Clinical Rheumatology (2019) 38:1271–1276
https://doi.org/10.1007/s10067-019-04447-y

ORIGINAL ARTICLE

Silicone breast implants and depression, fibromyalgia and chronic fatigue syndrome in a rheumatology clinic population

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Received: 23 October 2018 / Revised: 6 January 2019 / Accepted: 21 January 2019 / Published online: 31 January 2019

Abstract

Introduction Silicone breast implants (SBI) may induce systemic autoimmune disease as part of autoimmune syndrome induced by adjuvants (ASIA). This syndrome bears similarities to fibromyalgia and chronic fatigue syndrome (CFS). We sought to determine whether there are any associations between SBI and depression, fibromyalgia and CFS in a rheumatology clinic population.

Methods The electronic files of rheumatology clinic patients at the Royal Adelaide Hospital between 2000 and 2017 were searched for patients who had received SBI prior to rheumatological diagnosis. Demographics, diagnosis, implant history and whether the patient had depression, fibromyalgia or CFS were recorded. Controls were rheumatology clinic patients, half of whom had systemic sclerosis (SSc) and the other half had systemic lupus erythematosus (SLE). They were matched to cases 3:1 for age (within 2 years) and gender.

Results Thirty patients had received SBI (mean age 47.9, 100% female). Twelve had a diagnosis of depression, 6 of fibromyalgia and 3 of CFS. Implant rupture was not associated with any of these ($p = 1$). There was no difference in the incidence of depression ($p = 1$), fibromyalgia ($p = 0.76$) or CFS ($p = 0.3$) between cases and SLE controls. When compared with SSc controls, there were significantly more patients with fibromyalgia and/or CFS in the case group (20.0% of cases vs 2.2% of SSc controls, $p = 0.01$) but no difference in depression ($p = 0.12$).

Conclusion Fibromyalgia and CFS are more common in patients with silicone implants than SSc controls but not SLE controls. Prospective study of development of depression, fibromyalgia and CFS in recipients of SBI is required.

Keywords Adjuvants · Breast implants · Chronic fatigue syndrome · Depression · Fibromyalgia · Silicone

Aim

The aim of this study is to determine whether there are any associations between silicone breast implants and mood disorder, fibromyalgia and chronic fatigue syndrome in a rheumatology clinic population.

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Introduction

Silicone is a silicon polymer which was first used in medicine in 1947 as a waterproof wound dressing [1]. At the time, it was considered an ideal substance to use as a synthetic mimic of human tissue because it could be modified to have a similar palpable consistency. Furthermore, it was believed to be inert and biologically stable, resistant to degradation and non-adherent [2].

Soon after, concerns were raised regarding severe localised reactions to silicone injections paralleled by histological findings of phagocytosis of silicone droplets, suggesting that silicone may not be as immunologically inert as initially believed [3]. By 1976, silicone liquid injections had been withdrawn from medical practice [4].

Silicone breast implants continued to be used in the belief that the outer solid membrane would limit exposure

of tissues to silicone. It was noticed, however, that local responses occurred involving breast pain, hardening and the formation of a fibrotic capsule around prostheses [4]. Silicone leakage was also noted to occur even without macroscopic implant rupture [5].

The possibility of an association of systemic illness with silicone breast implants was first published about in 1982, with three case studies of patients who developed autoimmune disease (systemic lupus erythematosus, mixed connective tissue disease and rheumatoid arthritis/Sjögren's syndrome) between 2 and 2½ years after enclosed silicone gel breast implantation [6]. More recently, this phenomenon has been formally proposed to be part of an autoimmune syndrome induced by adjuvants (ASIA), otherwise known as Shoenfeld's syndrome, an umbrella term encompassing post-vaccination phenomenon, macrophagic myofasciitis syndrome, Gulf War syndrome and sick building syndrome [7]. It is, however, an ongoing cause of controversy. A meta-analysis by Janowsky et al. in 2000 included 20 studies examining breast implants and systemic autoimmune disease, and concluded that there was no association [8]. No further formal meta-analyses have been conducted since then, though notably, four systematic reviews published in the last year have supported the existence of silicone-related autoimmune disease as part of ASIA syndrome [9–12].

ASIA has been described with protean manifestations including sicca symptoms, joint stiffness, body aches and unexplained fever [11, 13]. Previously, associations have been demonstrated with a variety of autoimmune diagnoses with a recent large cohort study of 99,993 patients with breast implants by Coroneos et al. finding that the silicone variety were associated with incidence rates double that of the general population for Sjögren's syndrome, scleroderma and rheumatoid arthritis [14]. Another recently published large population-based study found a hazard ratio of 1.45 for a diagnosis of at least one rheumatological condition among women with silicone breast implants compared to those without [15].

At risk populations for ASIA syndrome have been proposed to include patients with prior documented autoimmune reactions to adjuvants, patients with known autoimmune conditions, patients with a history of allergic or atopic disorders and as part of familial/genetic clustering [16]. In particular, Maijers et al. previously reported a high prevalence of pre-existing allergies in women who demonstrate symptoms in keeping with silicone-induced autoimmunity, suggesting that multiple medication allergies or atopy may predispose to autoantibody production to adjuvants [17].

It has previously been observed that ASIA shares many systemic features with fibromyalgia, chronic fatigue syndrome and mood disorders. The non-specific symptoms of these diseases have even been proposed to represent a milder manifestation of the systemic autoimmune phenomena observed in ASIA syndrome [18]. It remains unclear, however, if this inter-related triad of fibromyalgia, chronic fatigue syndrome and depression [19] has any association with silicone breast implants as part of an evolving ASIA syndrome. The aim of this study was to investigate any such associations in a rheumatology clinic population.

Methods

In this retrospective study, the electronic medical files of patients seen in the rheumatology clinic at the Royal Adelaide Hospital between 2000 and 2017 were searched for the following terms: "silicone", "implant", and "augmentation".

We recorded demographic data, rheumatological diagnosis, implant details (indication, date of insertion, whether ruptured or not and date of removal if applicable), comorbidities and allergy profile. In particular, we focused on whether a diagnosis of fibromyalgia and/or CFS had been made. Given the retrospective nature of this study, the degree to which these diagnoses were based on diagnostic criteria or physician judgement was not known.

Patients who had received their breast implants after rheumatological diagnosis/presentation to the rheumatology clinic were excluded.

Controls were also identified from the Royal Adelaide Hospital rheumatology clinic. These were limited to patients with systemic lupus erythematosus (SLE) or systemic sclerosis (SSc) seen between 2000 and 2017 who had not received silicone implants, with an even distribution between the two diagnoses. These conditions were chosen as controls to allow comparison with our case group as they are diseases for which an autoimmune pathophysiology is relatively well understood and further, as these conditions are seen in sufficiently large numbers in our clinic and are also well characterised in our electronic patient records. They were age-matched 3:1 to controls (within 2 years) and were all female. Their medical records were reviewed for the presence of depression, fibromyalgia and/or CFS, as well as allergy profile.

Comparison of cases with controls was performed using Fisher's exact test, comparing cases with the SLE group and the SSc group for the individual diagnoses of depression, fibromyalgia and CFS as well as in combination. Atopy and documented medication allergies were also compared.

Results

During the 18-year period, 30 patients who had previously received silicone breast implants presented with autoimmune disease (mean age 47.9, 100% female). Duration between breast implantation and initial rheumatology clinic presentation was very variable (mean time 16.1 years, range 2–

38 years). Nine had experienced implant rupture with four of these patients undergoing subsequent implant removal. Four other patients underwent implant removal without documented preceding rupture. Rheumatological diagnoses among the 30 patients included SSc ($n = 7$), Sjögren's syndrome ($n = 4$), fibromyalgia ($n = 3$) and rheumatoid arthritis (RA) ($n = 3$) (Table 1). Twelve patients had been diagnosed with depression, six with fibromyalgia and three with CFS. These groups entirely overlapped, with all patients with fibromyalgia and CFS having comorbid depression. Six patients had atopy and medication allergies were documented in five.

Comparing cases with SLE controls ($n = 45$), there was no statistical difference in the incidence of depression, fibromyalgia or CFS (Table 2). Medication allergies were significantly more common in SLE vs cases (55.6% vs 16.7%, $p = 0.0008$, Fisher's exact test).

Comparing cases with the SSc controls ($n = 45$), significantly more cases than controls had a diagnosis of fibromyalgia and/or CFS (20.0% vs 2.2%, $p = 0.01$, Fisher's exact test) (Table 2). There was no statistical difference in atopy or medication allergies between these two groups.

Among patients with silicone breast implants, there was no increased risk of depression, fibromyalgia or CFS among those who had experienced a breast implant rupture compared with those who had not (Table 3).

Discussion

In the present study, we sought to determine whether silicone breast implants in a rheumatology clinic population are associated with one or more features of the inter-related triad of depression, fibromyalgia and CFS. We show that fibromyalgia and CFS are more common in patients with silicone implants than SSc controls but not SLE controls.

Although the prevalence of SSc (233/million population in Australia [20]) is lower than that of RA (6000/million population in Australia [21]), we further show that among recipients of silicone implants, SSc was the commonest rheumatological diagnosis (7/30), being more common than RA (3/30). This skewing in the relative prevalence of these diagnoses towards an over-representation of SSc suggests silicone may play a role in selectively triggering SSc.

The proposed immunologic theories of silicone induced autoimmune inflammation involve both direct specific antigen responses resulting in adaptive immune activation and high levels of IgG antibodies in the silicone implant capsule [22], as well as cross-reactions between silicone molecules and connective tissue components [23]. This pathogenesis is still largely unclear but it has been proposed that silicone particles engulfed by macrophages induce a cascade of inflammatory events since they are unable to be digested by lysosomal enzymes. Cytokines, especially interleukin 1β [15], and reactive oxygen species are overproduced and eventual macrophage lysis releases silicone which can then be taken up by other macrophages to perpetuate the unregulated inflammation [10]. Dysregulation of T cell responses have been found both in local silicone reactions [22] as well as systemically with 60% of patients having a significantly elevated T-helper/T-suppressor ratio in one lymphocyte subpopulation analysis [24]. A significant rate of humoral immunodeficiency (hypogammaglobulinaemia or specific IgG deficiency) has previously been demonstrated in patients with ASIA but whether this represents an adjuvant effect or a susceptibility factor for ASIA development is uncertain [25].

Fibromyalgia is a syndrome of chronic, widespread pain associated with unspecific systemic symptoms including fatigue, sleep disorder, cognitive alteration and mood symptoms [26]. Its pathogenesis is unclear but likely multifactorial resulting in abnormality of pain processing with central sensitisation and pain amplification. There is growing evidence that upregulated inflammation may be part of the fibromyalgia disease process. Cytokine studies have shown increased IL-6, IL-8 and IL-1RA in

Table 1 Cases grouped by rheumatological diagnosis

Rheumatological diagnosis	Number of patients	Mean age (years)	Implants ruptured	Implants removed
lcSSc	7	49.2	3	2
SS	4	57.0	2	3
RA	3	53.3	1	1
Spondyloarthropathy	3	49.7	0	1
Fibromyalgia	3	40.3	1	2
Myositis	2	42.0	1	1
Degenerative joint disease	2	49.0	1	0
SLE	1	36.0	0	0
Miscellaneous	8	46.3	2	2

lcSSc limited cutaneous systemic sclerosis, *RA* rheumatoid arthritis, *SS* Sjogren's syndrome, *SLE* systemic lupus erythematosus

Table 2 Comparison of cases with controls diagnosed with systemic lupus erythematosus (SLE) and systemic sclerosis (SSc)

	Cases ($n = 30$)	SLE (n = 45)	p value*	SSc ($n = 45$)	p value*
Depression	12 (40.0%)	19 (42.2%)	1.0	10 (22.2%)	0.12
Fibromyalgia	6 (20.0%)	7 (15.6%)	0.76	1 (2.2%)	0.01
CFS	3 (10.0%)	1 (2.22%)	0.3	0 (0%)	0.06
FM and/or CFS[#]	6 (20.0%)	8 (17.8%)	1.00	1 (2.2%)	0.01
Depression and/or FM and/or CFS[#]	12 (40.0%)	23 (51.1%)	0.47	10 (22.2%)	0.12
Atopy	6 (20.0%)	3 (6.67%)	0.14	5 (11.1%)	0.33
Medication allergy	5 (16.7%)	25 (55.6%)	0.0008	9 (20.0%)	0.77

FM fibromyalgia, *CFS* chronic fatigue syndrome, *SLE* systemic lupus erythematosus, *SSc* systemic sclerosis

*Compared with cases

[#] Patients with one or a combination of these diagnoses

patients with fibromyalgia [27, 28]. Considering silicone adjuvants, it has previously been postulated that breast implants may represent an initial inflammatory nociceptive stimulus for fibromyalgia development [11] though this remains a matter of debate [29] with some studies even suggesting lower rates of fibromyalgia in these patients [14].

Though CFS has many overlapping characteristics with fibromyalgia, it is currently considered to be a different clinical entity with a central symptom of unremitting, debilitating fatigue [30]. Like fibromyalgia, it has a complex, multifactorial aetiology. Relating to adjuvants, previous investigation has found a temporal (though not causal) association of hepatitis B vaccination induced ASIA and CFS [31]. However, this has not yet been examined with silicone breast implants.

In the present study, fibromyalgia and CFS were found to be similarly represented in the case group with silicone breast implants as in the SLE control group but less common in the SSc controls. It is possible that this represents a common pathophysiological pathway between silicone induced ASIA and SLE which is not shared by SSc but further molecular studies would be required to define this.

Previous investigation into an association between silicone implants and depression has been inconclusive. A diagnosis of breast cancer may well predispose to developing depression [32] though it has also been proposed that reconstruction after surgery is associated with improvement in mood [33]. While Breiting et al. found that psychotropic medication use was higher in patients with silicone breast implants, an association was not found with a diagnosis of depression [34]. It remains controversial if suicide risk is higher in patients who have received breast implants. Coroneos et al. found similar suicide rates between recipients of breast implants and the general population [14]; however, studies focusing only on cosmetic breast augmentation suggest that there is an increased suicide risk in this population [35]. There is a higher prevalence of depression in women who receive cosmetic breast implants [36], perhaps due to body image dissatisfaction and dysmorphia [37].

Table 3 Comparison of patients with ruptured implants and those without

	Depression, FM or CFS	No depression, FM or CFS	Total (n)
Ruptured implant	4 (44.4%)	5 (55.5%)	9
No ruptured implant	8 (38.1%)	13 (61.9%)	21

$p = 1$ (using Fisher's exact test)

FM fibromyalgia, *CFS* chronic fatigue syndrome

It has previously been theorised that implant rupture results in greater exposure to the silicone adjuvant and this has been associated with an increase in diagnoses of both fibromyalgia as well as connective tissue diseases [38]. In the present study, patients with ruptured implants were no more likely to have depression, fibromyalgia or CFS than those without (recognised) implant rupture (Table 3). Interestingly, imaging studies using magnetic resonance imaging (MRI) and ultrasound have demonstrated that implant ruptures are detected more frequently radiologically than clinically suspected [39] though routine MRI follow-up is rare [14]. While instrumentation and trauma are clear risks for rupture, most ruptures appear to be spontaneous and of uncertain aetiology [40]. In addition, age of implant is positively correlated with risk of rupture/leakage [41, 42]. Given that this was a retrospective study, there was also limited data on whether patients experienced clinical improvement after breast implant explantation.

Our results show that there was no increase in atopy in patients with silicone implants compared with controls (Table 2). However, medication allergies were significantly more common in the SLE controls, in keeping with the knowledge that adverse drug reactions, especially to sulphonamides [43] are more common in patients with SLE than other inflammatory arthritides [44].

There are some salient limitations to this study to acknowledge. There is no clear epidemiological data in Australia regarding silicone breast implant prevalence, potentially given

the divide between the public and private healthcare sectors as well as less regulation on implants for augmentative purposes. Consequently, we are unable to comment on the prevalence of silicone implants in a rheumatology clinic population compared to background population prevalence.

A confounding factor is the high background prevalence of fibromyalgia and CFS in our rheumatology patient population. It is well known that patients with chronic diseases including those with rheumatological conditions are at risk for both depression and fibromyalgia, and certainly the high prevalence in our cohort may obscure an ability to detect a difference between the groups.

We also do not have complete information regarding seroconversion rates to autoantibody-positive status following breast implant insertion which may assist in further defining the autoimmune effects of silicone.

Longitudinal studies are required to prospectively evaluate patients undergoing silicone breast implants to determine their risk for autoimmune disease, depression, fibromyalgia and CFS. Clear documentation of mood and pain scores should be undertaken pre-operatively and periodically thereafter to clearly study any possible relationships.

Acknowledgments This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. We would like to extend our gratitude to the patients who have contributed their information to the electronic database of the Royal Adelaide Hospital. All patient identifiers or details that may disclose the identity of patients have been removed.

Compliance with ethical standards

This was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Disclosures None.

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