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The effect of a bacterial contamination on the formation of capsular contracture with polyurethane breast implants in comparison with textured silicone implants: An animal study☆

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Summary *Introduction:* One of the most common complications following breast augmentation is capsular contracture. The subclinical infection of the implant is often considered to be one of the main risk factors. It is believed that polyurethane (PU) implants, because of their larger foam-like surface, have lower capsular contracture rates due to better tissue integration. It remains unclear if bacterial contamination and biofilm formation result in higher capsular contracture rates under the condition of the increased surface of PU implants compared to textured silicone-gel implants. The effect of this bacterial contamination was examined in an animal-based study.
Methods: A total of 80 mini implants (40 textured silicone-gel implants and 40 PU implants) were implanted in the dorsum of female Wistar rats. In each group, 20 implants were inoculated before implantation with a standard amount of *Staphylococcus epidermidis*. Capsules and implants were explanted after 60 days, followed by double-blind histological, immunohistochemical, and microbiological examinations.

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Results: Macroscopic separation of the total capsule in the textured implant group was possible whereas the growth of surrounding tissue into the foam structure of PU implants made separation in that group difficult. After contamination, a thicker capsule could be observed in both groups without significant differences. Histologically, capsules around PU implants showed significantly lower expression of parallel myofibrils. We were able to describe a significant higher infiltration with inflammatory cells in capsules around PU implants both with and without contamination. Microbiological investigations revealed positive growth of *S. epidermidis* around one PU implant without related signs of capsular contracture.
Discussion: This study demonstrates that aside from the surface of silicone implants, bacterial contamination has major impact on the architecture of capsule formation. In our study, we were able to demonstrate that bacterial contamination leads to a thicker capsule and an increased tissue reaction with a higher amount of inflammatory cells. However, a resulting bacterial infection was only demonstrated in one case and had an insignificant influence on capsule architecture. The observed inflammatory reaction around PU implants was observed as a nonbacterial, granulomatose foreign body reaction.
EBM rating: Level I: Evidence obtained from at least one properly designed randomized controlled trial.

Introduction

Breast augmentation with silicone implants is one of the most common procedures performed by plastic surgeons around the world.[1] Silicone implants were first introduced in 1963 by Gronin and Gerow. Five different generations of silicone implants have been developed since then.[2] The first generation had a smooth surface, a thick capsule, and a Dacron patch to stabilize the implant.[3,4] In the second generation, the capsule was thinner and the cohesiveness of the gel was reduced to achieve a natural feeling.[5] In the third generation, a second layer from Diphenyl- or Fluorosilicone was introduced to avoid gel bleeding.[2,3,6] Textured implants denote the fourth generation.[2] The cohesiveness of the gel is increased to maintain a stable shape of the implant in fifth generation implants.[2]

Polyurethane (PU)-covered implants were first described in 1970 by Ashley et al.[7] It was thought that they built a stronger adherence to the surrounding tissue, causing better aesthetic results and lower capsular contracture rates.[7] The thin PU foam architecture interacts with the surrounding tissue and prevents hardening by encouraging surrounding fibroblasts to grow into the porous foam and produce collagen, facilitating a richly vascular capsule around the implant.[8] Since their introduction, they have been widely used in breast augmentation and reconstruction all over the world. In 2007, Vasquez and Perez demonstrated that capsular microscopic architecture of the capsule around PU implants is completely different to the one around smooth and textured implants. The orientation of collagen fibers in capsules around PU implants is in contrast to textured and smooth silicone implants not organized in a linear and parallel manner.[9] A more distinct chronic foreign body reaction has been histologically verified.[9] In another study by Vasquez in 1999, five layers around the capsule were described from the inside out: 1) a single layer of macrophages, epithelioid cells, and foreign body giant cells, 2) a layer of subacute inflammatory tissue with edema, neoformation of vessels, and presence of lymphocytes, 3) an infiltrate of plasmocytes, 4) a thick layer of fibrous connective tissue, and 5) loose connective tissue.[10] A lower incidence of capsular contracture with PU implants has been reported in several clinical studies.[11–17] Hester et al. reported an incidence of 11% in aesthetic patients and 20% in reconstructive patients.[11]

In the early 1990s, considerations were raised because of a potentially carcinogenic breakdown product of PU, in particular 2, 4-toluendiamine (TDA).[18] In 1991, an update published by the American Food and Drug Administration (FDA) clarified that a potential cancer risk was negligible and further studies have stated that 2,4-TDA is not a carcinogenic agent.[19] Despite their clinical benefits regarding capsular contracture, PU implants are no longer in use in the USA and rarely used in Europe, despite continued popularity in South America.

Capsular contracture is one of the most frequent complications with an incidence between 4% and 60%.[20,21] The exact pathogenetic mechanism remains unclear, but possible causes suggested include foreign body reaction, hematoma, bacterial colonization of the implant, implant position, and the implant's surface. The parallel myofibrils around the implants play an important role in the formation of the capsule. Furthermore, a synovial-like metaplasia (SLM) has been detected around implants in several studies. It has been recommended that the formation of SLM could trigger the formation of the periprosthetic capsule.[22,23]

A number of studies have proposed that a subclinical infection of an implant could affect the pathogenesis of capsular contracture.[24–26] In studies published by Pajkos et al. as well as by Virden et al., a significant correlation between a bacterial contamination and the incidence of capsular contracture was noted.[26,27]

The role of biofilm in the pathogenesis of capsular contracture remains unclear.[26,28] Biofilm is defined as a

group of microorganisms in which cells adhere to each other on a surface. These adherent cells are frequently embedded within a self-produced matrix of extracellular polymeric substance, composed of extracellular DNA, proteins, and polysaccharides. The development of biofilm can lead to an increased antibiotic resistance.[29] It has been confirmed that bacterial biofilms on breast implants, most commonly formed by *Staphylococcus epidermidis*, can cause chronic inflammation leading to capsular contracture.[30,31] It is suggested that PU implants with a larger foam-like structure than conventional silicone implants might be more susceptible to biofilm formation and therefore to chronic infection and to higher chances of capsular contracture.

We examined the effect of controlled bacterial contamination of PU implants on the formation of a periprosthetic capsule in an animal-based study. Our aim was to demonstrate the differences in capsule architecture, capsular contracture risk, and the infection ratio of PU versus textured silicone implants.

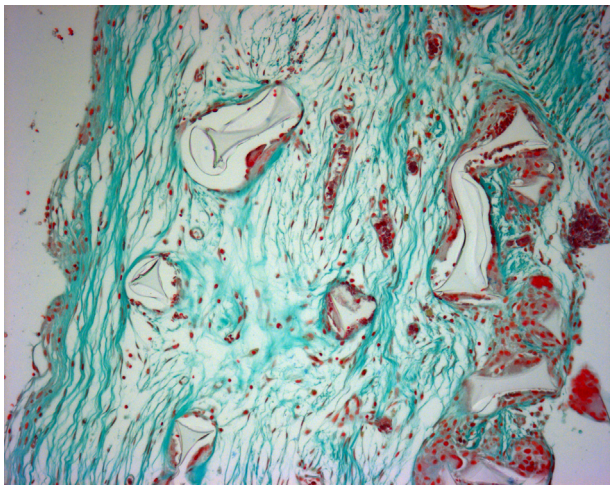

Figure 1 Example of a capsule around PU implant with a multidirectional collagen structure and visible PU foam parts within capsule, Trichrom, original magnification ×10.

Methods

This animal experiment has full compliance with local ethical and regulatory principles as well as local licensing arrangements by University of Lübeck. Two different implant types (textured and PU silicone implants) were implanted submuscular in the dorsum beneath the panniculus carnosus muscle in 80 female Wistar rats, with an average weight of 200 g. We implanted 40 silicone-gel-filled textured silicone implants and 40 PU, silicone-gel-filled implants, each 6 ml (Silimed®, Rio de Janeiro, Brasil). In each group, 20 implants were inoculated before implantation with a standard of 3.2×10^7 CFU/ml of *S. epidermidis* (biofilm-producing strain 1457; Table. 1). The dose of bacterial suspension was tested before ex vivo according to former studies. Testing was done to result a contamination of the implant without increasing the infection risk of the animal.[29] No intraoperative or postoperative antibiotic treatment was needed.

Postoperatively, animals were monitored daily. No postoperative wound infection, hematoma, or infection was noticed; all the animals survived. After 60 days, implants and capsule tissue were explanted. Tissue material was fixed in 4% formalin (PFA), embedded in paraffin, and sectioned to 3-μm width. Hematoxylin–eosin (HE), trichrom (TC), naphthol-ASD-acetatesterase (ASD), and immunohistochemical staining was performed with CD3 (Labvison®, Fremont, CA, USA), CD138 (Biocarta®, San Diego, CA, USA), Lysozyme (Dako®, Glostrup, Denmark), Pax5 (Santa Cruz®, Santa Cruz, CA, USA), and small-muscle-actin (Dako®, Glostrup, Denmark) antibodies.

The stained material was analyzed under light microscopy by two independent examiners under double-blind conditions. Intraoperatively, microbiological swab test was performed. The capsule tissue was examined for bacterial detection (broth culture technique). An ultrasonic bath of the implants to detect the formation of biofilm on the implants was performed in 20 ml saline solution immediately after explantation.[32]

Capsule architecture was numerically rated "one" (only one homogeneous collagen tissue), "two" (two compartments of collagen – loose and tight or SLM), or "three", a three-layer structure (compartments of loose and tight collagen and an SLM layer). Capsule, SLM thickness, and thickness of parallel myofibrils were measured as the average of three measurements taken at the thickest area. The capsule density of myofibrils is expressed in percent (%) of total capsule thickness. Inflammatory cell count was taken as the average of counts taken from three visual fields.

The comparison of metric parameters was performed with Mann–Whitney-*U*-test or *t*-test and of scored data with chi-square test. Differences between scored data and metric parameters were examined by Kruskal–Wallis test. Probability values of <0.05 were considered significant. All tests, including Kolmogorov–Smirnov for normal distribution and Mann–Whitney-*U*-test, chi-square test, and Kruskal–Wallis test, were performed with SPSS Statistic-Packet 20.0 (IBM, Amonk, NY, USA).

Results

In textured implants, we were able to macroscopically separate a complete capsule. PU implants grew entirely into the surrounding tissue. The histological analysis of periprosthetic capsule showed significant differences regarding the total capsule thickness. A significantly thicker

Table 1 Group classification.

Group A	Group B	Group C	Group D
20 Not contaminated PU implants	20 Not contaminated textured implants	20 Contaminated PU implants	20 Contaminated textured implants

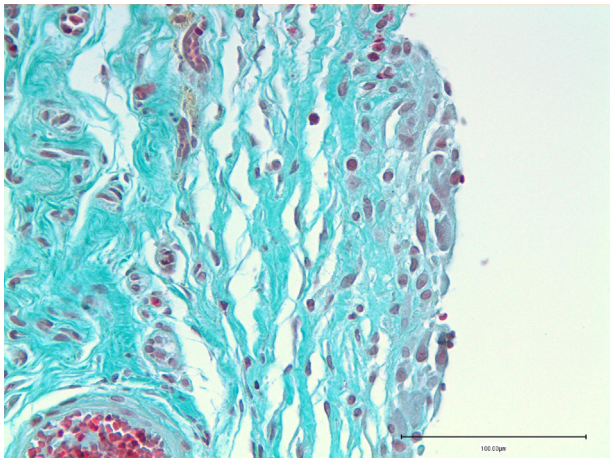

Figure 2 Synovia-like metaplasia (SLM) around textured silicone implant; a pseudoepithelial formation with metaplastic cells, Trichrom, original magnification ×40.

capsule around PU implants (Figure 1) was observed ($p < 0.001$). The average thickness of capsules around PU implants without contamination (group A) was 906.9 μm (±173.6 μm), and around non-contaminated textured implants (group B) was 444.7 μm (±183.3 μm). In contaminated PU implants (group C), the average thickness was 995.6 μm (±125.7 μm) and 464.2 μm (±120.1 μm) in contaminated textured implants (group D).

An SLM was not detected in group A. Average SLM thickness in group B was 14.5 μm (±10.8 μm; Figure 2), 6.8 μm (±6.4 μm) in group C, and 20.1 μm (±9.4 μm) in group D. In both implant groups, the development of SLM was larger after contamination (PU, $p = 0.002$/textured, $p = 0.149$). In both contaminated and non-contaminated groups, significant differences between capsules around PU versus textured implants were observed ($p < 0.001$).

PU implants showed significantly lower expression of parallel myofibrils within the capsule. The average thickness of the parallel myofibrils in group A was 23.3 μm (±19.6 μm), and 18.0 μm (±13.2 μm) in group C whereas in group B (textured implants), thickness was 157.3 μm (±97.9 μm) and 94.0 μm (±31.3 μm) in group D. We observed a significant difference in the percentage of myofibrils layer of total capsule thickness between PU and textured implants (Table 2). These findings were similar in contaminated as well as non-contaminated group ($p < 0.001$; Figure 3a and b).

Capsules around PU implants showed significantly higher inflammatory cells infiltration compared to capsules around textured implants. A statistically significant difference in the number of T-lymphocytes between textured and PU implants in both the contaminated ($p < 0.001$) and non-contaminated group ($p = 0.010$) was found. Neither implant group demonstrated statistically significant influence on the number of lymphocyctes within the capsule after contamination.

Similar findings could be demonstrated with histiocytes, B-lymphocytes, plasmocyctes as well as with the number of giant cells detected in the explanted tissue. A statistically significant ($p < 0.001$) number of inflammatory cells were measured per visual field in capsule tissue around PU implants but was uncorrelated to bacterial contamination.

The dominant inflammatory cells, particularly distinctive in the group of PU implants, were histiocytes and giant cells (Figure 4).

Bacterial contamination within the explanted capsule tissue could be detected in one sample by broth culture technique. In this case, no correlation to a higher inflammatory cell infiltration, thicker capsule, or larger fibrosis was observed.

Discussion

The use of various implant types has been recommended in order to achieve lower incidence of capsular contracture. Past studies observed a lower incidence of capsular contracture in textured silicone implants compared to smooth ones.[33–35] PU implants were observed to have significantly lower capsular contracture rates compared to silicone implants explained by their foam-like structure and due to different healing process.[20,36,37] Despite these investigations, long-term studies have not been able to support these findings.[38]

In recent years, bacterial contamination has been discussed as a possible main factor in capsular contracture.[24,26,33,39,40] Local skin flora may gain access to breast implants during or following their placement. *S. epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, and *Propionibacterium acnes* are the most commonly isolated pathogens.[40,41]

It has been shown that biofilms forming around the implant stimulate fibrosis and lead to capsular contracture.[26,27,39,42] In a study performed by Virden et al., 56% of implants surrounded by contracted capsules were infected with bacteria. Pajkos et al. could confirm the presence of extensive biofilm on implants with a Baker III and IV capsular contracture. Biofilm, especially that produced by *S. epidermidis*, was detected significantly more often in patients with capsular contracture.[27,40,43]

Moreover, the SLM detected around implants is nowadays considered to be one of the critical factors involved in the formation of capsules.[22,23] A reported incidence of SLM in capsules around implants varies between 40% and 87%, regardless of time.[22,33,44–49] This layer was first described

Table 2 Expression of myofibrils in percentage of total capsule thickness, *$p < 0.001$.

Group A	Group B	Group C	Group D
Not contaminated PU implants	Not contaminated textured implants	Contaminated PU implants	Contaminated textured implants
2.6%	35.8%*	1.9%	21.6%*

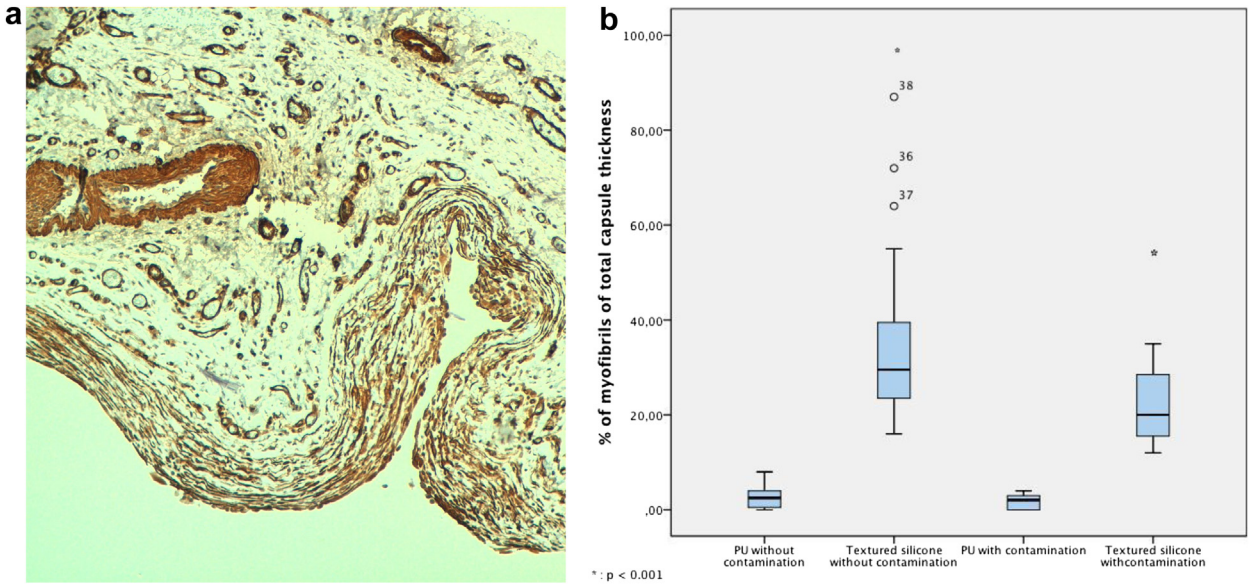

Figure 3 a)Parallel myofibrils within collagen fibers in capsule around textured implant, α-muscle-actin staining, original magnification $\times$20. b)Percantage of myofibrils of total capsule thickness.

in 1994 by Copeland et al. and Raso et al. as the inner zone of the capsule[49–51] and consists of a series of broad, pseudopapillary formations, resembling synovial tissue. This tissue is discontinuous and holds epithelial cells.[49] The function of this layer remains vague, but it is certain that there is a connection between SLM and the formation of a periprosthetic capsule. It has been suggested that the formation of SLM is the beginning of fibrotic remodeling of the capsule.[22] An inflammatory reaction in association with the existence of SLM has been reported. In specific, neutrophils and granulocytes, which indicate an acute inflammatory reaction, were detected in this metaplastic zone along with lymphocytes and plasmocytes, which could potentially cause a chronic reaction.[46] In our study, an SLM was only detected around contaminated PU and around both contaminated and non-contaminated textured implants. Both groups demonstrated increased SLM thickness after bacterial contamination.

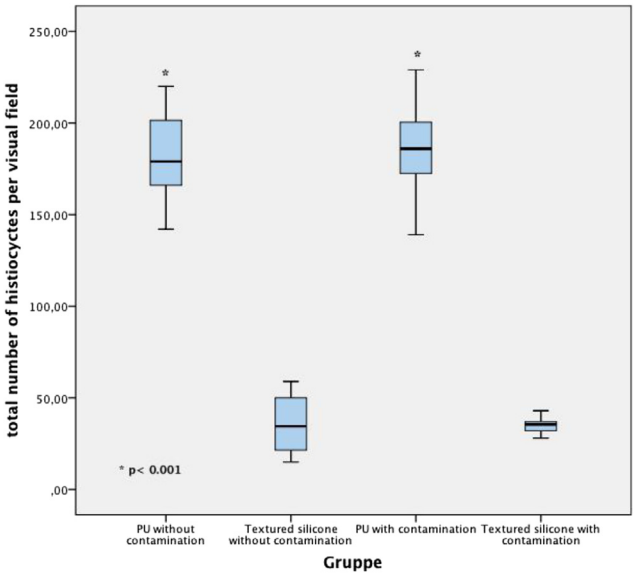

Figure 4 Total number of histiocyts per visual field.

The time between implantation and explantation of the implant was chosen to be 60 days in order to be able to find a fibrous capsule and still seeing histological signs of an acute infection process and an acute bacterial contamination.[23,29]

The use of PU breast implants has been controversial over the last decades. Studies demonstrate that the larger foam-like surfaces of PU implants show better tissue integration.[8] PU foam coating is believed to cause an inflammatory reaction that impedes the formation of a capsule of fibrous collagen tissue.[41] A significantly lower expression of parallel myofibrils in the capsule around PU implants could also be measured in our study, leading to the formation of an architecturally different capsule. Myofibrils are composed of long proteins such as actin and myosin organized into thin and thick filaments, which repeat along the length of the myofibril. Muscles contract by sliding the thin (actin) and thick (myosin) filaments along each other. It has been suggested that parallel myofibrils influence significantly the quality and existence of a periprosthetic capsule.[22,23] The lower expression around PU implants could explain the reported lower capsular contracture rates.

Vieira et al. showed that the capsule formed around PU implants is significantly thicker. Moreover, they measured an overexpression of vascular endothelial growth factor showing better vascularization in capsules surrounding PU implants.[52] We also showed significantly a thicker capsule around PU implants; however, capsule architecture, in particular, the existence of parallel myofibrils, differs significantly from that of capsules around textured implants. We observed incorporation of the PU implant into

the surrounding tissue without the existence of a separate capsule with fibrotic potential. The bacterial contamination influenced the thickness of the capsule as well as the development of myofibrils in capsules around both PU and textured silicone implants positively, but without statistical significance ($p = 0.063$).

In an animal-based study conducted by da Silva Mendes et al., it was shown that the inflammatory reaction around PU implants is of a foreign body granulomatose chronic type.[41] We were able to detect increased infiltration of inflammatory cells, especially histiocytes and giant cells, corresponding to a chronic foreign body reaction around PU implants. We suggest that, in our study, PU coating of the implant causes a nonbacterial inflammatory reaction that results in increased concentration of inflammatory cells which, in turn, leads to the foreign body granulamatosis described above. Particularly, both routine swab culture and broth culture technique were negative for bacterial growth in all samples, except one. This positive tissue around a PU implant showed no conspicuousness regarding capsule architecture or cellular infiltration.

PU implants showed a higher infiltration of inflammatory cells but no signs of acute infection or tendency toward positive bacterial growth.

Our results suggest that the larger foam-like structure of PU creates no higher risk of a biofilm-dependent fibrosis of the surrounded capsule. The observed reaction around PU implants is rather similar to that observed around textured implants and can be described as an increased, nonbacterial, granulomatose foreign body reaction.

Ethical approval

This animal experiment has full compliance with local ethical and regulatory principles as well as local licensing arrangements by University of Lübeck.

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Textured and Polyurethane silicone implants were given for free by Silimed®, Rio de Janeiro, Brasil.

Conflict of interest

None.

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