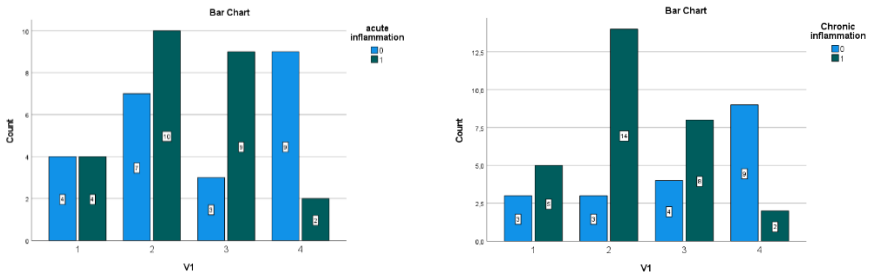


Figure 9. Correlations between acute or chronic inflammation and treatment of silicone implant. Count: number of rats in group VI: groups of rats in study; 0: number of rats without acute/chronic inflammation; 1: number of rats with acute/chronic inflammation.

Correlations between types of inflammatory cells in the contracture capsule of the silicone implants in the studied groups showed a significant statistical association of macrophage, mastocytes and gigantocellular reaction and the type of treatment applied in each group (Table 2). Also chronic inflammation was statistical significant associated in our

study in group 1 and 2, highlighting the protective role of silicone coating with autologous centrifugated fat (Table 3).

Table 2. Correlations of inflammatory type cells.

		V1	PMN	Ly-PL	EOZ	Macrophage	Gigantocellular Reaction	Mastocyte
V1	Pearson Correlation	1	102	−35	−77	357 *	−354 *	417 **
	Sig. (2-tailed)		492	816	601	13	14	3
	Sum of Squares and Cross-products	49,917	87,917	−42,042	−542	133,917	−243,792	81,500
	Covariance	1062	1871	−895	−12	2849	−5187	1734
	N	48	48	48	48	48	48	48

V1: capsular contracture; PMN: Polymorphonuclear leukocytes; Ly-PL: lymphocytes and plasma cells; EOZ: Eosinophils. * Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed).

Table 3. Correlations of inflammation.

		V1	Acute Inflammation	Chronic Inflammation	Chronic Active Inflammation
V1	Pearson Correlation	1	−186	−364 *	−94
	Sig. (2-tailed)		206	11	526
	Sum of Squares and Cross-products	49,917	−4542	−8708	−2042
	Covariance	1062	−97	−185	−43
	N	48	48	48	48

V1: capsular contracture. * Correlation is significant at the 0.05 level (2-tailed).

4. Discussion

The body reacts to the silicone implant by forming a capsule around it, but is yet unknown why some of them contract [18–20].

Ji Ung Park et al. demonstrated in vivo study that the implant triggered a foreign body reaction, which led to a cascade of inflammatory cell recruitment, fibroblast proliferation and collagen synthesis which eventually led to capsule formation. At the same time, they showed that a stronger reaction of the foreign body leads to the formation of a denser capsule with a higher density of collagen, reason why they considered that the collagen is a decisive factor in capsular formation. They also correlated the impact of the capsular thickness in the appearance of the capsular contracture as being directly proportional [21,22].

Capsular contractures typically form in the early postoperative period, but they also may appear many years later with an increasing incidence over time [23,24]. Two commonly accepted hypotheses exist: an infectious process theory describing a chronic subclinical infection located immediately adjacent to the implant sheath in a microscopic biofilm that is relatively inaccessible to cells and immune humoral function; this apparent process is determined by contamination and a hypertrophic scar theory in which the mechanism involved is to stimulate the activity of myofibroblasts that are present in the capsule, which determines the subsequent formation of hypertrophic scars that contracts due to a series of phenomena similar to those of an inflammatory reaction [25–29].

The type of cells that predominate in the capsule are macrophages, lymphocytes and fibroblasts. More recent studies have shown the role of mast cells present in significant numbers in the capsule. Apparently mast cells play an important role in the formation of capsular contracture through their contribution in the formation of fibrotic tissue; mast cells have profibrotic mediators renin-*angiotensin II*, histamine and *transforming growth factor beta*

(TGF-β) on their cell surface that activate angiotensin *receptors* (AT1R) and TGF-β receptors on the surface of the fibroblasts also present in the capsular tissue. It appears that these cells are responsible for the initial production and storage of collagen, which subsequently causes the formation of fibrotic tissue [4].

The occurrence of capsular contraction is known to be a result of the inflammation caused by the surface of the implanted silicone material [4,5]. As a result, it's critical to comprehend the mechanism of capsular contraction development and identify appropriate preventive techniques.

Fibroblasts and macrophages are principal elements detected in microscopic analyses of the fibrotic capsule adjacent to the breast implant [30]. They are detected in large number in 'the contact zone' of the implant, reason why they are associate with the capsular contracture severity.

Litong Ji et al. claim that the macrophages are the cells that produce initiation of repair and remodelling process entering the first in action before fibroblasts being possible that macrophages have an influence on the functions of fibroblasts. However, the exact relationship between macrophages and fibroblasts in the process of capsular formation it has not been sufficiently explored [31].

Numerous methods have been described in the literature to prevent and reduce the risk of capsular contraction such as: placing the implant in the submuscular plane, dissecting a larger pocket, performing a rigorous haemostasis to prevent hematoma, using implants with a textured surface, minimizing exposure, contact and handling of the implant, irrigation of the pocket with antiseptic solutions or bactericidal solution to prevent infectious processes, use of steroid therapy, immunomodulatory and anti-inflammatory drugs [32–40].

The autologous fat graft offers potential applications in breast reconstruction. While smaller volumes of fat injection are used to correct contour asymmetries, larger amounts of injection offer alternatives for augmenting the entire breast [17]. The use of autologous fat transfer for the purpose of breast reconstruction extends beyond the remodeling of breast volume or asymmetry. Other therapeutic applications considered include the treatment of postmastectomy pain syndrome, pain due to capsular contracture, and irradiated tissue fibrosis [16,41–43].

Recent studies in the literature suggest that adipose tissue contains a cell fraction (adipose-derived stromal cells and/or stem cells) that contributes to improving wound cicatrisation process, tissue repair, and extracellular matrix remodelling [44].

Papadopoulos et al. found that autologous fat transfer can relieve pain caused by capsular contracture and reduce the degree of contracture from Baker 4 to 3. Treatment is in several stages of fat injection around the implant requiring a longer period of time. The authors attributed the pain relief to the differentiation and softening of the tissues that decreased the compression of nerves [43].

Studies performed on burn scars using autologous adipose tissue grafting have shown a reduction in tissue thickness, with improved elasticity and decreased stiffness both subjectively quantified by patient perception and objectively by histopathological examination [44].

We investigated the efficacy of different strategies that can reduce inflammation and decrease peri-implant fibrosis. Comparing the results from our four study groups we revealed that fat grafting has the capacity to determine the favourable impact on dermal elasticity and thickening by reducing tissue inflammation.

The study's main limitation was that it was ended after the eighth week. However, long-term experimental and clinical studies are needed to evaluate the evolution of the capsule around the silicone implant over time and the impact of autologous fat transfer in reducing the degree of capsular contracture.

5. Conclusions

The study proved that fat grafting may play a role in minimizing and avoiding capsular contractures after silicon implants by reducing inflammation and histological structure in an animal model, suggesting that it could be a viable therapy option for high-risk patients.

Author Contributions: Conceptualization, N.A. and M.P.; Data curation, M.M.P., C.U. and T.C.M.; Formal analysis, A.-M.T., E.C., V.I., C.C.B. and T.C.M.; Investigation, N.A., M.M.P., E.C., V.I. and E.M.; Methodology, N.A., M.M.P., A.-M.T., C.U., V.I., E.M., C.C.B. and T.C.M.; Project administration, E.C., C.U., E.M. and T.S.; Resources, A.-M.T. and E.M.; Software, M.M.P., A.-M.T., C.U., C.C.B. and T.C.M.; Supervision, T.S.; Validation, E.C., C.C.B. and M.P.; Visualization, V.I. and T.S.; Writing–original draft, N.A., A.-M.T. and M.P.; Writing–review & editing, M.P. All authors have read and agreed to the published version of the manuscript.

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