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The Inflammatory Reaction to Silicone Implants: Polyurethane Foam Versus Nanotextured Surface—An Experimental Study in Rats

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Background: The interaction between the surface of the implant and the human body results in a local and systemic inflammatory reaction that leads to the formation of a peri-implant capsule and entails complications. This study aimed to evaluate and compare the local and systemic inflammatory reactions of silicone implants coated with polyurethane foam and those with a nanotextured surface.
Methods: Using indirect enzyme-linked immunosorbent assay, the levels of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) were measured in the serum and per-implant capsule of rats submitted to surgical placement of the 2 different types of implants. The statistical analysis was conducted within each group, comparing the parameters according to the times at which the rats were euthanized at 3 distinct durations of exposure (30, 60, and 90 d).
Results: The results show that at both 30 and 60 days, there was no significant increase in the levels of markers in either group; however, a change becomes evident at 90 days. The nanotextured surface showed a decreased production of inflammatory markers at 30 and 60 days as compared with the polyurethane group. Nevertheless, at 90 days, there is a marked increase in these markers observed in the nanotextured group and a decrease in the polyurethane group, yet without any statistical significance between either group at that time.
Conclusions: After a lapse of an extended period of time (90 d), nanotextured surface implants cause a local and systemic inflammatory reaction similar to those with a polyurethane foam surface. *(Plast Reconstr Surg Glob Open 2025;13:e6596; doi: 10.1097/GOX.0000000000006596; Published online 21 March 2025.)*

INTRODUCTION

Since their introduction in 1963 by Cronin and Gerow,[1] silicone implants have been developed and improved to reestablish or augment breast volume. To improve their biocompatibility, new surface textures have been introduced, and modified.[2] The polyurethane-coated breast prosthesis was introduced by Ashley in 1970.[3] Unlike other types of breast implants, the polyurethane degradation process mobilizes giant cells and macrophages that phagocytose small fragments of polyurethane. This phagocytosis forms thousands of microcapsules around the implant that lack the power to coalesce or act synergistically, reducing the likelihood of capsular formation. These implants accommodate well to their receiving site and demonstrate high adhesiveness to the breast and surrounding tissue.[4]

With the surge of nanotechnology, nanotextured implants were fashioned through negative printing using 3-dimensional technology.[5] These implants do not require external material like salt or sand in the manufacturing process, allowing control of the thickness of the implant's shell and maintaining its uniformity. In 2017, Barr et al[6] proposed a classification based on the roughness of the surface, dividing them into nano, micro, intermediary, and macrotextured polyurethane surface. Nanotextured implants were concepted to decrease the

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acute inflammatory response and the rate of capsular contracture, by reducing fibroblast adhesion activity.[7,8]

The local and systemic inflammatory reactions are associated with the time of implant insertion. Complications can result from possible extravasation and migration of the gel, causing capsular contracture and even calcification and rupture of the implant due to wear and tear.[9]

The number of breast augmentation procedures has been declining from 2018 till 2021, according to the International Society of Aesthetic Plastic Surgery, but in 2020, there was a significant increase of 29% in procedures totaling more than 2 million procedures worldwide.[10]

In fact, an increased number of cases have established a relationship between silicone implants and the development of systemic diseases, in addition to capsular contractures. Autoimmune/inflammatory syndrome induced by adjuvants, or Shoenfeld syndrome (ASIA) and breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) are pronounced examples, but research studies are still underway to evaluate the relationship between implant insertion and their occurrence. ASIA is common in patients genetically predisposed to inflammation, and BIA-ALCL has been associated with chronic inflammation and increased T-cell count. In 2019, Magnusson et al[11] observed a greater number of cases of BIA-ALCL in patients with implants coated with polyurethane than other surfaces.

The interaction between the implant surface and the body results in a local and systemic inflammatory reaction that leads to the release of inflammatory markers that may be related to the development of BIA-ALCL or systemic disorders such as ASIA. In the literature, BIA-ALCL has a low incidence rate, with 1355 reported cases until 2023, according to the American Association of Plastic Surgery; however, it has been increasing in the last few years. On the other hand, the hypothesis that autoimmune diseases have a well-established relationship with silicone implants lacks considerable scientific support.

The objective of this study was to evaluate and compare the local and systemic inflammatory reactions to the insertion of silicone implants coated with polyurethane foam to those with a nanotextured surface using the inflammatory markers interleukin IL-1, IL-6, and TNF-α measured in the serum and peri-implant capsule in rats.

Takeaways

Question: How do silicone implants coated with polyurethane foam compare to nanotextured surface implants regarding inflammatory responses in rats, as measured by serum and peri-implant levels of interleukin-1, interleukin-6, and TNF-α?

Findings: No significant differences in inflammatory marker levels at 30 and 60 days. At 90 days, nanotextured implants showed an increase in markers, and polyurethane implants showed a decrease in markers, though not statistically significant.

Meaning: Both implant types exhibit comparable inflammatory responses over time. Differences in inflammatory markers arise at 90 days but lack statistical significance, suggesting equivalent biocompatibility.

MATERIALS AND METHODS

This work was carried out in the vivarium and laboratory of operative techniques and experimental surgery at the State University of Ponta Grossa, in partnership with the State University of Rio de Janeiro, approved by the Ethics Committee for the Use of Animals[12] of the State University of Ponta Grossa (041/2018, protocol 16450/2018).

Sixty female albino rats were used in this study, of species *Rattus norvegicus albinus, Roentia mammalia*, of the Wistar lineage, weighing between 190 and 250 g, aging between 60 and 90 days who did not present any disease. Exclusion criteria included were surgical-site infection, implant extrusion, and death of the animal.

The rats were divided into 2 groups, 30 for each group, and subdivided into 3 subgroups of 10 animals each, according to the time of euthanasia (30, 60, and 90 d). In the polyurethane group (n = 30), an implant with polyurethane coating (Silimed, Rio de Janeiro, Brazil) was placed, and in the nanotextured group (n = 30), an implant with a nanotextured surface (Silimed, Rio de Janeiro, Brazil) was placed. The rats were allocated to either the group to be given the implant coated with polyurethane foam and or the implant with the nanotextured surface (Fig. 1). The implanted prostheses had the same layers as a human breast implant, with a discoid shape, 24 ± 1 mm diameter and 11 ± 1 mm height, for the implants covered by polyurethane foam, and with 22 ± 1 mm diameter and 9 ± 1 mm height, for the implants with a nanotextured surface. Height was defined as the point of greatest projection of the implant on the vertical axis.

The pores on the surface of polyurethane foam-coated implants had a diameter of 120–320 μm, an average roughness of 1500 μm, and a depth of 480–1200 μm (an average of 840 μm). Nanotextured implants had the

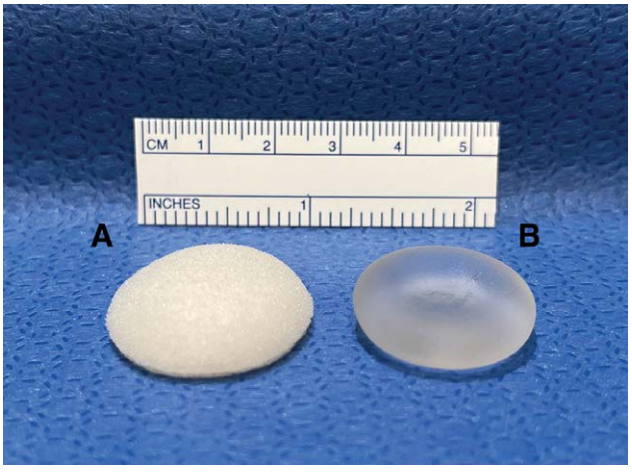

Fig. 1. A photograph of the surface texture of the silicone microimplants. A, Implant with a polyurethane surface. B, Implant with a nanotextured surface.

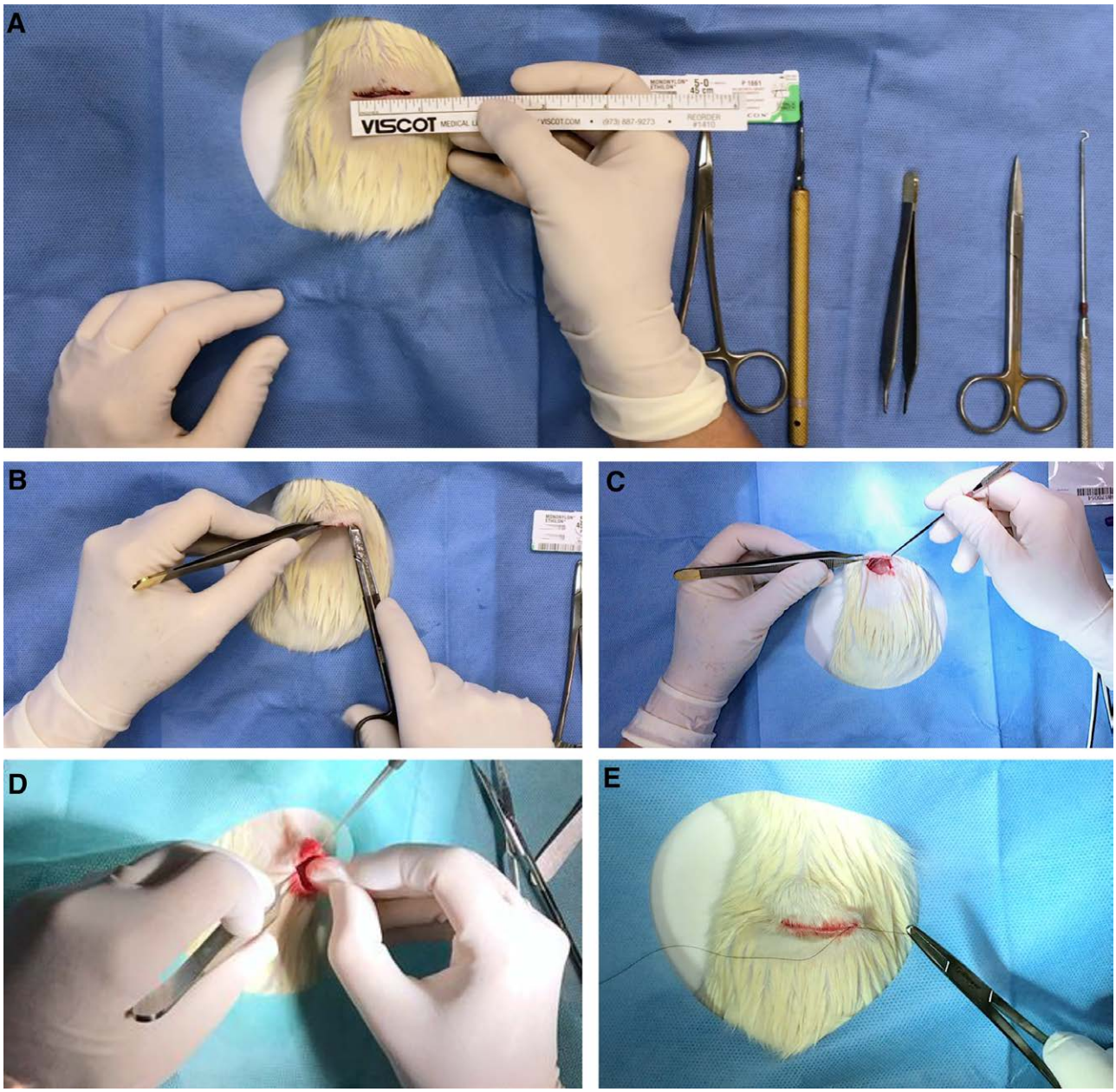

Fig. 2. Photographs of the surgical protocol for implant insertion. A, Horizontal dorsal incision of 20 mm away from the horizontal subcostal line. B, Dissection of the implant site (pocket) with scissors. C, Securing of pocket site before implant placement. D, Placement of silicone implant. E, Surgical wound suture.

following pore dimensions on their surface: a diameter of 0.3–8.7 µm, an average roughness of 4.12 µm, and a depth of 3.08–10.74 µm (an average of 6.37 µm).

SURGICAL PROCEDURE

An incision was made using a subcostal horizontal line as a reference, following the posteroinferior costal margin, which meets the midsagittal line at an intersection. There, a 20-mm horizontal incision was made (Fig. 2A). A square-shaped pocket was created for the implant in the submuscular plane (below the panniculus carnosus) (Fig. 2B), in a cranial direction, 5 mm from the skin incision (Fig. 2C). The implant was introduced and positioned vertically, depending on the polyurethane or nanotextured group. After its introduction, it was positioned horizontally 5 mm from the incision (Fig. 2D). No external dressing was applied to the surgical wound; it was kept exposed (Fig. 2E), with no need for hemostasis.

The rats were euthanized at 30, 60, or 90 days, according to their respective subgroups by applying 4 times the therapeutic dose of ketamine hydrochloride and subsequent cervical dislocation. These durations of time were selected in accordance to the relative lifespan of rats and humans, with 90 days of life in rats corresponding to approximately 10 years of life in humans.[13]

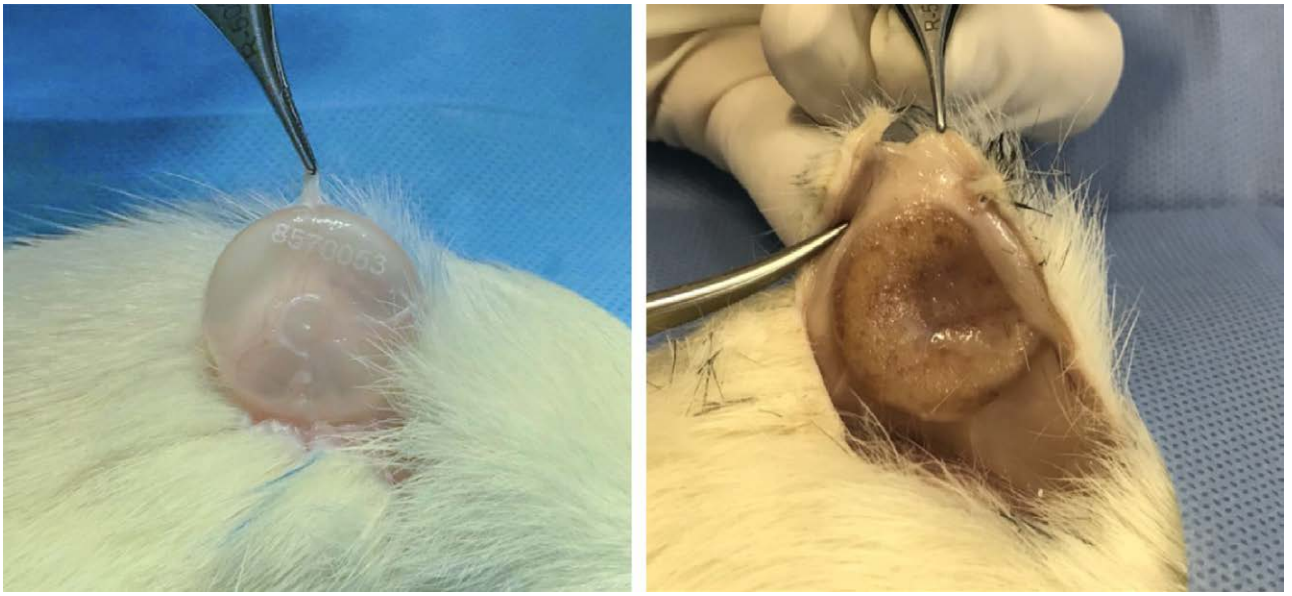

Fig. 3. Photographs showing implant removal with the capsule.

After euthanasia, a cardiac puncture was performed to collect blood, and the implants were removed with their capsules through the same incision created to place them (Fig. 3). The blood was placed in tubes with separating gel and centrifuged at 3000 revolutions per minute for 5 minutes. The serum and capsule samples were placed in an Eppendorf microtube and stored in an ultrafreezer, model CL700-80V (Coldlab), at −80°C for 12 months.

At the time of the indirect enzyme-linked immunosorbent assay, the material was thawed to room temperature, and the analyses were carried out using serum and capsule macerate.

Presensitized commercial kits were utilized, according to the wavelength indicated by the kit manufacturer using an enzyme-linked immunosorbent assay microplate reader (Kasuaki. Model DR-200BN-BI), for serum and capsule macerate inflammatory marker evaluation. The inflammatory markers IL-1, IL-6, and TNF-α were chosen according to their well-established functions in the pathophysiology of inflammation in addition to our ability to monitor their levels both locally and systemically, giving us a comprehensive overview of the inflammatory reaction.

The statistical evaluation was initially carried out within each group, comparing the inflammatory markers in the capsule and in the serum, according to the euthanasia times (30, 60 and 90 d), using a multiple comparison test, according to the test of assumptions. In this case, the hypotheses of normality were validated using the Shapiro test and homoscedasticity using the Bartlett test, and since the times of death are independent, the analysis was carried out using analysis of variance. Otherwise, a nonparametric multiple comparison test was used, specifically the Kruskall–Wallis test. Subsequently, the 2 groups (nanotextured and polyurethane) were compared according to each euthanasia time using an unpaired *t*-test or the Wilcoxon test, depending on the validation of the assumptions.

RESULTS

Cytokine Variation Over Time

Figures 4 and 5 show the variation of the median concentration of cytokines as a function of time in the serum and capsule, respectively. The inflammatory markers all showed a similar pattern of variation in both groups. There was a statistically significant decrease in the concentration of the markers between days 30 and 90 and between days 60 and 90 in the polyurethane group. On the other hand, there was a statistically significant increase in concentration of the markers between days 30 and 90 and between days 60 and 90 in the nanotextured group ($P < 0.005$, Table 1). There was no statistically significant difference in the levels of the markers between days 30 and 60 ($P > 0.005$, Table 1).

Comparing the Response to Polyurethane Versus Nanotextured Implants

Figure 5 also shows a significantly higher concentration ($P < 0.005$, Table 1) of all inflammatory markers at days 30 and 60 in both the polyurethane and nanotextured groups. However, at day 90, there was no such significant difference between both groups ($P > 0.005$, Table 2) in the serum and capsule for TNF-α and IL-6. IL-1 demonstrated no significant difference between the nanotextured and polyurethane groups at day 90 in the capsule only ($P > 0.005$, Table 2), yet a significant difference was seen in the serum ($P < 0.005$, Table 2).

In the serum, the median levels of TNF-α, IL-6, and IL-1 were 56.25%, 56.25%, and 80.93% higher, respectively, in the polyurethane group when compared with the nanotextured group at day 30. The percentage difference diminished to 6.52%, 6.52%, and 66.01%, respectively, at day 90.

In the capsule, the median levels of TNF-α, IL-6, and IL-1 were 76.41%, 56.25%, and 75.57%, respectively, higher in the polyurethane group when compared with

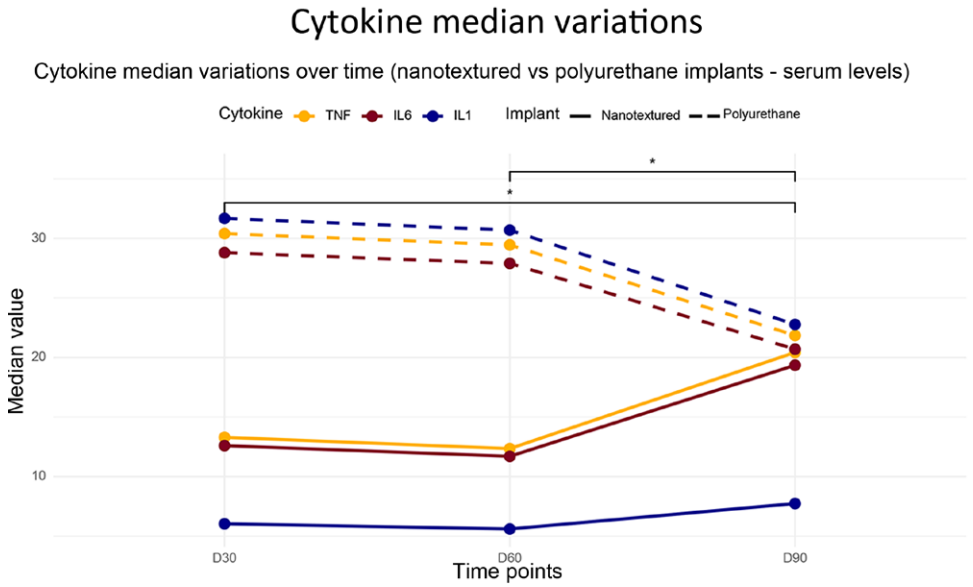

Fig. 4. A graph that shows the variation in median TNF-α, IL-6, and IL-1 concentration over time in the serum for both nanotextured and polyurethane groups.

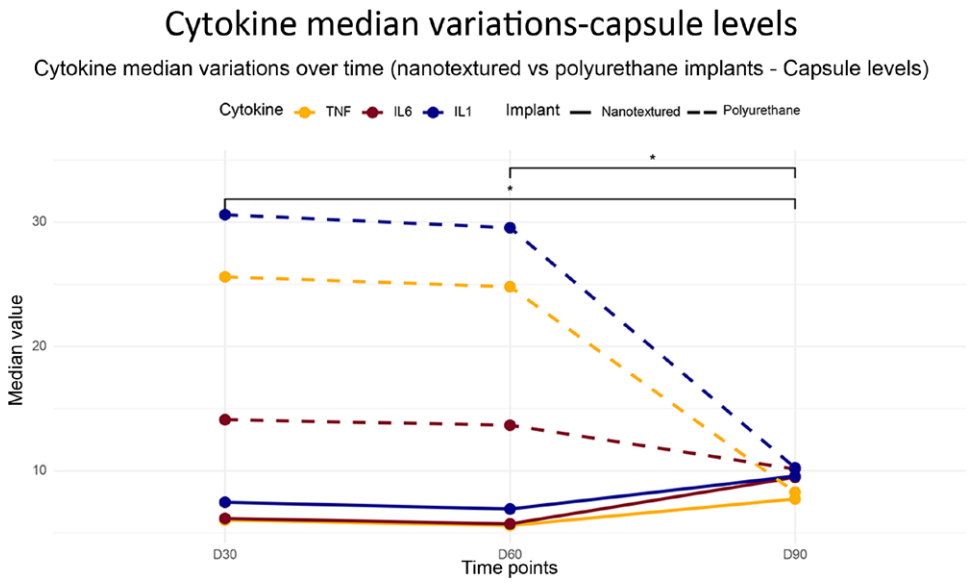

Fig. 5. A graph that shows the variation in median TNF-α, IL-6, and IL-1 concentration over time in the capsule for both nanotextured and polyurethane groups.

the nanotextured group at day 30. The percentage difference diminished to 6.52% for all markers at day 90.

DISCUSSION

Since the invention of silicone implants, many studies on its local scarring process and the systemic inflammatory reaction were published. Our results showed no significant increase in markers from 30- to 60-day time interval. However, a change becomes significantly apparent from the 60- to 90-day time interval. It was also observed that compared with polyurethane implants, implants with a nanotextured surface resulted in a lower production of inflammatory markers in the first time interval, from 30 to 60 days. Yet, there was an observed increase in the level of these markers from 60 to 90 days. On the other hand, the polyurethane group showed a decrease in markers, with no statistically significant difference between the nanotextured groups at 90 days in the capsule. Only in serum, IL-1 showed the same behavior of falling after 90 days in polyurethane and increasing in nanotextured, but it still maintained higher levels in the polyurethane group compared with nanotextured, suggesting a higher inflammatory reaction. As the behavior of variations in the levels of each marker were similar within the period studied, there is currently homogeneity in the study.

Table 1. Results of the Kruskal–Wallis Nonparametric Multiple Comparison Test

		Serum		Capsule	
	Comparison	Nanotextured	Polyurethane	Nanotextured	Polyurethane
TNF-α	Days 30–60	0.73	0.89	0.57	0.89
	Days 30–90	0.00021*	0.0047*	0.0048*	0.00041*
	Days 60–90	0.00018*	0.0035*	0.0024*	0.00041*
IL-6	Days 30–60	0.73	0.89	0.73	0.89
	Days 30–90	0.00021*	0.0047*	0.00021*	0.0047*
	Days 60–90	0.00018*	0.0035*	0.00018*	0.0035*
IL-1	Days 30–60	0.82	0.89	0.82	0.89
	Days 30–90	0.00065*	0.0047*	0.00065*	0.00041*
	Days 60–90	0.0024*	0.0035*	0.0024*	0.00041*

*A significant difference between the time points for each of the cytokines (TNF-α, IL-6, and IL-1) in the nanotextured and polyurethane groups.

Table 2. Results of the Wilcoxon Test

	Timepoint	Serum	Capsule
TNF-α	Days 30	0.00028*	0.00028*
	Days 60	0.00027*	0.00027*
	Days 90	0.14	0.14
IL-6	Days 30	0.00028*	0.00028*
	Days 60	0.00027*	0.00027*
	Days 90	0.14	0.14
IL-1	Days 30	0.00028*	0.00028*
	Days 60	0.00027*	0.00027*
	Days 90	0.00027*	0.14

*A significant difference in the levels of the inflammatory markers between the nanotextured and polyurethane groups.

In 2020, Segan et al[14] studied the human immunological reaction to textures of different roughness of polyurethane biomaterial in vitro, measuring the change in inflammatory interleukins to the change in textures and observed no significant difference between them. In 2018, Kang et al[15] proposed that implants using nanotextured or microtextured technology reduce the peri-implant acute and chronic inflammatory responses. However, no long-term follow-up results of the use of these implants have been reported in the literature. To our knowledge, our study was the first to show that there is no significant difference in long-term inflammation between the 2 types of surfaces.

Pontes et al,[16] in 2021, carried out an immunohistochemical analysis of the capsule formed around nanotextured implants placed in female rats and observed a lower inflammatory reaction in the initial phase (30 and 60 d), based on the levels of αlpha-smooth muscle actin (α-SMA), transforming growth factor beta, CD34, and CD68. In the 90-day subgroup, α-SMA and CD34 immunoexpression was observed to be more pronounced in the nanotextured group; however, transforming growth factor beta and CD68 immunoexpression remained lower. There was an increase in the reaction to the nanotextured surface over time, according to α-SMA and CD34 immunoexpression. This goes in line with the findings from our study, but even with the decrease in the polyurethane group inflammatory markers over time, there was no significant difference between the groups at 90 days ($P = 0.14$). This study also showed that nanotextured implants resulted in reduced capsular thickness and greater formation of type I collagen in all analyzed subgroups, suggesting that these implants led to a reduced immune and inflammatory reaction compared with polyurethane according to these analyzed variables.[16]

Doloff et al,[17] in 2021, studied the foreign body immune response, in rats, rabbits, and humans, to silicone implants according to surface topography and showed that surface roughness influences the control of the host's immune response and the formation of the peri-implant capsule, as well as suggesting that implants with a 4-μm texture (nanotextured) cause less inflammation and fibrosis than other surfaces.

In clinical practice, we observe that nanotextured implants tend to dislocate over time with the formation of a thin capsule that is poorly adhered to the implant and adjacent tissues. This was seen in reoperations, as polyurethane-coated implants that form a more adherent capsule tend to be more stable and cause less friction as they do not move as much in the capsule space.

In 2016, Duxbury and Harvey[18] conducted a systematic review that confirmed a decrease in capsular contracture rates in cosmetic and reconstructive mammoplasties and other benefits of polyurethane, compared with textured implants. However, the aforementioned authors concluded that the magnitude of the benefit cannot yet be established due to the lack of sufficient scientific evidence.[18] In a more recent systematic review, the combined rate of capsular contracture rates in patients with primary augmentation was 3.80% (95% confidence interval [CI]: 2.19–5.40) for printed-textured implants, 4.90% (95% CI: 3.16–6.64) for foam implants, 5.27% (95% CI: 3.22–7.31) for salt-loss-textured implants, and 15.56% (95% CI: 13.31–18.16) for smooth implants.[19]

Other recent studies have focused on studying the systemic inflammatory reaction to silicone implants and have shown an association with diseases of chronic inflammation such as BIA-ALCL and ASIA syndrome. IL-6 was one of the markers measured in this study and showed an increase in the nanotextured group over time. Yet, these levels remained significantly lower in the nanotextured group compared with the polyurethane group in the serum and capsule at days 30 and 60 but lost statistical significance at day 90. This may explain the higher incidence of ALCL polyurethane-coated implants that is noted in the literature. Cytokine receptor signaling is required for the survival of BIA-ALCL. Studies of cell lines have suggested that tumor cells are dependent on the cytokine environment

resulting from the inflammatory process in reaction to the implant or secreted by the tumor cells themselves. Lechner et al[20] in 2012 attributed IL-6 receptor signaling as one of the main drivers of BIA-ALCL. However, preliminary studies did not reveal a significant difference between IL-6 levels when comparing benign and malignant seromas, although the numbers are still too small to reach a definitive conclusion.[21] A study showed that a larger surface area/texture seems to be more associated with BIA-ALCL; therefore, nanotextured implants, as they have a smaller contact surface, have a lower incidence of anaplastic large cell lymphoma.[22] Just like the study by Collett et al,[23] the reported cases of BIA-ALCL are more associated with implants with macrotexture or polyurethane coating rather than nanotextured ones.

Chronic inflammation related to repeated antigenic stimulation has been shown to cause prolonged activation and recruitment of T cells and is associated with T-cell lymphomas. The mechanism of lymphomagenesis is related to genetic instability in the inflammatory microenvironment, favoring the emergence of malignant clonal T-cell populations, and a subsequent upregulation of tumor-promoting cytokines, such as IL-6, IL-10, and IL-17A, 19–21.[24] Kadin et al[25] confirmed a Th17/Th1 phenotype of BIA-ALCL tumor lymphocytes, supporting the potential role of antigenic stimulation and chronic inflammation in the initiation and promotion of BIA-ALCL.[24] The mechanism involved in the development of lymphomas and their pathogenesis is currently under investigation. The mechanism may involve an immune response induced by the silicone or polyurethane material of the implant, which can cause an exaggerated immunological reaction and induce monoclonal neoplasia with activated T lymphocytes. Other postulated mechanisms involve an indirect reaction mediated by cytokines and silicone-induced toxic damage.[26]

In addition to the changes already described, the placement of mini silicone implants in rats may result in hypochromic anemia with normal leukocyte count at the expense of neutrophilia and lymphopenia, and thrombocytopenia.[27] This may contribute to other adverse effects of silicone implants that should be more studied.

The 3 biomarkers used to describe the inflammatory process are certainly not comprehensive and do not reflect the extensive cellular and matrix biology activity of interest. It is necessary for future work to cover more markers with longer periods of time, which will make it possible to complement the results of the present study. Therefore, it is suggested that prospective studies be carried out, including clinical studies, with a design that allows the assessment of the inflammatory response to different types of nanotextured or polyurethane-coated implants, aiming to clarify the mechanism of biotolerance to these devices.

CONCLUSIONS

Silicone implants incite a local and systemic inflammatory reaction that varies in intensity with respect to time and type of implant surface. Nanotextured surface implants demonstrated a decreased production of IL-1, IL-6, and TNF-α in the early time interval of 30–60 days as compared with the implants coated with polyurethane foam, suggesting a blunting of the initial inflammatory response. At 90 days, nanotextured surface implants showed an increase in the level of inflammatory markers, reaching similar levels to the polyurethane-coated implants, which have decreased over time. Our data showed that, over long periods of time, implants with a nanotextured surface cause local inflammatory reactions similar to those coated with polyurethane. In relation to systemic reactions, it is necessary to work with more markers over a longer period of exposure.

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DISCLOSURES

The authors have no financial interest to declare in relation to the content of this article. This study was financed by internal sources.

ETHICAL APPROVAL

All procedures performed in this study were approved by the Ethical Committee on Animal Protection of the State University of Ponta Grossa (041/2018 protocol 16450/2018).

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