SILICONE IMPLANTS AND AUTOIMMUNE DISEASES

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A. SILICONE AND BREAST IMPLANTS

- Silicone, an element that appears throughout nature, bears the generic name for a family of silicon-carbon-based polymers.

- Depending on the length and complexity of the polymer, silicone may exist:
  + as a liquid (short, simple polymer chains), gel, foam, resin or rubbery material (elastomer; long, complex polymer chains).

- 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.

Silicone breast implants have been used for reconstruction and cosmetic breast augmentation since the early 1960’s.

Silicone breast implants are composed of a silicone elastomer envelope, filled with silicone-gel or saline.
A. SILICONE AND BREAST IMPLANTS

- There is no medical concern over the safety of the silicone elastomer envelope.
- However, the “silicone controversy” exists over the silicone-gel filling.
- Implants with silicone-gel filling provide a superior aesthetic result and a natural feeling to the breast, as compared to the saline filled implants.
- The plastic surgeons as well as the patients insist to date on the continued use of silicone-gel filled breast implants.
A. SILICONE AND BREAST IMPLANTS
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

a. Introduction

+ Few implantable medical devices have been studied for their safety more extensively than silicone gel–filled breast implants.

+ Silicone breast implants have been in use for breast reconstruction and breast augmentation for a long time.

+ In the late 80’s anecdotal reports describing a possible association between silicone-gel filled breast implants, and autoimmune diseases was accumulating.
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

- Due to the growing concern about the safety of silicone-gel implants, the FDA restricted their use to:
  - Participants in controlled clinical trials, including women having reconstructive surgery.

- These review articles summarize the epidemiologic evidence on the safety of breast implants, most of which is drawn from large cohort studies with long-term follow-up.

- The topics addressed in these review articles include:
  - Cancer, breast cancer detection, connective tissue disease, suicide, offspring effects, neurologic disease, implant rupture, and local preoperative complications and additional surgery.

- These topics represent those for which there has been considerable scientific investigation and which appear to be of greatest interest to regulatory agencies.
b. Specific Safety Issues

1. Connective Tissue Diseases

- In the past decade, over 60 cases of connective tissue diseases following mammoplasty with silicone-gel filled implants have been reported.

- About half of these patients developed scleroderma or scleroderma-like illnesses.

- Many individual case reports and case series have implicated silicone-gel filled breast implants in the development of connective tissue disease-like syndromes.
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

- Data from studies published through 2004 have been summarized in:
  - Numerous meta-analyses, weight-of-the-evidence, and critical reviews.

- These have concluded:
  - No evidence of an association between breast implants and any of the traditional CTDs evaluated individually or combined, or atypical CTD

- The only finding of a relationship between CTDs and breast implants:
  - From a single large retrospective cohort study of female health professionals in the Women’s Health Study
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

- This study found a small increased risk of self-reported (not validated) CTDs overall among women with breast implants.

- Compared with women without implants, the relative risk (RR) for any self-reported CTD combined was 1.24 (95% CI, 1.08 –1.41).

- This study used outcome data that were self-reported by female health professionals in a mailed questionnaire.

- In a subsequent medical record validation of these data by the same research group, evidence of over reporting of disease by the subjects was observed.
Such overreporting could easily have accounted for a slight excess of CTDs among women with implants.

Janowsky et al. conducted a comprehensive series of meta-analyses of the largest group of studies to date.

Their meta-analyses were the first to perform a separate analysis focused exclusively on silicone-gel filled breast implants.

The authors found no evidence:

- Of an association between breast implants in general, or silicone-gel filled breast implants specifically, and any of the individual connective-tissue diseases, all definite connective-tissue diseases combined or other autoimmune or rheumatic conditions.
Women with breast implant rupture were no more likely than women with intact implants to report a diagnosis of any of the definite CTDs studied.

An association has also been conjectured:

- Between silicone breast implants and the existence of a new disease, which does not fulfill established diagnostic criteria for any known CTD.

It has been suggested that breast implant recipients experience:

- Symptoms of apparent connective tissue, rheumatic, or autoimmune origin that do not fit the profile for a defined CTD, including:
  - Cognitive dysfunction, severe joint and muscle pain, incapacitating fatigue, and skin abnormalities.
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

- Attempts have been made to:
  - define these syndromes, which may be referred to as "undifferentiated," "atypical," or "mixed" CTD, and it has been suggested that the symptomatology of the proposed new disease bears some resemblance to fibromyalgia.

- Most of the published epidemiologic studies to date evaluated traditional CTDs rather than atypical symptoms.

- Those studies that did attempt to include a category for undefined or atypical CTD as an outcome have been remarkably consistent in:
  - finding no convincing evidence of an association between silicone breast implants and atypical connective tissue disease.
It was evaluated the presence of 20 auto-antibodies in 116 breast implant patients compared to 134 controls.

The breast implant patients’ main complaints were: arthralgia, fatigue, musculoskeletal pain, morning stiffness and memory impairment.

It was found a high prevalence of auto-antibodies among the breast implant patients group.

Several of the breast implant patients had more than one auto-antibody: 20% had four antibodies, 8% had six.

It was concluded that:

+ The association between breast implants and auto-antibodies suggests an adjuvant-like action of the silicone or its by-products.

Tenenbaum et al. showed in a multicenter blinded study, the presence of an anti-polymer antibody (APA) in breast implant patients as compared to controls.
They further showed a correlation between the breast implant patients’ severity of symptoms and the proportions positive for the APA.

The authors concluded that the APA assay can objectively contribute to distinguishing between breast implant patients with limited symptoms, mild symptoms and severe symptoms.

It has been recently used the APA assay to test the sera of 109 breast implant patients, of whom 80 were symptomatic and 29 asymptomatic.

Thirty of the 80 sera of the symptomatic women (37.5%) were positive for APA, whereas none of the asymptomatic sera was found to be positive for APA.

A genetic predisposition for developing connective tissue disease symptoms has been investigated and may be a factor in the development of symptoms in women with breast implants.

Young et al. have showed a higher incidence of HLA-DR53 and DQ2 among symptomatic breast implant women.
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

- Morse et al. found in nine patients with scleroderma and silicone breast implants a higher frequency of Glycine or Tyrosine in position 26 at the hyper-variable first domain of HLA-DQB1 instead of Lysine.

- In recent years an association between fibromyalgia (FM) and silicone breast implants has been reported.

- The American College of Rheumatology criteria for FM include a history of widespread pain and tenderness at specified tender points.

- Symptoms reported by women with silicone breast gel implants are common in patients diagnosed with FM, suggesting that an atypical syndrome in women with breast implants reported by rheumatologists may be FM.
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

- Brown *et al.* of the FDA, found that:

  - breast implanted women with silicone leaking outside the capsule, as seen by MRI, were almost three times more likely to report having FM than breast implanted women without “extracapsular silicone”.

  - FM is a wide spread disease with a prevalence of 2% in the United States and up to 3.4% in women.

- The above studies are all preliminary, with a rather small study population.

- Larger studies are thus necessary to address the issue.

- Recent studies suggest that many of the symptoms of women with silicone breast implants might be attributed to somatisation, stress and mass somatisation.
Ahren et al. found these women to have significant psychiatric morbidity and show significant high anxiety levels.

The cause for these high anxiety levels maybe related to the reasons these women sought breast implants.

These raised trait-anxiety levels maybe a risk factor for somatisation.

Due to the uncontrolled nature of these studies, larger controlled studies must be held before we can come to conclusions.
Immunologists have raised concerns that:

- silicone implants might act as antigens, provoking antibody complexes made of silicone and protein and ultimately resulting in a delayed hypersensitivity reaction.

Additional findings of local inflammation around implants and migration of silicone particles to locoregional lymph nodes have contributed to concerns of possible health hazards.
The term *human adjuvant disease* has been used to describe an array of symptom complexes (joint and muscle pain and chronic fatigue), implying a potentially enhanced antigenicity caused by the adjuvant, silicone.

Serum levels of silicone may be elevated in patients with silicone implants, but this finding is unreliable.

Results show that:

- A genetic predisposition to development of certain symptoms similar to those of fibromyalgia may exist based on a specific genotype, and that precise serum markers may have value in predicting an adverse outcome in these individuals.
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

2. Cancer

- Large-scale incidence studies have consistently found no credible evidence of a causal association between breast implants and any type of cancer.

- Sporadic lung or cervical cancer mortality and incidence excesses are likely due to confounding by lifestyle and behavioral factors and/or reproductive characteristics.

- They have been shown to differ between women with implants and women with other types of cosmetic surgery and women in the general population.
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

3. Breast Cancer Detection

+ Implants may make screening mammography more challenging by obscuring a variable part of breast tissue.

+ Fortunately, none of the mortality studies to date has demonstrated:

  ✗ an increased risk for death from breast cancer among women with implants compared with women in the general population.
4. Suicide

- The epidemiologic evidence regarding suicide among women with breast implants is remarkably consistent, as is the strength of the general association between prior psychiatric illness and suicide.

- Further etiologic epidemiologic studies are needed to:
  - Identify whether history of psychiatric illness or other factors prior to breast augmentation surgery may place some women with cosmetic breast implants at high risk of suicide.
5. **Offspring Effects**

- There were isolated case reports of children born to or breast-fed by women with silicone breast implants who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms.

- The epidemiologic evidence indicates that offspring of women with breast implants are not at increased risk for esophageal disorders, rheumatic diseases, or congenital malformations.
6. **Neurologic Disease**

- Sporadic case reports have described neurologic disorders, including a multiple sclerosis–like syndrome and motor and peripheral neuropathies, among women with cosmetic breast implants.

- Three large, nationwide cohort studies with long-term follow-up have found no evidence of a causal association between silicone breast implants and neurologic disease.
7. **Implant Rupture**

- It is defined silicone breast implant rupture as a breach of any size in the implant shell and reported that all silicone gel implants were susceptible to silicone bleed through the implant shell.

- Estimates of breast implant rupture prevalence range wide from 0.3% to 77%.

- It is concluded that, for most women, rupture is a harmless condition which does not appear to progress.
8. Local Complications

- Women with silicone gel–filled breast implants sometimes develop local and preoperative complications, including serious infections, severe or chronic breast pain, hematoma, and the need for additional surgery.

- The reported frequency of local complications among silicone breast implant patients ranges between 17% and 36%.

- Typically, the most frequent local complication is capsular contracture, while complications such as pain, hematoma, and wound infection are substantially less common.

- The incidence of short- and long-term local complications following breast implantation is low and does not typically require additional surgery.

- Surgical intervention occurs most frequently as a result of capsular contracture.
B. THE SAFETY OF SILICONE GEL-FILLED BREAST IMPLANTS

c. Conclusion

+ The conclusion arising from the recent studies, as opposed to studies in the early 90’s, rules-out the risk of connective tissue disease in women with breast implants.

+ There might be a genetic predisposition for developing symptoms.

+ In these “genetically predisposed” women the silicone might take the role of an “environmental trigger”.

+ Accordingly, it might be smart to avoid breast augmentation with silicone breast implants in women with a family history of autoimmune diseases.

+ Another emerging issue is a possible connection between FM and women with silicone breast implants.

+ All studies are preliminary, with a rather small study population.

+ Larger studies are necessary to address this issue.
The safety of silicone gel–filled breast implants has been studied extensively.

Much of the epidemiologic evidence to date is drawn from large cohort studies with long term follow-up, often longer than 3 decades.

Based on the review of the published epidemiologic literature, through September 2007, on the safety of breast implants, it is concluded:

- That the weight of the epidemiologic evidence does not support a causal association between breast implants and breast or any other type of cancer, definite or atypical CTD, adverse offspring effects, or neurologic disease.

- Women with breast implants do not present with more advanced stages of breast cancer or suffer from impaired survival after breast cancer diagnosis.
C. THE ASSOCIATION BETWEEN SILICONE IMPLANTS AND BOTH ABS. AND CTDS

a. 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.
C. THE ASSOCIATION BETWEEN SILICONE IMPLANTS AND BOTH ABS. AND CTDS

a. Introduction

+ Several researchers have investigated the role of silicone in immunity.

+ 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 and higher levels of certain other antibodies (antisilicone antibodies).

+ In this study, researchers 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.
b. Materials and Methods

+ They 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.

+ *Evaluation of Capsular tissue*

+ They collected capsular tissue samples in patients with silicone tissue expanders at the expansion ends of healthy tissue.
C. THE ASSOCIATION BETWEEN SILICONE IMPLANTS AND BOTH ABS. AND CTDS

- Five-micron frozen sections of capsular tissue were stained for IgG, IgA, IgM, and IgE by immunofluorescence.

- Capsular tissue samples were homogenized and then incubated for 4 h with rabbit antibodies to human IgG.

- Antisilicone antibodies in capsular tissue were detected by ELISA.

- **Evaluation of serum**
  - Blood samples were studied for immunoglobulins.
  - Silicone antibodies were identified by ELISA.

- **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.
C. Results

_Capsular tissue_

+ Capsular tissues in silicone-implant patients exhibited strong immunofluorescence for IgG and limited immunofluorescence for IgM, but there was no detectable binding at all for IgA or IgE.

+ Levels of capsular antisilicone abs. were significantly higher in silicone-implant patients.

+ Capsular tissues in control patients did not exhibit any immunofluorescence.
C. THE ASSOCIATION BETWEEN SILICONE IMPLANTS AND BOTH ABS. AND AUTOIMMUNE DISEASES

**Serum**

- Only IgE levels were significantly higher in the sera of silicone-implant patients vs controls.
- Levels of other immunoglobulins were in the normal range.
- Antisilicone antibodies were slightly higher in silicone-implant patients.
C. THE ASSOCIATION BETWEEN SILICONE IMPLANTS AND BOTH ABS. AND CTDS

d. Discussion

+ 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.
C. THE ASSOCIATION BETWEEN SILICONE IMPLANTS AND BOTH ABS. AND CTDS

- In the present study, they identified significantly increased antisilicone antibodies in capsular tissue.

- They 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.
Microscopic evidence of silicone has been discovered in other bodily tissues in breast-implant patients.

Combining the results of this 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.

They discovered elevated serum IgE levels possibly because of a foreign body reaction.
Whether silicone implants lead to the development of rheumatologic or immunologic disorders remains unknown.

In other studies, several types of auto antibodies have been found to be increased.

The previous reports and the results of this study, taken together, suggest that silicone implants cause a negligible and nonspecific foreign body reaction.

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.
D. FEW NOTES ON SILICONE SYNOVITIS

- Silicone synovitis is a form of chronic foreign-body synovitis caused in response to shedding of silicone particles from damaged silicone polymer prostheses.

- It has been most frequently reported in cases with carpal implants.

- Clinically: local pain, limitation of motion, and swelling
D. FEW NOTES ON SILICONE SYNOVITIS

- Radiologic changes: nodular soft tissue and well-defined subchondral lytic lesions; cartilage space is preserved; prosthesis is often fragmented, deformed, or subluxed

- MRI: lytic lesions show intermediate to mildly increased signal on PD and T2-weighted images (not typical of fluid-filled cysts)

- Disintegrated silicone fragments appear as hypointense regions on all sequences, as does the prosthesis itself.
REFERENCES

THANK YOU