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Altered systemic serologic parameters in patients with silicone mammary implants

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ABSTRACT

Background: The most common local complication in patients with silicone mammary implants (SMIs) is excessive peri-SMI connective tissue capsule formation and its subsequent contracture. However, considerable controversy remains as to whether these implants also cause systemic side effects. The present study was undertaken to identify possible alterations of serological markers in SMI patients that may herald systemic side effects.
Methods: We investigated several systemic serological parameters in 143 individuals, 93 of whom had received SMIs and 50 controls. The patients were grouped according to the severity of capsular contracture (Baker scores I–IV) and the duration of SMI implants (less than 1 year, between 1 and 5 years, more than 5 years). We also included control groups (female blood donors, nurses with possible professional silicone exposure). Patients with breast cancer and subsequent SMI-reconstruction were excluded from the study since they are generally considered immunocompromised. The following parameters were determined: anti-neutrophil cytoplasmatic auto-antibodies (cANCA), anti-nuclear auto-antibodies (ANA), anti-cardiolipin antibodies (CL-Ab), rheumatoid factor (RF), complement components (C3, C4), circulating immune complexes (CIC), procollagen III (a marker of active fibrosis), anti-polymer antibodies (APA) and soluble intercellular adhesion molecule-1 (sICAM-1).
Results: The following parameters were increased in the sera of SMI patients: CIC, procollagen III, APA, sICAM-1.
Conclusions: We found a set of parameters in serum that correlate with fibrosis development and the duration of the implants in otherwise healthy SMI carriers. Future studies will clarify whether these serological abnormalities will be useful in predicting clinical disease, and also further assess the sensitivity and specificity of these parameters. Our present recommendation as a result of this study is that patients with persistent abnormal serological parameters should be monitored closely by a clinical team that includes rheumatologists.

1. Introduction

Silicone mammary implants (SMIs) for breast augmentation and reconstruction have been in use for more than 55 years. The most common complication is capsular contracture resulting in excessive firmness and pain [1–3]. In general, tissue capsules develop around every foreign body, including silicone breast implants [4]. The developmental mechanism of reinforced capsular fibrosis is not yet known, but appears to be related to individual patient physiology and surgical circumstances (surgical approach, wound environment, postoperative hematoma or seroma). Both platinum and low grade bacterial contamination have been also suggested as important factors in the constrictive fibrotic process around ~~the~~ SMIs [5,6]. The capsule around the SMI includes a band of dense fibrous tissue with a variable number of inflammatory (~~immune~~) cells. Our previous immunohistological analyses have shown that silicone induces a T-cell dependent immune response [7] comprised of primarily CD4/CD3 α/β^+ T-cells, and a considerable number of γ/δ^+ T-cells were detected as well. Subsequently, we detected 184 proteins, many of them biochemically altered, deposited on the surface of medical grade silicones [8]. They are the most plausible inducers of the chronic immune reaction that gives rise to

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peri-implant fibrosis and contracture of connective tissue surrounding the implant.

Although many aspects of the local immune response to silicone have been elucidated, it is still unclear whether women with silicone breast implants experience a systemic activation of their immune systems. Several studies showed increased prevalence of serologic markers of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, polymyositis or scleroderma [9–11], but even meta-analyses have not provided an unequivocal link between SMI and systemic autoimmune diseases [12,13]. In contrast to these meta-analyses, there are numerous case reports of SMI patients showing defined rheumatologic disorders that were greatly ameliorated by implant removal [14]. We have also made such observations at our institution, and indeed some patients have shown prompt remission of symptoms upon removal of the implant [15]. Hence, these observations suggest that women could have a combined illness based on both a genetically determined predisposition to a connective tissue disease and a co-expressed silicone-driven component.

In 2003, Vermeulen and Scholte published a study of 319 women with SMIs in which 227 presented with chronic fatigue syndrome [16]. In 176 of these SMI patients, the relation between ruptures of the implant vs. implant integrity was analysed; 75% of patients with ruptured implants showed symptoms of chronic fatigue vs. 51% of women with intact implants. However, "fibromyalgia" or "chronic fatigue-like illness" has still not been clearly and consistently defined. Obviously, it would be of enormous benefit to have the clinicians (rheumatologists, plastic surgeons and epidemiologists) and basic scientists who observe this phenomenon more stringently document such cases and promote further preventive and therapeutic recommendations for these women [17,18].

Present study was initiated to identify patients with potential risk to fibrotic complications upon implantation of SMIs. We analysed numerous serum parameters and correlated them with degree of fibrosis and time of SMI implantation. Our results indicate that women with strong fibrotic reaction to SMIs have increased serum concentrations of several proteins involved in immune response and fibrosis development. Those findings have both practical and theoretical significance for the SMI carriers, their doctors and scientists clarifying the underlying mechanisms of adverse effect development. Although similar studies did not find correlation of various serological parameters with clinical symptoms of SMI carriers, they either examined different parameters, or had smaller/different cohorts.

2. Patients and methods

2.1. Study design

After obtaining informed consent from blood donors and permission from the Ethical Committee of the Innsbruck Medical University (IMU), we analysed sera from 143 individuals, 93 of whom were SMI patients (median age 44 years, age range 19–73 years) and 50 controls (median age 42 years, age range 20–68 years). All patients and their surgeons answered a battery of questions regarding the date of implantation, type, size and location. Additionally, the patients were also asked about any potentially systemic side effects such as arthralgia, myalgia (muscle pain), weight loss and/or fatigue. Any local contracture was assessed according to the Baker classification, the international classification for grading the severity of capsular contracture. Patients having reconstructive breast surgery due to cancer were excluded from the study since as their oncologic therapies generally render them immunocompromised and subsequently inappropriate for comparison to healthy individuals. None of the patients presented clinical symptoms of autoimmune disease.

Patients were divided into groups depending on the severity of local fibrotic reaction (Baker scores I and II—light fibrosis; Baker scores III and IV—severe fibrosis), and on the duration of their implants: less than 1 year, 1–5 years and more than 5 years. Individuals were classified into groups in pairs by binary matching.

2.2. Serological investigations

Women who undergo cosmetic surgery are generally healthy, thus any subsequent serologic alterations can be readily associated with the implant. The following parameters were examined either via cell-culture-based preparations or from commercially available kits.

Anti-neutrophil granulocyte cytoplasmatic auto-antibodies (cANCA, on HL-60 cells), anti-nuclear auto-antibodies (ANA, on Hep-2 cells), anti-cardiolipin antibodies (CL-Ab (Immuno Concepts N.A. Ltd., Sacramento, CA 95827), rheumatoid factor (RF, Dade Behring Austria GmbH, Vienna), complement components (C3, C4, Dade Behring Austria GmbH), circulating immune complexes (CIC, IMTEC Immundiagnostika GmbH, D-13125, Berlin), procollagen I (C-terminal peptide, ICTP and N-terminal peptide, PINP, Orion Diagnostica Oy, Espoo, FL-02101, Finland), procollagen III (Pro III, Schering, Vienna), anti-polymer antibodies (APA, Autoimmune Technologies LLC, New Orleans, LA 70112), and human soluble intercellular adhesion molecule-1 (sICAM-1, R&D Systems Inc., Minneapolis, MN 55413).

2.3. Statistics

Since the majority of the data sets did not have normal distribution (as tested with the Kolmogorov–Smirnov test), the Mann–Whitney *U*-test was used to estimate differences between groups, and their respective *p*-values. All calculations were performed in statistical software package SPSS 14.0 for Windows (Lead Technologies, USA).

3. Results

Of the measured parameters, only APA, procollagen III and CIC were increased among the different groups of SMI patients (Fig. 1). Other parameters showed no such differences between the observed groups. While strong fibrotic reaction to silicone (Baker scores III and IV) correlated with serum levels of APA, CIC and procollagen III, this was only partially the case for patients with minor fibrotic reactions (Baker scores I and II), which showed statistically significant differences in comparison to controls only for CIC. Mean values of the groups showed a correlation with fibrosis progression (control → Baker scores I and II → Baker scores III and IV) for both CIC and procollagen III.

Differences in CIC, procollagen III and s-ICAM were observed when patients with various implantation durations were compared with controls (Fig. 2). CIC were significantly increased in all groups of SMI carriers, and procollagen III only in patients with SMIs in place <1 year and >5 years. Patients who had implants for more than 5 years also showed increased serum s-ICAM levels compared to controls. APA did not vary significantly among any of the groups of patients regardless of the duration of their implants. Interestingly, SMI carriers showed no statistically significant differences when the duration of the implant was used as the dividing parameter. Means of various implant durations for CIC and procollagen III peaked immediately after implantation in the patients with implants for <1 year, with no direct correlation with duration of the implant in different groups.

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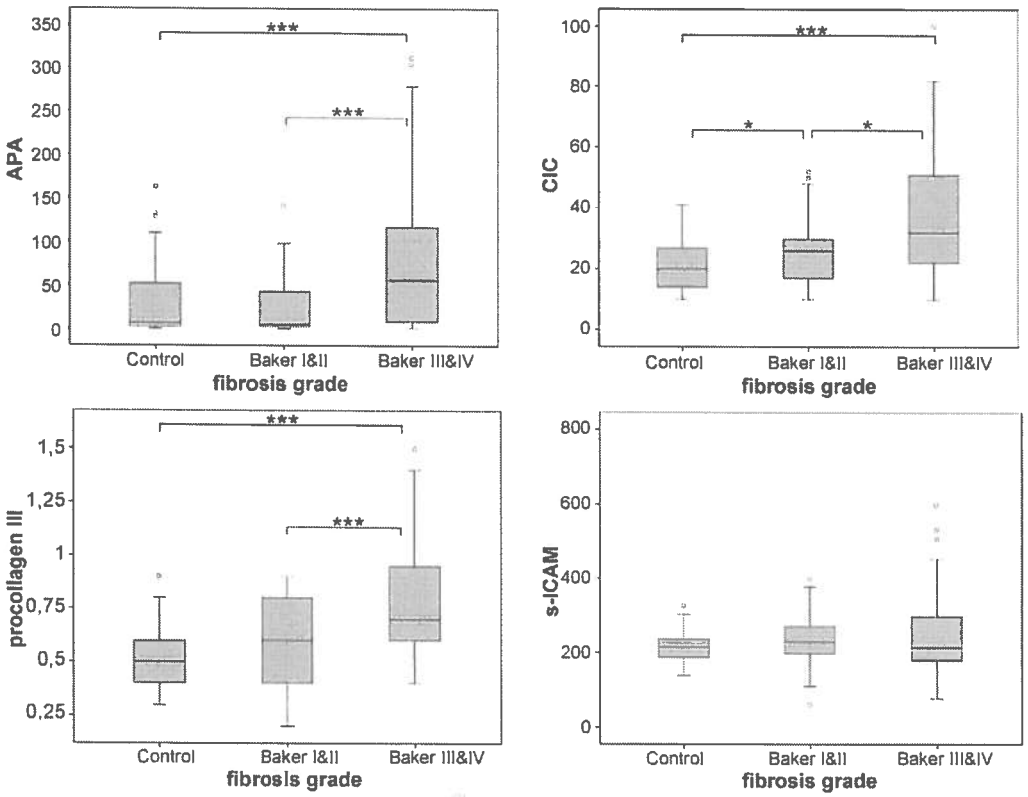

Fig. 1. Elevated serological parameters in silicone mammary implant (SMI) carriers with various fibrosis grades. Patients with SMIs were divided into two groups regarding their local fibrotic complication in response to implants (Baker grades I and II—light fibrosis; Baker grades III and IV—severe fibrosis). When compared to female controls, they showed elevated levels of anti-polymer antibodies (APA) (U/ml), circulating immune-complexes (CIC) (μg/ml) and procollagen III (units/ml). No differences were observed in levels of soluble intra cellular adhesion molecule (s-ICAM) (ng/ml) between patient groups (*$p < 0.05$; ***$p < 0.005$).

4. Discussion

Although only a relatively small percentage of women with cosmetic breast implants show systemic complications, the identification of parameters that are important predictors of the increased risk for systemic side effects as well as development of serologic tests to monitor women with silicone breast implants is highly desirable [19–21]. Since systemic side effects have been primarily attributed to autoimmune responses, we screened a cohort of patients for potential changes in standard serum parameters associated with autoimmune diseases. In addition, we analysed antibodies against polymerized acrylamide, which was originally developed for the diagnosis of fibromyalgia and reactions to foreign materials [22]. Although previous studies analysing several systemic immunologic parameters failed to provide unequivocal proof of an association between rheumatologic diseases and silicone contact, those studies did not analyse sICAM-1, APA, Pro III or CIC [12,23–25], which we found to be altered in various groups of SMI patients.

An increase in ANA-positive patients is the most frequently reported alteration in serum auto-antibody content in SMI patients [26,27]. We found no significant difference in SMI patients compared to normal sera in this regard. However, in our opinion, the practical value of auto-antibodies or other serological abnormalities in general, has not been fully exhausted in the majority of diseases in which they can be detected. Auto-antibodies could reflect the disease process, but they might also predict outcome during a prolonged disease [28,29].

APA reacts against polymer synthetics, and their quantification in serum was originally developed to diagnose fibromyalgia and reactions to foreign materials. Although previous studies with the APA assay found no increased antibody production in SMI patients [30–32], in our hands, the APA assay emerged as an important marker for monitoring SMI recipients for possible side effects. Although it did not correlate with implant duration, this assay clearly delineated patients with various grades of fibrosis. It is noteworthy that a relatively high percentage of controls also showed elevated APA-titres. We intend to follow those individuals over the next few years in order to discover any potential predisposition of these subjects to various forms of connective tissue diseases and complications in case of contact with polymer-coated implants.

Procollagen III is a sensitive marker of active fibrosis [33,34], and it is elevated in a variety of fibrotic diseases as well as during wound-healing, after burn trauma or inflammatory bowel disease [35]. If active proliferation of fibroblasts and overproduction of extracellular matrix proteins occur in the liver as a result of parenchymal damage, increasing amounts of procollagen III peptide are first formed and the respective N-and C-terminal peptides appear in the circulation. The replacement of functioning liver tissue by connective tissue is detectable by raised serum procollagen III peptide levels. We believe our data reflect the same kind of remodelling process in the connective tissue surrounding the SMIs. Procollagen III differed in patients with different fibrosis grades, but also in patients with various implant durations. In comparison to the control group, patients carrying SMIs for less than 1 year showed the highest increase in mean procollagen III content in the serum, indicating more intensive fibrotic processes in that group of patients.

The formation CIC is a physiological process for fast elimination of antigens. CIC occur in the serum under various infectious and other inflammatory or malignant conditions. In autoimmune

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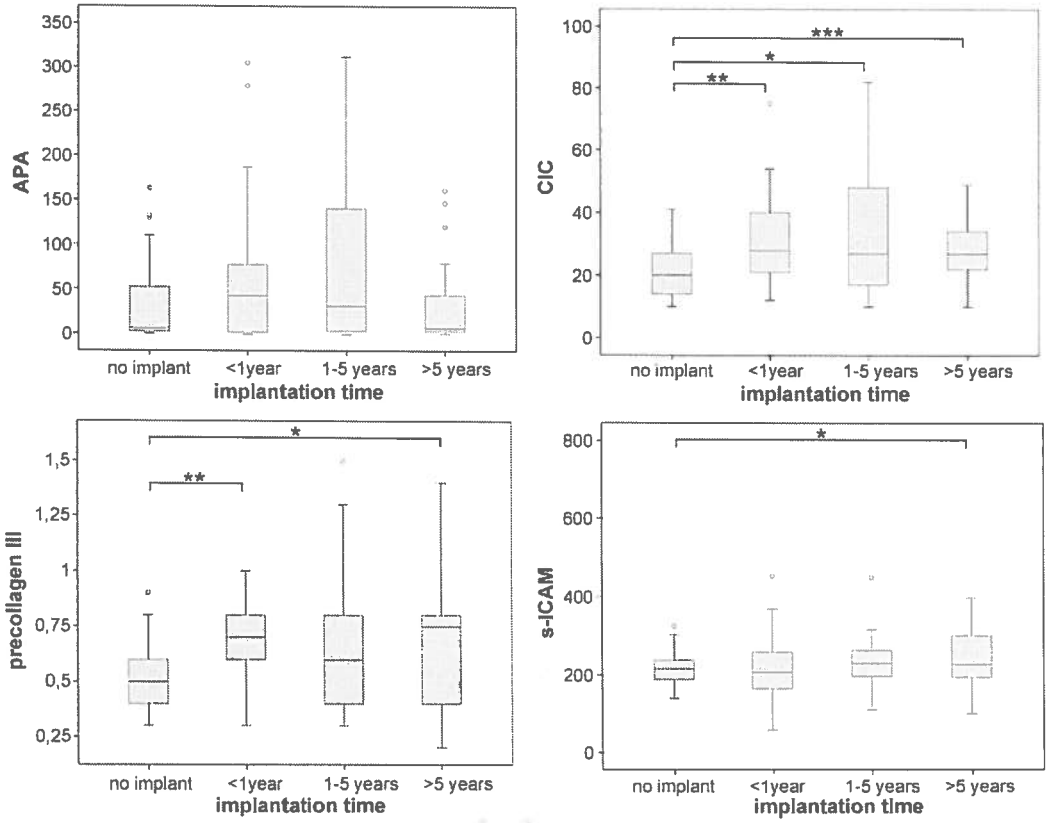

Fig. 2. Elevated serological parameters in silicone mammary implant (SMI) carriers with various times of SMI implantation prior to analysis. Patients were divided into groups according to the time they had SMIs implanted prior to this survey. CIC were increased in all groups of patients compared to healthy female controls, while procollagen III only in groups of patients having silicone implants <1 year and >5 years. s-ICAM was increased only in the group of patients having SMIs for more than 5 years. APA levels were not elevated in any of the analysed groups ($^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.005$).

diseases, CIC levels are an important tool to assess disease progression and organ involvement [36–38]. In our study, CIC correlated significantly with fibrosis progression and with the duration of the SMI implants. The reactivity of complement-fixing antibodies with foreign or autologous antigens is maximal in SMI groups with implantation periods of more than 5 years.

Differences in distribution were also found for soluble ICAM-1, a marker of inflammation and a member of the immunoglobulin superfamily of adhesion molecules. During acute inflammatory processes, the extracellular domain of ICAM-1 is cleaved off the plasma membrane and appears as soluble propeptide (sICAM-1). The only group showing increased serum s-ICAM was patients with SMIs of more than 5 years duration, which suggests a possible role of s-ICAM in chronic inflammatory responses to silicone.

In conclusion, we have established a battery of four serological parameters that show changes in patients with silicone implants, and that occur prior to overt development of capsular contracture or systemic disease. These parameters reflect changes of local immune system activation and subsequent fibrosis on a systemic level. Further study into their sensitivity and specificity will be required to establish these parameters as the basis of clinical and surgical decisions, but persistent serological abnormalities strongly support the utility of careful clinical and serologic monitoring. If this concept is supported by further studies, the parameters may be used to identify patients at risk prior to clinically apparent complications.

Q1 Uncited reference

[31].

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