Autoantibodies Against Autonomic Nervous System Receptors in Women with Silicone Breast Implants: Association with Dry Eyes and Dry Mouth

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ABSTRACT **Background:** Silicone breast implants (SBIs) are associated with subjective and autoimmune related manifestations, ranging from reported symptoms such as depression and fatigue to diseases such as Sjögren's syndrome and systemic sclerosis.

Objectives: To examine whether autoantibodies directed against autonomic nervous system receptors are associated with reported symptoms of dry mouth and eyes in patients with SBIs.

Methods: ELISA assays were used to evaluate a panel of 11 autoantibodies in the sera of patients with SBIs and age-matched healthy controls.

Results: Four autoantibodies (anti-angiotensin II type 1 receptor, anti-β1 adrenergic receptor, anti-muscarinic receptors M2, and anti-muscarinic receptors MR) had significantly lower median titers in SBI recipients who reported dry mouth compared to the control group (9.9 vs. 15.7, $P < 0.001$; 8.8 vs. 23.3, $P < 0.001$; 3.2 vs. 4.7, $P < 0.001$; and 6 vs. 8.8, $P = 0.0011$, respectively). Anti-muscarinic receptor M4 had significantly lower median titers in patients with SBIs who reported dry eyes compared to the control group (5.9 vs. 8.8, $P = 0.0039$).

Conclusions: A dysregulation of the autonomic nervous system in SBI recipients was correlated with the presence of dry mouth and dry eyes. Our results emphasize the need to further investigate the proposed involvement of the autonomic nervous system in subjective symptoms reported by SBI recipients.

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KEY WORDS: autoantibodies, autonomic nervous system, G-protein coupled-receptors (GPCRs), muscarinic receptors, silicone breast implants (SBIs)

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Silicone breast implants (SBIs) have been in use for augmentation and reconstruction for over six decades and remain widely in use today [1]. Despite extensive use and research, immune-related complications of SBIs are unclear. While there are some well-established risks of SBIs, such as ACLC lymphoma and capsular contraction [2], the association of SBIs and higher rates of immune disorders and systemic complaints remains controversial [3].

In the literature, a recent large epidemiologic study demonstrated an increased incidence of several autoimmune disorders in women with SBIs [4]. Moreover, SBIs have been associated with higher levels of systemic and possibly autoimmune-related complaints, such as dry eyes and mouth, cognitive impairment, and myalgias [5]. While a correlation between autoimmune symptoms and syndromes is suggested, the mechanism is unclear.

Functional autoantibodies that target G protein-coupled receptors (GPCRs) of the autonomic nervous system are identified in a range of diseases and can induce intracellular signal transmission and display agonist-like activity [6]. GPCR autoantibodies have also been found in the sera of healthy donors (HD) [6]. Whereas many disorders are characterized by higher levels of GPCR autoantibodies compared with HD, there are several disorders with the opposite association. The sera of patients exhibit lower levels of GPCR autoantibodies compared to HD [6]. These findings demonstrate that dysregulation of GPCR-autoantibodies may contribute to the pathogenesis of autoimmune and immune mediated diseases. However, the mechanistic and causative roles of many of the GPCR autoantibodies have not been established.

Sjögren's syndrome (SS) is one of several autoimmune syndromes that have been associated with a larger relative risk in SBI recipients compared to normative data [4]. The main symptoms of SS are keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth) [7]. The pathogenesis of SS is not completely clear but is postulated to be multifactorial. Autonomic dysfunction may also lead to an exocrine loss of function because of GPCR autoantibodies that antagonize M3R in SS patients. [7].

While SS and SS-like symptoms have been associated with increased prevalence in women with SBIs [4,5], it is unclear whether the pathogenesis in these patients is similar to that of classical SS. Biopsies of glands of a small number of SBI recipients with SS-related symptoms found infiltrates in their glands; however, the cellular composition was different from the characteristic SS infiltrate [8]. Furthermore, it is unknown whether the autonomic dysfunction found in SS patients is present in women with SBIs who reported SS-like symptoms. Our research group previously demonstrated a dysregulation of autoantibodies against GPCRs of the autonomic nervous system in women with SBIs who reported subjective autonomic-related symptoms and found specific autoantibodies to be associated with clinical symptoms of depression, cognitive impairment, and sleep disturbances [9,10].

PATIENTS AND METHODS

PARTICIPANTS

We conducted a single-center, cross-sectional prospective cohort study. Patients were recruited from the Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Israel. Ninety-three females with SBIs were included in the study (median age 41 years). Among the patients, 48 complained of dry mouth and 39 complained of dry eyes. The control group included samples from 36 age-matched healthy females (median age 40.5 years) provided by Magen David Adom, Israel's national emergency pre-hospital medical and blood services organization.

QUANTIFICATION OF CIRCULATING AUTOANTIBODY LEVELS

Levels of anti-adrenergic receptors (α1, α2, β1, β2), anti-muscarinic receptors (M1–M5), anti-endothelin receptor type A, and anti-angiotensin II type 1 receptors were assessed by sandwich ELISA kit (CellTrend GmbH, Luckenwalde, Germany) [10]. The ELISA kits were validated according to the U.S. Food and Drug Administration's Guidance for Industry: Bioanalytical Method Validation.

STATISTICS

A combination of box and violin plots was used to show both number summaries and the full distribution. The normality of data was assessed using the Shapiro–Wilk test. Continuous variables were presented as median (interquartile range) and compared using the Mann-Whitney test. Categorical variables were presented as n (%) and compared using the chi-square test. All tests were two-tailed, and $P < 0.05$ was considered significant. For differences in antibody levels, Bonferroni correction was applied to adjust *P*-values for multiple comparisons. Statistical analyses were performed using R Statistical Software, version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional review board of Sheba Medical Center (approval no: 6619-19-MSC; approval date: 4 March 2020). Informed consent was obtained from all patients involved in the study.

RESULTS

Among the group of participants with SBIs (93 women), 48 (51.6%) reported symptoms of dry mouth [Table 1] and 39 (41.9%) reported symptoms of dry eyes [Table 2].

DRY MOUTH

Levels of autoantibodies against GPCRs of the autonomic nervous system were compared in three groups: women with SBIs who reported dry mouth, women with SBIs who did not report dry mouth, and healthy controls. Of the 11 autoantibodies tested, 4 had significantly lower median titers in women with SBIs who reported dry mouth compared to SBI recipients who did not report dry mouth: AT1R (9.9 vs. 11.3, $P = 0.035$), β1AR (8.8 vs. 10.7, $P = 0.029$), M2R (3.2 vs. 4.9, $P = 0.0032$), and M4R (6 vs. 8.9, $P = 0.0079$). Women with SBIs who reported dry mouth had significantly lower median titers of the same autoantibodies when compared with the control group: AT1R (9.9 vs. 15.7, $P < 0.001$), β1AR (8.8 vs. 23.3, $P < 0.001$), M2R (3.2 vs. 4.7, $P < 0.001$), and MR4 (6 vs. 8.8, $P = 0.0011$). Women with SBIs who did not report dry mouth had significantly lower median titers of AT1R (11.3 vs. 15.7, $P = 0.0058$) and β1AR (10.7 vs. 23.3, $P < 0.001$) compared to the healthy control group [Table 1, Figure 1].

Dry eyes

Levels of autoantibodies against GPCRs of the autonomic nervous system were compared in three groups: wom-

Table 1. Circulating autoantibodies against GPCRs in patients with SBIs who reported dry mouth, patients with SBIs who did not report dry mouth, and healthy patients

	SBI patients with reported dry mouth		SBI patients without reported dry mouth		Controls	
	(n=48)		(n=45)		(n=36)	
	Median	[Q1–Q3]	Median	[Q1–Q3]	Median	[Q1–Q3]
AT1R-Ab	9.9	[8.0–11.4]	11.3	[9.0–17.2]	15.7	[11.8–22.9]
ETAR-Ab	8.3	[6.7–10.3]	9.1	[7.7–13.1]	11.3	[9.4–14.2]
A1-adr-R-Ab	12.7	[9.1–17.7]	14.0	[10.1–18.1]	14.5	[11.1–19.6]
A2-adr-R-Ab	10.9	[9.3–15.6]	12.9	[11.5–16.2]	12.2	[9.1–14.5]
B1-adr-R-Ab	8.8	[6.2–12.2]	10.7	[8.2–19.8]	23.3	[17.2–43.9]
B2-adr-R-Ab	6.3	[3.9–8.5]	8.4	[4.7–10.6]	6.9	[5.1–11.5]
M1R-Ab	2.2	[1.7–3.7]	3.1	[2.2–4.0]	3.0	[2.3–3.9]
M2R-Ab	3.2	[2.2–4.2]	4.9	[3.0–8.1]	4.7	[3.5–8.2]
M3R-Ab	6.2	[4.9–8.9]	7.7	[5.9–9.3]	7.9	[6.4–10.1]
M4R-Ab	6.0	[4.3–8.4]	8.9	[5.3–12.0]	8.8	[6.7–12.5]
M5R-Ab	6.8	[5.2–9.4]	7.2	[5.8–10.7]	6.8	[5.3–9.3]

GPCR = G protein-coupled receptors, SBIs = silicone breast implants

Table 2. Circulating autoantibodies against GPCRs in patients with SBIs who reported dry eyes, patients with SBIs who did not report dry eyes, and healthy patients

	SBI patients with reported dry eyes		SBI patients without reported dry eyes		Controls	
	(n=39)		(n=54)		(n=36)	
	Median	[Q1–Q3]	Median	[Q1–Q3]	Median	[Q1–Q3]
AT1R-Ab	10.5	[8.9–13.3]	10.1	[8.5–15.0]	15.7	[11.8–22.9]
ETAR-Ab	8.7	[7.1–11.2]	8.7	[7.1–11.9]	11.3	[9.4–14.2]
A1-adr-R-Ab	12.6	[10.1–17.9]	13.7	[8.9–18.0]	14.5	[11.1–19.6]
A2-adr-R-Ab	11.5	[9.6–17.8]	12.4	[10.4–15.7]	12.2	[9.1–14.5]
B1-adr-R-Ab	10.1	[6.2–15.2]	9.6	[7.3–17.3]	23.3	[17.2–43.9]
B2-adr-R-Ab	6.8	[4.2–12.1]	6.9	[4.5–9.7]	6.9	[5.1–11.5]
M1R-Ab	2.6	[2.0–4.4]	2.5	[1.8–3.5]	3.0	[2.3–3.9]
M2R-Ab	3.4	[2.4–5.0]	3.9	[2.7–5.6]	4.7	[3.5–8.2]
M3R-Ab	6.9	[5.3–9.7]	7.1	[5.0–8.8]	7.9	[6.4–10.1]
M4R-Ab	5.9	[4.2–8.7]	7.7	[5.3–11.3]	8.8	[6.7–12.5]
M5R-Ab	7.0	[5.1–9.1]	7.4	[5.5–10.6]	6.8	[5.3–9.3]

GPCR = G protein-coupled receptors, SBIs = silicone breast implants

en with SBIs who reported dry eyes, women with SBIs who did not report dry eyes, and healthy controls. Of the 11 autoantibodies tested, one was found to have significantly lower median titers in patients with reported dry eyes compared to women with SBIs who did not report dry eyes: M4R (5.9 vs. 7.7, $P = 0.042$). Women with SBIs who reported dry eyes had significantly lower median titers of M4R compared to the healthy control group (5.9 vs. 8.8, $P = 0.0039$). There was no significant difference in the median titer of M4R between the women with SBIs who did not report dry eyes and the healthy control group ($P = 0.26$) [Table 2, Figure 2].

DISCUSSION

In our study, circulating autoantibodies against GPCRs of the autonomic nervous system correlated with reported symptoms of dry eyes and mouth in women with silicone breast implants. These results correspond with previous research reported by our group, which found autoantibodies against GPCRs to be associated with other autonomic-related symptoms such as memory impairment and sleep disturbance [9,10]. Fifty-one percent and 41.9% of women with SBIs reported symptoms of dry mouth and dry eyes, respectively [Table 1, Table 2]. The association of SBIs with autoimmune related symptoms has been researched extensively in the past, and to this day remains inconclusive [3,5]. Importantly, several recent studies have found SS, or SS-like symptoms of dry mouth and eyes, are associated with SBIs [4].

Of the eleven autoantibodies tested, AT1R, β1AR, M2R, and M4R were significantly dysregulated in women with SBIs who reported symptoms of dry mouth. M4R autoantibody was significantly dysregulated in women with SBIs who reported symptoms of dry eyes. The autonomic nervous system innervates the salivary glands, and parasympathetic muscarinic receptors play a large role in salivary production [11]. Several studies found higher levels of autoantibodies targeting M3R in SS patients. They may play a pathogenic role in the loss of glandular function [7]. However, not all studies found a correlation between M3R and SS, and they were not included in the criteria for diagnosis of SS [12]. Similarly, we did not find a significant correlation between M3R and dry mouth or dry eyes in the current study. In addition, several studies found dysregulation of other autoantibodies, such as those targeting anti-salivary gland protein 1, anti-carbonic anhydrase 6, and anti-parotid secretory protein in patients with idiopathic dry eyes and mouth, as well as in patients with SS [13,14].

Figure 1. Levels of circulating autoantibodies against GPCRs in women with SBIs who reported dry mouth, women with SBIs who did not report dry mouth, and healthy patients

GPCRs = G-protein coupled-receptors, SBIs = silicone breast implants

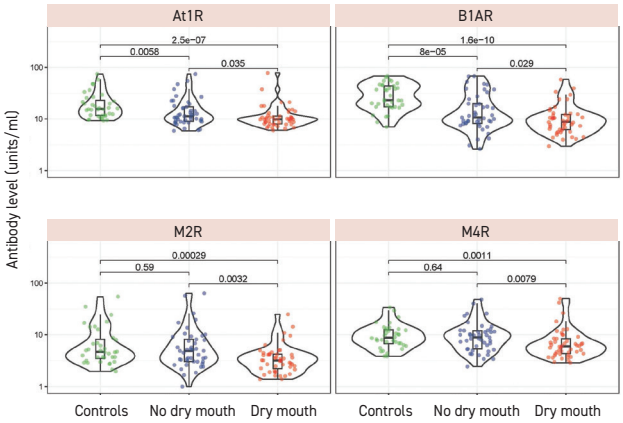
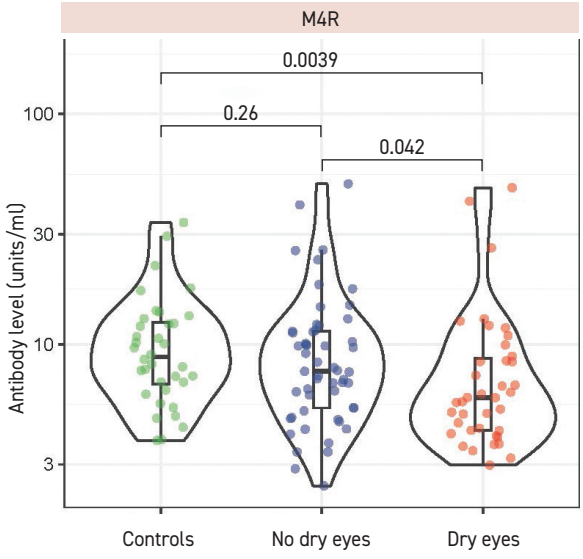


Figure 2. Levels of circulating autoantibodies against GPCRs in women with SBIs who reported dry eyes, women with SBIs who did not report dry eyes, and healthy patients

GPCRs = G-protein coupled-receptors, SBIs = silicone breast implants



Other muscarinic receptors, including M4, may be a factor in salivary mediation [15]. Involvement of the muscarinic receptors in salivation is also demonstrated by the effectiveness of drugs that target muscarinic receptors in treating dry mouth symptoms. The U.S. Food and Drug Administration approved two muscarinic agonist drugs, pilocarpine and cevimeline, for the treatment of dry mouth, and both reduce sicca complaints in patients [16]. Adrenergic β1AR and α1AR are also involved in salivary secretion [17]. Furthermore, the use of β1AR selective and non-selective beta blockers has been associated with dry mouth and eye symptoms, as well as with salivary dysfunction [17,18]. The dysregulation of muscarinic and beta-adrenergic receptors found in our study may be related to autonomic dysfunction and symptoms of dry eyes and mouth.

Notably, our results revealed significantly lower levels of autoantibodies in women with SBIs who reported dry mouth and eyes when compared with controls. These findings contrast the higher levels of autoantibodies commonly found in autoimmune syndromes. However, recent studies have reported finding lower levels of GPCR autoantibodies in several autoimmune diseases compared with healthy controls. For example, rheumatoid arthritis and SS were associated with lower levels of several GPCR autoantibodies including C3Ar1, CXCR3, and CXCR4 [12]. Autoimmune vasculitis was associated with lower levels of anti-C5a GPCR autoantibodies [19]. Moreover, autoantibodies against AGTR1, EDNRA, ADRA1A, ADRB1/2, and CHRM3 were associated with dry mouth and dry eye symptoms in patients with post-COVID syndrome. These symptoms were observed in individuals diagnosed with conditions such as myalgic encephalomyelitis and chronic fatigue syndrome [20]. The negative correlation between autoantibodies and symptoms of dry eyes and dry mouth in patients with SBIs in the current study matches with these recent findings.

It is imperative to consider several limitations in our study. First, there was no information regarding symptoms in the control group. Second, the sample size was small. In addition, the study examined results obtained at a single time point. Long-term studies may help further understand the autonomic dysfunction.

CONCLUSIONS

Our results demonstrate different levels of GPCR autoantibodies in women with SBIs depending on the presence or absence of reported symptoms of dry eyes and dry mouth. Furthermore, there were significant differences in the autoantibody levels of symptomatic women with SBIs compared to healthy controls. These results indicate that there may be an association between symptoms of dry eyes and mouth and dysregulation of the autonomic system in women with SBIs. Future work is necessary to determine whether autoimmune dysautonomia has a pathogenic role in the development of dry mouth and eyes in patients with SBIs.

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Conflict of interest
Harald Heidecke and Kai Schulze-Forster are co-owners of CellTrend GmbH, Luckenwalde, Germany.

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Capsule

Aberrant T follicular helper cells generated by TH17 cell plasticity in the gut promote extraintestinal autoimmunity

Much remains unknown regarding T follicular helper 17 (TFH17) cells commonly found in autoimmune patients. **Fan** et al. previously showed that egress of gut segmented filamentous bacteria (SFB)-induced TFH cells from Peyer's patches (PP) to systemic sites promotes arthritis. The authors found splenic TFH17 cells are gut derived. Functional analyses using fate-mapping mice revealed a c-Maf-dependent and SFB-induced TH17-to-TFH cell reprogramming that dominantly occurs in PPs. Unlike conventional TFH cells, TH17-derived TFH cells are highly migratory and atypically concentrated in the dark zone of germinal centers (GCs). Compared to conventional TFH cells, TH17-derived TFH cells express higher levels of TFH-associated functional molecules and more robustly conjugate with B cells. Gain- and loss-of-function studies demonstrated their dominance in promoting GC B cells and arthritis. Notably, murine gut TH17-derived TFH signatures exist in rheumatoid arthritis patients. Thus, gut T cell plasticity generates atypical, potent TFH cells promoting systemic autoimmunity.

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