Original Article

Immunological Changes After Mammary Silicone Implant

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Abstract

Objectives To determine whether mammary silicone implanted in human females results in a measurable and significant inflammatory and immunological changes after mammary silicone implant insertion. **Background** Silicones are widely used materials in many fields of medicine and largely are believed to be biologically inert. However, several reports suggest that silicone products are associated with various complications that may involve inflammatory and immune reactions to silicone or development of systemic autoimmune and connective tissue diseases. In this study, we evaluated the sera of silicone implanted patients to detect inflammatory and immunological response. **Methods** This was a prospective (Cohort) clinical study that was done for 33 female patients operated for augmentation mammoplasty with silicone implant. Patients were operated at Plastic Surgery Department, Menoufia University Hospitals, from February 2019 to November 2022. All patients were operated for unilateral or bilateral augmentation mammoplasty by insertion of textured or smooth mammary silicone implants, either inserted at sub-mammary or sub-pectoral plane pocket. Single brand of silicone implants were used for all patients at this study (Sebbin, Paris, France). Lab investigations were done by same laboratory. **Results** In this study we examined serum blood samples of 33 women planning for augmentation mammoplasty by mammary silicone implants to determine whether mammary silicone implanted in human females results in a measurable and significant inflammatory and immunological changes after silicone insertion. The results demonstrated that there was statistically significant elevation of CRP, anti-silicone antibody, anticardiolipin IgG and IgM levels after 6 months post-operatively compared to pre-operatives results. **Conclusion** The increasing levels of anti-silicone antibody and other antibodies can be useful to physicians and surgeons who wish to assess the integrity of an implant when rupture is suspected. The high specificity of the test suggests that continuous monitoring of anti-silicone antibody levels in implanted patients on a regular schedule could be used as a screening procedure for suspected implant failure. While, to determine any causative association between silicone implants with autoimmune and connective tissue diseases, further long-term studies are recommended.

Key words: Augmentation mammoplasty – silicone implants- immunological changes – antisilicone antiboy

INTRODUCTION

Augmentation mammaplasty with silicone implants has been conducted regularly since 1962, though not without controversy. Between 1992 and 2006 a moratorium was established in the USA for aesthetic devices due to suspicion of immune reactions and rheumatologic complications, besides implant rupture, silicone leakage, and local complications **(1, 4).** The majority of studies, including extensive analysis by the Institute of Medicine, eventually dispelled such fears **(2, 3, 5).** Moreover, new-generation products are made of cohesive silicone gel and carefully engineered shells, thus implant rupture or gel bleed has become uncommon, minor, and asymptomatic **(7, 8).** In this sense, manufacturers all over the world offer devices of multiple sizes, forms, and textures that became so widespread.

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 **(9, 10).** Several researchers have investigated the role of silicone in immunity **(2, 3).** Studies have identified increasing levels of antisilicone antibodies in silicone-implant patients **(4, 5, 6).**

The aim of this study was to identify inflammatory markers (blood lymphocytes and CRP) and immunological markers (specific antisilicone antibodiy, anticardiolipin IgG and IgM) in blood serum of women with silicone breast implants.

Materials and Methods

This study was carried out after approval of the ethical committee of faculty of medicine, Menoufia University and included 33 women planning for augmentation mammoplasty by silicone breast insertion. The study was done at Plastic Surgery Department, Menoufia University Hospital, Egypt, from March 2019 to November 2022. Informed consent was obtained from all patients and agreed voluntarily to share and use investigation results and photos for research with protection of their confidentiality and anonymity. Patients age ranging from 19 to 55 years old, BMI = 18.5-32 kg/m^2.

Statistical Analysis

Data collected entered and analyzed using Microsoft Excel software. Data was then imported into Statistical Package for the Social Science (SPSS version 20.0) software for analysis where quantitative variables were expressed as mean, SD and range and qualitative variables as number and percentage.

Inclusion criteria Patients planning for augmentation mammoplasty for cosmetic and aesthetic reasons and presented with small sized breast with stable general condition.

Exclusion criteria Pregnancy or lactation, smoker patients, patients with autoimmune, connective tissue, chronic diseases, cardiac problems, Patients unfit for surgery, history of previous breast surgery, history of breast cancer, radiotherapy, burn, patients received immunosuppressive drugs, patients with psychological instability, unrealistic expectations and refusal to participate in the study.

Preoperative preparations All patients subjected to full history taking, general examination, breasts and axillae examination and breast measurements obtained involving: suprasternal notch to nipple distance and nipple to infra mammary fold distance. Implant type, size, shape, plane pocket and type of approach were discussed in details with all patients. Photographs were taken preoperatively for all patients.

Preoperative investigations Routine pre-operative investigations. Mammogram was done for Patients older than 40 years old and Ultrasound for those younger than 40 years old.
Venous blood samples were obtained from all patients at this study at two occasions for laboratory investigations (pre-operative and after 6 month post-operative) and were collected into Ethylene Diamine Tetra Acetic Acid (**EDTA)** tube (purple top). **EDTA** also called edetic acid, which is used in medicine to prevent blood samples from clotting by removing or chelating calcium from it **(fig, 1)**. Clotted or hemolyzed samples were un-acceptable and discarded. The test were done by highly experienced laboratory consultant at high quality lab (Al-Mokhtabar, Egypt) with CAP accredited (College of American Pathologists).

These blood samples were sent to the lab and examined for
Inflammatory markers Blood lymphocytes by flow cytometry semi-conductor laser light multi-dimensional cell classification (Hematology analyser BIO-TEC®. CO.LTD. Egypt). Lymphocytes normal reference range is 1- 4.5 $\times 10^9$/L. C-reactive protein (CRP) is an in vitro diagnostic test for quantitative determination of concentration of CRP in serum blood (Elabscience® Biotechnology Incorporation, United States). CRP reference range is 0- 5 mg/L.

Immunological markers Anti-silicone antibody by ELISA (normal reference range is negative). Anti-cardiolipin antibodies IgG by ELISA (normal reference range is negative < 9.9 GPL u/ml). GPL refers to IgG phospholipid units. One GPL unit is 1 microgram of IgG antibody. Anti-cardiolipin antibodies IgM by ELISA (normal reference range is negative < 6.9 MPL u/ml). MPL refers to IgM phospholipid units. One MPL unit is 1 microgram of IgM antibody. Antibodies were tested by a commercially available enzyme-linked immunosorbent assay (ELISA) kits specific for each type of antibodies (Elabscience® Biotechnology Incorporation, United States).

These investigations were done to determine whether mammary silicone implanted in human females results in a measurable and significant inflammatory and immunological changes either early or late after mammary silicone implantation.

Fig. (1) Venous blood sample into EDTA tube (purple top), that was obtained from one of the patients in this study and was sent for laboratory investigations.

Informed consent was taken including preoperative photography documentation.

Markings It was done while patients were in standing position, suprasternal notch and mid-clavicular points were marked, infra mammary lines were marked bilaterally. A line was drown extending from suprasternal notch downward to the umbilicus. Meridian of the breast was marked in each side by a line drown from mid-clavicular point down until crossing infra-mammary fold, dividing the breast to equal halves.

Surgical technique The procedure was done under general anesthesia while the patient was in supine position with both arms abducted 90 degree and fixed to arm support. A prophylactic antibiotic (cefuroxime 1.5 gm.) was given intravenously after induction of anesthesia. Following sterilization by 10% bovidone iodine solution, and toweling, Infra-mammary incision approach was done for all patients at this study. Single brand of silicone breast implant was used for all patients (Sebbin, Paris, France) with different shapes and sizes. Implant plane pocket was created (submammary or subpectoral), good hemostasis was done, irrigation with antibiotic solution, suction drain was inserted, implant was inserted (smooth or textured) into the plane pocket, closure was completed in multiple layers. All patients were successfully operated on, without any intra-operative complications.

Post-operative care

Medications Acetaminophen (paracetamol) or non-steroidal anti-inflammatory oral tablets for routine pain control. Muscle relaxant oral tablets (helps pectoralis relax). Antibiotics oral tablets for 3-5 days.

Brassier and dressing Steri-Strips for 4 weeks. Patients were advised to wear supportive Brassier for 6 weeks.

Activity For smooth implants, displacement exercises and massage were initiated between postoperative day 1 and day 3 or when it does not cause pain. Push implant medially and superiorly (10 pushes three times a day for 1 month, then once daily). Heavy lifting and aerobic activity were restricted for 6 weeks.

Post-operative evaluation was at the outpatient clinic which included early follow up for 1-2 month for evaluation of the operation results and patient satisfaction. The late follow up intervals 3 months and 6 months at which lab investigation was repeated. Photos were taken at each postoperative visit.

Patients were instructed to avoid lifting heavy objects or doing vigorous activity for 4-6 weeks. Remaining suture ends were trimmed about 2 weeks after surgery, and silicon sheet or gel was advised to be used for 3 months to help scars to fade out.

Postoperative follow up was performed as early follow up for 1 month and the late follow after 6 months for evaluation of the procedure and repeating the lab investigations.

Results

In this study we examined serum blood samples of 33 women having silicone breast implantation at Plastic surgery department, Menoufia University Hospital, to determine whether mammary silicone implanted in human females results in a measurable and significant inflammatory and immunological changes .The age of women ranged between 19 years and 55 years with mean age was 34.24 (± 9.63) years. The mean BMI was 28.21± 2.03 Kg/ m^2 and ranged from 24.9 Kg/ m^2 to 32 Kg/ m^2.

The implant pocket was subglandular in 23 women (69.7%) while it was subpectoral in 10 women (30.3%). Regarding type of implant, smooth implant was inserted in 23 women (69.7%) while it was textured type in 10 women (30.3%). The mean volume of the silicone breast implant was 258 ± 21 ml (range = 220-280 ml). A single brand of silicone implant product was used (Sebbin, Paris, France) with various types, shapes and sizes. The incision approach was made at the inframammary fold (IMF) for all patients in this study.

The mean lymphocytic count before silicone breast insertion was 1.95± 0.52×10^9/L that changed to 3.88± 0.92×10^9/L after 6month post-operative. There was significant increase in lymphocytic count postoperative compared to its level preoperative ($p<0.001$), but this increase was still within normal value without clinical manifestations during this time **(Table, 1).**

The mean CRP level before silicone breast implantation, was 0.92± 0.49 that changed to 4.34± 2.33 after 6month post-operative. There was significant increase in CRP postoperative compared to its level preoperative ($p<0.001$) **(Table, 2).** Pre-operative anti-silicone antibody test was done and it was negative and non-significant for all patients at this study. While there was significant increase of anti-silicone antibody levels (6 months post-operative) and the mean level was 0.034± 0.019 and ranged from 0.012 to 0.075 of studied women **(Table, 3).**

The mean anticardiolipin IgG before mammary silicone insertion was 1.72± 0.23 that changed to 5.61±3.21 after 6month post-operative. There was significant increase in anticardiolipin IgG postoperative compared to its level preoperative ($p<0.001$) **(Table, 4).**

The mean anticardiolipin IgM before mammary silicone insertion was 1.75± 0.21 that changed to 3.92± 2.43 after 6month post-operative. There was significant increase in anticardiolipin IgM postoperative compared to its level preoperative ($p<0.001$) **(Table, 5).**

Perioperative complications were limited to one allergic reaction to the antibiotic cephalexin (1st generation cephalosporin), which was discontinued. No infectious or rheumatologic abnormalities were observed. When last examined, all mammary implants were soft, painless, and cosmetically adequate. Careful physical examination showed no evidence of rupture.

Table (1) Distribution of the studied women as per Lymphocytic count before and after mammary silicone insertion.

Description		Studied women					Test value	P-value
		Mean	SD	Median	Min.	Max.		
Lymphocyte (×10^9/L)	Preoperative	1.95	0.52	1.90	1.24	3.50	5.01	<0.001 (HS)
	Postoperative	3.88	0.92	3.90	2.30	7.50		

$p\leq0.05$ is considered statistically significant, $p\leq0.01$ is considered highly statistically significant, SD: standard deviation, analysis done by Wilcoxon signed rank test

Table (2) Distribution of the studied women as per CRP before and after silicone breast implantation.

Description		Studied women					Test value	P-value
		Mean	SD	Median	Min.	Max.		
CRP	Preoperative	0.92	0.49	0.80	0.20	1.90	5.01	<0.001 (HS)
	Postoperative	4.34	2.33	3.80	2.10	15.00		

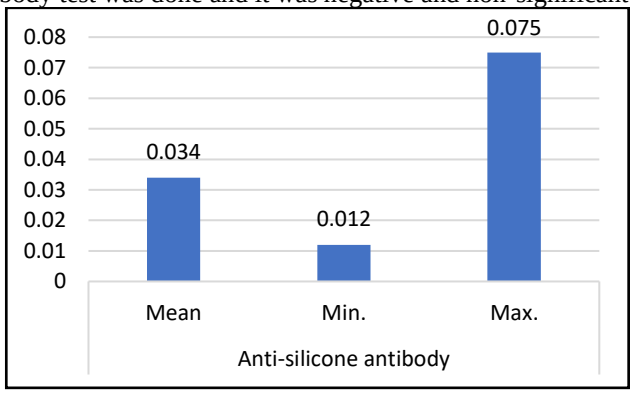
P≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by Wilcoxon signed rank test.

Table (3) Distribution of the studied women as per anti-silicone antibody after 6 months post-operative.

Description		**Studied women**
Anti-silicone antibody (6 month post-operative)	Mean± SD	0.034± 0.019
	Median	0.032
	Range	0.012 – 0.075

SD= standard deviation,

Pre-operative anti-silicone antibody test was done and it was negative and non-significant for all patients at this study.



Graph (1) Mean and range of anti-silicone antibody in the studied women (6 months post-operative).

Table (4) Distribution of the studied women as per anticardiolipin IgG before and after mammary silicone insertion.

Description		**Studied women**					**Test value**	**P-value**
		Mean	**SD**	**Median**	**Min.**	**Max.**		
Anti-cardiolipin IgG	Preoperative	1.72	0.23	1.70	1.10	2.20	5.01	**<0.001 (HS)**
	Postoperative	5.61	3.21	4.60	2.40	12.70		

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by Wilcoxon signed rank test

Table (5) Distribution of the studied women as per anticardiolipin IgM before and after mammary silicone insertion**.**

Description		**Studied women**					**Test value**	**P-value**
		Mean	**SD**	**Median**	**Min.**	**Max.**		
Anti-cardiolipin IgM	Preoperative	1.75	0.21	1.70	1.30	2.30	5.016	**<0.001 (HS)**
	Postoperative	3.92	2.43	2.70	1.80	10.50		

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by Wilcoxon signed rank test

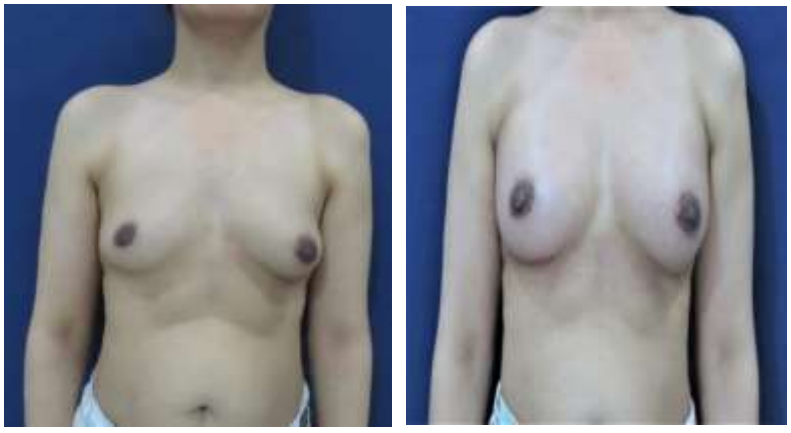


Fig. (2) A case of 43 years old female before and after silicone breast implantation (pre-operative photo at the left and 6 months post-operative photo at the right).

Discussion

Ojo-Amaize et al. (2017) in their prospective study which reported that there was mild to moderate elevation in the levels of lymphocytes in the examined blood serum of female patients after mammary silicone implants insertion **(10).**
In the present study, the mean lymphocytic count before augmentation mammoplasty (pre-operative) was 1.95± 0.52×10^9/L that changed to 3.88± 0.92×10^9/L after 6 month post-operative. There was statistically significant increase in lymphocytic count postoperative compared to its level preoperative ($p<0.001$). But this increase was within normal value without clinical manifestations during this time **(Table, 1).**

In a prospective study by ***Silva et al. (2011)*** that compared CRP before and after 6 months of silicone breast implantation. The results indicated that lymphocytes had mild increase but still within normal levels. While, C-reactive protein (CRP) level pre-operatively was 1.3 ± 1.2 mg/l and after 6 month post-operatively was 4.3 ± 6.4 mg/l. There was statistically significant increase in CRP level **(2).**

Similarly, in our study, pre-operative mean CRP level before silicone breast implantation, was 0.92± 0.49 that changed to 4.34± 2.33 after 6 month post-operative. There was statistically significant increase in CRP level postoperative compared to its level preoperative ($p<0.001$) **(Table, 2).** These results demonstrated that these results indicate the probability of inflammatory reactions related to the silicone breast prosthesis. Findings consistent with systemic inflammation were present in the early postoperative months. After 6 month post-operative, C-reactive protein elevation was not a circumstantial or random finding, as associations that were absent before operation robustly suggested an integrated postoperative pro-inflammatory and pro-coagulatory response. Not only relatively nonspecific correlations were demonstrated, but also with prosthesis volume itself at the 6-month assessment when perioperative trauma could no longer be involved.

Bekerecioglu et al. (2014) in their study, serum blood samples of patients, with silicone breast implants, were sent to a laboratory using ELISA (pre-operatively and after 6 month post-operatively) to detect specific anti-silicone antibody levels. Test results showed that patients with silicone breast implants 6 month post-operatively demonstrated statistically significant elevation in anti-silicone antibodies compared with pre-operative test that was negative. The highest anti-silicone antibody levels were measured in implanted women with either frank implant ruptures or leakage of their silicone gel implants **(3).**

In addition to our study, serum blood samples were examined to detect anti-silicone antibody levels. Preoperative anti-silicone antibody was negative and non-significant for all patients. While, after 6 months post-operatively there was

statistically significant elevation in anti-silicone antibodies. The mean anti-silicone antibody postoperative was 0.034± 0.019 and ranged from 0.012 to 0.075 of studied women **(table, 3)**.

Silva et al. (2011) in their prospective study on women with silicone breast implanted, they examined the serum blood levels to detect anti-cardiolipin IgG and IgM (pre-operative and 6 month post-operative). Their study demonstrated that anticardiolipin IgG and IgM levels increased significantly after 6 month post-operatively in comparison with pre-operative levels **(2).**

In our study, the pre-operative mean anti-cardiolipin IgG was 1.72± 0.23 that changed to 5.61±3.21 after 6 month post-operatively. There was statistically significant increase in anticardiolipin IgG postoperative compared to its level preoperative ($p<0.001$) **(table, 4).** In addition to the pre-operative mean anti-cardiolipin IgM was 1.75± 0.21 that changed to 3.92± 2.43 after 6 month post-operatively. There was statistically significant increase in anti-cardiolipin IgM postoperative compared to its level preoperative ($p<0.001$) **(table, 5).**

On the other hand, ***Peters et al. (2014)*** identified no increase in auto-antibodies in those with silicone implants. They suggest that silicone implants cause a negligible and non-specific foreign body reaction. However, they demonstrated 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 recommended **(9).**

Conclusion

Silicone breast implants act as a foreign body that do lead to a measurable and significant inflammatory and immunological changes consisting of elevated levels of CRP, anti-silicone antibodies and anti-cardiolipin antibodies (IgG and IgM) without association of clinical finding that could be observed. The increasing levels of anti-silicone antibody and other antibodies in implanted patients can be useful to physicians and surgeons who wish to assess the integrity of an implant when rupture is suspected.

The high specificity of anti-silicone antibody test suggests that continuous monitoring of silicone antibody levels in implanted patients on a regular schedule could be used as a screening procedure and as a reliable indicator for suspected implant failure. While, to determine any causative association between silicone implants with autoimmune and connective tissue diseases, further long-term studies are recommended.

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