

The association between silicone implants and both antibodies and autoimmune diseases

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Abstract Silicones are widely used materials in many fields of medicine and largely are believed to be biologically inert. However, some investigators have reported that silicone implants are associated with an increased incidence of autoimmune disorders. In this study, we evaluated the capsular tissue of silicone implants and the sera of implant patients and controls for antisilicone antibodies and nonspecific immunoglobulins (IgG, IgA, IgM, and IgE). Our study group included 15 patients (eight men and seven women) undergoing reconstructive procedures for burn scars, in whom we used silicone implants, and 15 sex-matched controls undergoing reconstructive surgery for burn scars without using

silicone implants. By immunofluorescence, we discovered strong capsular binding of IgG and weak capsular binding of IgM; antisilicone antibody levels were significantly higher in capsular tissue than elsewhere. Serum IgE also was higher in patient vs control subject sera. In conclusion, silicone materials do lead to an immune response consisting of anti-silicone antibodies most evident immediately adjacent to the implant itself.

Keywords Antisilicone antibody · Capsular tissue · Immunoglobulins · Silicone

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Introduction

Currently, silicones are used commonly in medicine. An increasing number of patients receive silicone implants during the course of plastic surgery. These implants may cause foreign body reactions and local or systemic symptoms. Silicone implants have been accused of precipitating rheumatic disorders and nervous and pulmonary system dysfunction by means of auto-antibodies and abnormalities in cellular immunity [1]. Several researchers have investigated the role of silicone in immunity [2, 3]. Studies have identified several kinds of antibodies (antinuclear antibodies, rheumatoid factor, anticardiolipin antibodies IgG and IgM, anti-Ro and anti-La) in silicone-implant patients [4, 5] and higher levels of certain other antibodies (antisilicone antibodies) [6]. In this study, we examined both for nonspecific immunoglobulins (IgG, IgA, IgM, and IgE) and for specific antisilicone antibodies in blood and capsular tissue samples. The aim of this study was to identify specific and nonspecific Ig expression in capsular tissue and in the sera of patients with silicone implant expanders.

Table 1 Demographic characteristics and antibody results in silicone-implant patients

Patients		Serum				Tissue				Silicon antibody	
		Biochemical analysis				Immunofluorescence technique				ELISA ^a	
Number	Age/sex	IgG g/l	IgM g/l	Ig E IU/ml	IgA g/l	Ig G	Ig M	Ig E	IgA	Serum	Tissue
1	25/M	8.57	0.92	175.4 ↑	1.42	++	+	—	—	0.012	0.310
2	32/M	9.63	0.56	107.2 ↑	3.66	++	+	—	—	0.022	0.620
3	17/F	8.03	2.44	220.4 ↑	1.15	++	+	—	—	0.032	0.256
4	42/M	12.46	1.51	170.9 ↑	2.77	++	+	—	—	0.009	0.608
5	12/F	10.03	3.00	141.5 ↑	4.20	++	+	—	—	0.005	0.762
6	54/M	17.11	2.97	238.1 ↑	1.02	++	+	—	—	0.032	0.437
7	14/F	9.58	1.46	344.3 ↑	3.97	++	+	—	—	0.043	0.651
8	4/F	13.05	0.73	224.8 ↑	2.17	++	+	—	—	0.065	0.873
9	15/M	14.70	2.65	218.5 ↑	1.83	++	+	—	—	0.053	0.597
10	33/M	9.80	3.05	162.7 ↑	4.49	++	+	—	—	0.029	0.486
11	30/F	10.71	0.93	229.1 ↑	1.23	++	+	—	—	0.071	0.629
12	28/M	9.93	1.16	256.4 ↑	1.11	++	+	—	—	0.048	0.695
13	21/M	12.04	1.41	167.3 ↑	3.09	++	+	—	—	0.026	0.572
14	14/F	9.57	2.38	182.3 ↑	2.61	++	+	—	—	0.081	0.773
15	35/F	9.98	1.53	242.6 ↑	1.79	++	+	—	—	0.046	0.698

M Male, F female, ++ strong positive immunofluorescence, + weak positive immunofluorescence

^a Values of IgG binding to silicone capsular tissue expressed in optical density units

Materials and methods

We included 15 patients, eight men and seven women, who had undergone reconstructive operative procedures between January 1997 and December 2002. All patients had burn scar contractures. Study and control groups consisted of healthy individuals, except for their burn scars. Baseline serum Ig A, G, M, and E levels were measured for all subjects. Anyone who had a history of allergic or rheumatological diseases or high baseline levels of any of the antibodies of interest was excluded. Tissue expanders were placed adjacent to normal tissue. Mean tissue expander volume was 250 cc (70–450 cc). Only one tissue expander was used per patient. The expanders were left in place from 8 to 12 weeks (mean 9.3 weeks).

Evaluation of capsular tissue

We collected capsular tissue samples in patients with silicone tissue expanders at the expansion ends of healthy tissue. Five-micron frozen sections of capsular tissue were stained for IgG, IgA, IgM, and IgE by immunofluorescence (Dako Lab, Denmark). Capsular tissue samples were homogenized and then incubated for 4 h with rabbit antibodies to human IgG. Silicone capsule antibodies were expressed in optical density units. Antisilicone antibodies in capsular tissue were detected by ELISA (Sigma BioSciences, St. Louis).

Evaluation of serum

Blood samples were studied for immunoglobulins (Pharmacia and Upjohn Diagnostics, Freiburg, Germany). Silicone anti-

bodies were identified by ELISA (Beckman Instruments, Fullerton) [7].

Control group

A control group consisted of 15 patients (eight men and seven women) undergoing reconstructive surgery for burn scar contractures without using any silicone products. They had no rheumatologic or immunological disease. Blood samples were collected as part of the routine preoperative assessment. Tissue samples were collected during the surgical procedure.

Statistical analysis

Between-group analyses were performed using Mann–Whitney *U* tests. Spearman's correlation tests were conducted to investigate for bivariate correlations. Data were analyzed using SPSS software (version 13.0). All analyses were two-tailed, and $p < 0.05$ was set as the threshold for statistical significance.

Results

Patients with tissue expanders vs controls

a. Capsular tissue

Patient characteristics are shown in Table 1. Capsular tissues exhibited strong immunofluorescence for IgG and limited immunofluorescence for IgM, but there was no detectable binding at all for IgA or IgE (Table 1, Fig. 1). In

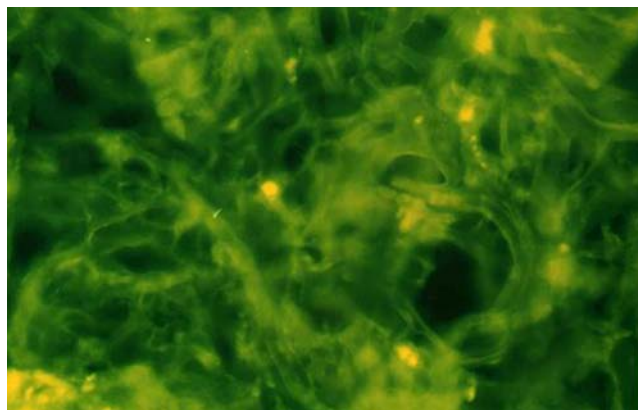


Fig. 1 IgG staining of capsular tissue by immunofluorescence ($\times 400$ magnification) 183×116 mm (72×72 DPI)

the figure, strong immunofluorescence is demarcated with two 'plus' signs and weak immunofluorescence with a single plus sign. Levels of capsular antisilicone antibodies were significantly higher in silicone-implant patients (0.59 ± 0.16 vs 0.030 ± 0.012 ; $p < 0.001$). Control patient characteristics are presented in Table 2. Capsular tissues in control patients did not exhibit any immunofluorescence.

b. Serum

Only IgE levels were significantly higher in the sera of silicone-implant patients vs controls (205.3 ± 56.9 vs 32.4 ± 8.7 ; $p < 0.001$). Levels of other immunoglobulins were in the normal range. Antisilicone antibodies were slightly higher in silicone-implant patients; however, the difference between means was not statistically significant ($0.038 \pm$

0.022 vs 0.032 ± 0.018 ; $p = 0.24$). Bivariate correlations between serum IgE and antisilicone antibodies, both in serum and capsular tissue, were not statistically significant.

Discussion

Polydimethylsiloxane (PDMS) is the simplest silicone structure in medical usage. Silicone is highly biocompatible, nontoxic, nonallergic, and resistant to biodegradation. Silicones can simulate different soft tissues as a liquid, gel, or rubber by varying the length and degree of cross-linking of the PDMS chains.

After a silicone implant is placed, a tissue response occurs. This reaction generally is limited to a mild foreign-body reaction, which then is followed by encapsulation. Capsular tissue forms around any nondegradable material that is too large to be engulfed by macrophages and that is so inert that it causes no more than a local foreign body reaction [8].

This study is different from prior studies in that we examined for the presence of antisilicone antibodies and nonspecific immunoglobulins in the capsular tissue, itself, something which has never been studied before. In several animal models, silicone gel has been discovered to increase antigenicity. There have been a few reports demonstrating antibodies to silicone in human serum: Pastor et al. [4] and Wolf et al. [6] found increased levels of antisilicone antibodies in the majority of their patients but did not identify a relationship between these antibody levels and autoimmune disease. Goldblum et al. [9] detected increased IgG levels

Table 2 Demographic characteristics and antibody results in controls

Controls		Serum				Tissue				Silicon antibody	
		Biochemical analysis				Immunofluorescence technique				ELISA ^a	
Number	Age/sex	IgG g/l	IgM g/l	Ig E IU/ml	IgA g/l	Ig G	Ig M	Ig E	IgA	Serum	Tissue
1	5/F	11.41	2.71	23.12	1.19	—	—	—	—	0.019	0.027
2	40/M	9.01	1.44	43.28	1.07	—	—	—	—	0.012	0.015
3	19/M	9.37	1.71	41.76	2.26	—	—	—	—	0.022	0.031
4	24/M	13.81	0.83	32.78	1.20	—	—	—	—	0.015	0.010
5	32/F	12.07	0.96	33.45	1.81	—	—	—	—	0.017	0.020
6	11/F	11.72	1.47	54.27	2.75	—	—	—	—	0.030	0.028
7	14/F	9.87	1.73	21.38	1.39	—	—	—	—	0.036	0.041
8	23/M	13.46	1.62	35.67	3.01	—	—	—	—	0.035	0.047
9	15/M	11.65	2.06	31.29	1.93	—	—	—	—	0.032	0.024
10	30/M	12.08	1.14	23.65	1.32	—	—	—	—	0.031	0.033
11	29/F	11.56	0.94	26.33	1.70	—	—	—	—	0.054	0.055
12	13/F	12.65	3.51	28.91	2.62	—	—	—	—	0.039	0.046
13	15/M	14.13	1.35	34.68	1.78	—	—	—	—	0.036	0.029
14	35/M	9.69	0.78	27.72	1.14	—	—	—	—	0.018	0.027
15	16/F	10.59	2.56	29.43	2.06	—	—	—	—	0.014	0.018

M Male, F female

^a Values of IgG binding to silicone capsular tissue expressed in optical density units

against silicone medical implants [10]. However, these studies evaluated serum samples only.

In the present study, we identified significantly increased antisilicone antibodies in capsular tissue. We also discovered IgG and IgM antibodies, by IFA, in capsular tissues in silicone-implant patients. The levels of serum antisilicone antibody levels were slightly higher in implant patients vs controls, but this increase was not statistically significant. Nevertheless, if the sample size had been greater, the difference might have been significant. Evans et al. [11] reported that normal individuals have basal antisilicone antibody levels; however, they also reported that antisilicone antibody levels were significantly higher in their breast-implant patients. Microscopic evidence of silicone has been discovered in other bodily tissues in breast-implant patients [12]. Furthermore, Iannello [13] identified silicone compounds in the blood and liver of those with silicone implants. Combining the results of our study and previous studies, we might conclude that silicone particles, albeit in very small quantities, scatter throughout body tissues, leading the human body to produce specific antibodies. This body reaction seems to be related to the amount of silicone exposed in blood, body tissues, and the capsule. We identified a significantly greater reaction in capsular tissue than elsewhere. On the other hand, we discovered elevated serum IgE levels possibly because of a foreign body reaction. There was no correlation between serum IgE levels and the levels of capsular or serum antisilicone antibodies.

Whether silicone implants lead to the development of rheumatologic or immunologic disorders remains unknown. Several authors have speculated about the likelihood of a relationship. Karlson [14] reported on the activation of the immune system in female silicone-implant recipients. In other studies, several types of auto-antibodies have been found to be increased [9, 15, 16], and a single study identified an increased prevalence of rheumatic conditions in females with breast implants [17]. On the other hand, Peters et al. [18] identified no increase in antinuclear antibodies in those with silicone implants.

To summarize, taken together, the previous reports and the results of our study suggest that silicone implants cause a negligible and nonspecific foreign body reaction. However, we feel that these antibodies against the silicone implants have little or no clinical importance. To determine any causative association between silicone implants and autoimmune disease, further long-term studies are warranted.

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