Comparison of Capsular Morphology between two Different Surface Structures of Silicone Implants

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In Japan, the incidence of breast cancer is increasing every year, and the necessity for breast reconstruction using silicone implants is thus increasing. Such reconstructions result in a foreign body response, with formation of a fibrous capsule and thickening, resulting in capsular contracture during shrinkage, which are often accompanied by marked transformation and pain. The mechanisms underlying this phenomenon are unclear, although one report has described decreased capsular contracture following the use of an implant with a processed surface displaying enhanced ruggedness. The present study examined whether capsular contracture would be decreased by changing the outer structure of the silicone implant. Smooth- and textured-type implants were implanted dorsally in rats. Gross and histopathological examinations (hematoxylin and eosin staining, Masson’s trichrome staining, transforming growth factor (TGF)-β-staining, α-smooth muscle actin (α-SMA) staining, and collagen I and III staining) were performed at weeks 1, 2, 4 and 8 after implantation to examine capsule thickness. The textured-type implant showed a thinner capsule than the smooth type at weeks 4 and 8. The fibrous layer of the capsule was particularly thin. Moreover, TGF-β-positive cells decreased gradually with the smooth-type implant, while TGF-β-positive cells remained evident upon histopathological examination of the textured-type implant. Textured-type implants, α-SMA-positive cells gradually decreased and type III collagen fibers predominated, while smooth-type implants showed a gradual increase in α-SMA-positive cells and a predominance of type I collagen fibers. Based on these findings, the characteristics of the capsule for textured implants with irregular surfaces can be summarized as follows: 1) during the early stage after implantation, stronger inflammatory reactions are induced compared with the smooth type, and because the inflammation becomes chronic, remodeling from type III collagen to type I collagen is decreased, resulting in a type III collagen-dominant capsule; and 2) as irregular structures buffer the tension applied to the capsule due to body movement, the degree of increase in α-SMA-positive cells is lower compared with the smooth type. As a result, a thin capsule that is less likely to contract is formed. These factors are mostly responsible for reducing capsular contracture for textured implants.

Key wards: silicone implant, capsular contracture, textured type, α-SMA-positive cell


INTRODUCTION

Breast augmentation surgery and breast reconstruction surgery using breast implants are widely performed today as minimally invasive surgical treatments. However, because an artificial material is implanted, a fibrous capsule forms around the implant as a foreign-body reaction. When different factors cause the capsule to thicken or shrink excessively, capsular contracture accompanied by marked deformation and pain occurs, and this complication remains problematic. As a measure against capsular contracture, textured-type implants have been developed by making the surface of the silicone implant textured rather than smooth in order to reduce capsular contracture. However, the mechanism of action for reduced capsular contracture due to different surface structures of implants has not been fully clarified. Furthermore, while sporadic studies have followed patients months and years after implantation, few have examined capsular formation during the early stage of implantation when capsular induction is triggered.

Experimental models were therefore prepared by implanting silicone sheets with different surface structures subcutaneously into rats, and differences in capsular structures were compared at a time at which differences in tissue reaction are believed to be marked; i.e., from immediately after implantation (week 1) to the early period (week 8). We discuss the results with reference to the literature.

MATERIALS AND METHODS

The present study was carried out in accordance with the Guide for Animal Experimentation of Nihon University School of Medicine.
and textured silicone sheets (textured type) were prepared by cutting INAMED BIOCELL™ breast implant into 3-cm squares (Fig. 1).

2. Experimental model preparation
Under diethyl ether inhalation anesthesia, a 3 cm skin incision was made orthogonal to the body axis on the left and right sides of the back of male Wistar rats (20 rats; weight range, 250–300 g), and a subcutaneous pocket $3.5 \times 3.5$ cm in size was prepared by dissecting below the panniculus muscle. A smooth-type sheet was implanted to the right side, and a textured type sheet was implanted to the left side. Silicone sheets were implanted with different surface structures close to the skin side (Fig. 2). To prevent silicone sheets from being exposed, incisions were closed by two-layer suturing involving the panniculus carnosus muscle and skin.

3. Assessment methods
After preparing the experiment models, five rats were scarified at weeks 1, 2, 4 and 8 respectively. Each silicone sheet was excised in a single mass from the skin to the skeletal muscle. Each specimen was observed and assessed as follows.

1) Histological assessment
Hematoxylin and eosin (HE) staining was used to observe cells invading the capsule. Masson’s trichrome (MT) staining was used to observe collagen fibers. Immunostaining for transforming growth factor (TGF)-$\beta$ (1:1000, Yanaihara, Japan) was performed to assess fibroblast invasion into the capsule. Immunostaining for type I and III collagen (1:400, DAKO, Denmark) was performed to assess the structure of collagen fibers in the capsule. Finally, immunostaining for $\alpha$-smooth muscle actin ($\alpha$-SMA) (1:500, DAKO, Denmark) was performed to assess the expression of myofibroblasts in the capsule. Light microscopy was performed to observe chronological changes.

2) Capsule thickness measurement
MT-stained specimens that were suitable for observing collagen fibers were observed under light microscopy to measure capsule thickness.

Capsule thickness was measured under a microscope at $\times 100$ magnification using a micrometer. As for statistical analysis, Student’s t-test was performed with the level of significance set at $p < 0.05$.

RESULTS

1. Histological assessment

HE and MT staining
For up to 1 week after implantation, signs of acute
inflammation (i.e., infiltration of eosinophils, lymphocytes and macrophage into the capsule) were seen with both smooth and textured types (Fig. 3a, b). Both types also showed macrophages engulfing silicone (siliconoma) (Fig. 3c). The capsule gradually came to consist of three layers (Fig. 4). In areas that were in contact with silicone, a thin epithelioid layer consisting of macrophages was formed (medial layer), and on the lateral side, a fibrous layer rich in collagen fibers was formed (lateral layer). Between these two layers, an intermediate layer consisting mostly of loose connective tissue was formed\(^1\). With the smooth type, the medial layer was smooth, but with the textured type, disruption and detachment that appeared to be caused when the silicone sheet was removed from tissue were observed. With the textured type, the intermediate layer was seen throughout the course, but with the smooth type, the intermediate layer gradually decreased or was absent in some specimens. The lateral layer was observed in all specimens, but thickness was
markedly greater with the smooth type.

**TGF-β staining**

With the smooth type, cells invaded the intermediate layer at weeks 1-2, but spindle-shaped cells that appeared to be fibroblasts were only sporadically seen among collagen bundles at week 4, and TGF-β positive cells were barely observed at week 8. On the other hand, with the textured type, marked proliferation of TGF-β-positive cells was seen, mainly around the intermediate layer throughout the course (Fig. 5).

**Type I and III collagen staining**

With the smooth type, type I collagen was significantly increased at weeks 4 and 8, and density also tended to be increased. Conversely, with the textured type, type I collagen was most intensively stained at week 2, then thickness and density both tended to decrease.

With the smooth type, type III collagen was seen throughout the capsule at week 1, but then type III collagen was sporadically seen among type I collagen and tended to decrease. With the textured type, type III collagen was seen starting from week 1, and then was seen throughout the capsule. Gaps among fiber bundles were also noticeable.

**α-SMA staining**

With the smooth type, α-SMA-positive cells were barely seen at week 1, then gradually increased. At week 8, α-SMA-positive cells were densely seen throughout the capsule. At weeks 1 and 2, α-SMA-positive cells were markedly apparent from the intermediate to lateral layers for the textured type, but then decreased and were sporadically seen inside the fibrous layer (Fig. 6).

**2. Chronological changes in capsular thickness**

With the smooth type, thickness tended to gradually increase throughout the course. With the textured type, thickness of the entire capsule was highest at week 1 and then tended to gradually decrease. When comparing thickness at different weeks, thickness of the smooth type was significantly greater at weeks 4 and 8 (p < 0.05) (Fig. 7).

With both smooth and textured types, the non-fibrous layer consisting of the medial and intermediate layers tended to decrease gradually, but no significant differences were identified (p > 0.05) (Fig. 8).
With the smooth type, the fibrous layer tended to gradually increase throughout the course. With the textured type, the fibrous layer was the thickest at week 1, after which no marked changes were seen. The capsule for the smooth type was also significantly thicker at weeks 4 and 8 (p < 0.05) (Fig. 9).

**DISCUSSION**

The fibrous capsule formed after implanting a silicone breast implant represents the reaction of the body to a foreign object. However, excessive capsular thickening or contracture causes esthetic and functional problems, such as deformation and hardening of the subcutaneous tissue where the implant is placed, resulting in symptoms such as constricting pain; in other words, capsular contracture. Reported causes of capsular contracture include latent infection around the capsule, presence of foreign materials such as surgical glove talc, silicone particles dislodged from the implant surface, and radiation exposure. Studies have also reported that the onset of capsular contracture is related to the location of implantation, different silicone surface structures, and different implant filling materials.

Many clinical studies have reported that different implant surface structures reduce the onset of capsular contracture. That is, the incidence of capsular contracture for textured implants (5–20%) is lower than that for smooth implants (20–50%).

However, why the onset of capsular contracture is lower for textured implants has not been fully clarified. Here, we prepared experiment models and comparatively investigated capsular changes soon after implantation.

During the early stage after implantation, cell invasions appeared during the process of wound healing around both textured and smooth types, including white blood cells, macrophages and fibroblasts, and multinucleated giant cells engulfed silicone (existence of siliconeoma), suggesting that capsule formation is a reaction to silicone implantation. During the 1970s, Heppleston and Styles proved that silica stimulation causes macrophages to produce TGF-β, while Dolores reported that silicone not only induced proliferation of granulation tissue in response to foreign bodies, but also elicited strong immunoreactions consisting mostly of T lymphocytes. In the present study, white blood cells invading the capsule were mostly lymphocytes and eosinophils, with few neutrophils. In other words, capsular formation was mostly due to a reaction to silicone rather than latent infection.

In addition, compared to the smooth type, the capsule for the textured type was thicker at the early stage, and more cellular components were present because the surface area of the textured type was several times that of the smooth type due to structural features. Furthermore, at weeks 4 through 8, the number of TGF-β-positive cells for the textured type was significantly higher when compared to the smooth type, and the non-fibrous layer did not decrease much throughout the course because the reaction of tissue to silicone impacted both intensity and duration.

The present results showed marked differences in each form of capsular collagen. Collagen is produced by fibroblasts, and during the early stage of wound healing, type III collagen is mainly produced. In general, during the healing process, type III collagen is gradually replaced by type I collagen, and this change occurs as tension to tissue (fibroblasts) increases, and tension correlates positively with collagen fiber thickness and alignment. With the textured type, type III collagen was the dominant type throughout the course, and the replacement of type III collagen by type I collagen was not marked. Type III collagen is the dominant type in granulation tissue. Forrest reported that the collagen in granulation tissue differs from that in normal tissue, being rich in hydroxylation and added lysine sugars. When the amount of additional sugar is great, collagen fibers cannot come close to each other,
resulting in narrow collagen fibers. With the textured type, inflammatory reactions persisted, and signs of chronic inflammation were seen, suggesting that, as in granulation tissue, type III collagen was the dominant type for capsules. Increases in type I collagen were also not marked, as the irregular structure of the textured type served as an anchor to fix the implant to the capsule, thus buffering the tension (stretching force) applied to the capsule due to rat body movements (Fig. 10).

Conversely, with the smooth type, type III collagen was the dominant type during the early stage of implantation, and then replacement with type I collagen and elevated type I collagen were observed. The reason for this was that, with the smooth type, early-stage inflammation reactions finished quickly, and collagen remodeling occurred. Since the capsule was not fixed to the implant and tension (stretching force) due to rat body movements was applied directly to the capsule, a thicker fibrous layer was formed (Fig. 10).

Differences in the degree of tension and the inflammatory reaction of tissue to the two implant types were also seen with α-SMA-stained specimens. α-SMA staining stains primarily cells with actin, such as muscle fibroblasts. During the process of tissue repair, tissue is remodeled, and muscle fibroblasts differentiate from fibroblasts as tension increases. Wound contracture subsequently occurs due to strong contracture. When the healing reaction ends and tension disappears, collective apoptosis occurs, but the mechanisms have not yet been fully elucidated21).

With the textured type, the number of α-SMA-positive cells quickly increased after implantation and gradually decreased with time. However, with the smooth type, α-SMA-positive cells were barely seen during the early stages of implantation, but increased in both number and density over time. During the early stage, the irregular surface structure of the textured type increased the tissue reaction and mechanical stimulation, resulting in high secretion of cytokines including TGF-β, genetic transformation of fibroblasts, and elevated levels of a-SMA positive cells. However, when inflammation became chronic, the textured structure adhered to the capsule. As a result, compared to the smooth type, tension in the horizontal direction was less likely to be applied, and α-SMA positive cells became apoptotic to lower collagen production. Compared to the textured type, early-stage inflammatory reactions for the smooth type were milder, and the number of α-SMA positive cells was thus lower. When the capsule adhered to silicone during the healing process, tension (stretching force) due to body movements was more likely to be transferred, and in antagonism to this force, the number of α-SMA positive cells in the capsule increased, thus forming a capsule that was more likely to contract.

Based on the above findings, the characteristics of the capsule for textured implants with irregular surfaces can be summarized as follows: 1) during the early stage of implantation, stronger inflammatory reactions are induced compared to the smooth type, and because inflammation becomes chronic, remodeling from type III collagen to type I collagen decreases, thus forming a type III collagen-dominant capsule; and 2) because irregular structures buffer the tension applied to the capsule due to body movements, the degree of increase in α-SMA positive cells is lower when compared to the smooth type. As a result, a thin capsule that is less likely to contract is formed. These factors are mostly responsible for reducing capsular contracture for textured implants.

**CONCLUSIONS**

Silicone sheets with different surface structures, i.e., textured and smooth types, were implanted under the dorsal panniculus carnosus muscle of rats, and the re-
sulting capsules were compared and investigated. Compared to the smooth type, a significantly thinner capsule was formed for the textured type. The capsule for the textured type was characterized by more type III collagen and fewer α-SMA positive cells. When implanting an implant with a textured type surface, a capsule that is less likely to contract can be expected to form, and this is beneficial for reducing capsular contracture.

REFERENCES