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# Autoimmune dysautonomia in women with silicone breast implants

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ABSTRACT

*Importance and objectives:* There is unmet medical need to understand the pathogenic mechanism of the panoply of clinical manifestations associated with silicone breast implants (SBIs) such as severe fatigue, widespread pain, palpitations, dry mouth and eyes, depression, hearing loss etc. We aimed to determine whether autoantibodies against the autonomic nervous system receptors can explain the enigmatic and subjective clinical manifestation reported by women with SBIs.

*Results:* Circulating level of autoantibodies against G protein-coupled receptors (GPCRs) of the autonomic nervous system (adrenergic, muscarinic, endothelin and angiotensin receptors) have been evaluated in symptomatic women with SBIs using an ELISA method. These women with SBIs addressed our clinic due to various subjective and autonomic-related manifestations such as chronic severe fatigue, cognitive impairment, widespread pain, memory loss, sleep disorders, palpitations, depression, hearing abnormalities etc. We report for the first time, a significant reduction in the sera level of anti-β1 adrenergic receptor ($p < 0.001$), anti-angiotensin II type 1 receptor ($p < 0.001$) and anti-endothelin receptor type A ($p = 0.001$) autoantibodies in women with SBIs ($n = 93$) as compared with aged matched healthy women ($n = 36$). Importantly, anti-β1 adrenergic receptor autoantibody was found to significantly correlate with autonomic-related manifestations such as: sleep disorders and depression in women with SBIs.

*Conclusions:* Chronic immune stimulation by silicone material may lead to an autoimmune dysautonomia in a subgroup of potentially genetically susceptible women with SBIs. The appearance of autoantibodies against GPCRs of the autonomic nervous system serve as an explanation for the subjective autonomic-related manifestations reported in women with SBIs.

## 1. Introduction

Environmental factors enhancing immune adjuvant activity are well recognized following exposure to infectious agents, silicone and aluminum salts and have been widely reported as facilitators of animal autoimmune models and human autoimmune disorders [1–6]. Silicone injections and the subsequent use of silicone breast implants (SBIs) for breast reconstruction and breast augmentation have been first reported

*Abbreviations:* SBIs, Silicone breast implants; GPCRs, G protein-coupled receptors; ASIA, autoimmune/inflammatory syndrome induced by adjuvants; AR, Adrenergic receptors; HLA, Human leukocyte antigen.

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around 1960s [6–9]. During the past decades, the safety of SBIs has stirred an intense, highly polarized debate, in the scientific community, concerning their potential to induce an autoimmune diseases and lymphomas [10–19]. Recently, the US food and drug administration (FDA) recommended box warning against SBIs and proposed that breast implant manufacturers should underline the warnings of the risks, including the emergence of breast lymphoma. The complex link between SBIs and autoimmunity can be illustrated by the concept of autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome), which was introduced by our group in 2011 to gather all autoimmune phenomena that emerged following the exposure to an adjuvant stimulation [13,15,20,21]. Indeed, based on the international registry of ASIA syndrome, we recently analyzed 500 subjects exposed to adjuvants and found that polygenic autoimmune diseases, rather than innate or auto-inflammatory, represent the vast majority of the well-defined immune diseases reported under the umbrella of ASIA syndrome [22]. Interestingly, we found that silicone can trigger undifferentiated connective tissue disease (UCTD), systemic sclerosis and fibromyalgia [13,23,24]. Moreover, in a large population-based study, we have demonstrated an association between SBIs and the presence of autoimmune/rheumatic disorders. Sjögren's syndrome, systemic sclerosis and sarcoidosis were the disorders most strongly associated with SBIs. Women with SBIs had increased hazard ratio of 1.45 [95% confidence interval, CI, 1.21–1.73] for being diagnosed with at least one autoimmune/rheumatic disorder in comparison with women without SBIs [25], highlighting the need for further investigation of the antigenic/adjuvant activity of SBIs.

Adrenergic receptors (AR) are a subclass of G protein-coupled receptors (GPCRs). AR mediate their action through the binding of catecholamines. They regulate numerous cellular functions and physiological processes such as vasoconstriction of blood vessels, contraction of smooth muscle, heart rate, renin release and glucose metabolism [26,27]. Muscarinic receptors, another subclass of GPCRs, are the receptor sites for the neurotransmitter of the parasympathetic autonomic nervous system, acetylcholine. Their primary location is on the post-synaptic cell membranes of smooth muscle, cardiac muscle and glandular tissue at the ends of parasympathetic nerve pathways. Muscarinic receptors are therefore responsible for mediating the physiological effects of parasympathetic nerve activity. These responses include; cardiac slowing, contraction of a wide range of smooth muscles (gastro-intestinal tract, detrusor muscle of the bladder, bronchioles, urethra, gall bladder and ducts, iris circular muscle, seminal vesicles and vas deferens), vasodilatation and increased secretion from exocrine glands (salivary glands, mucosal glands of the airways, gastric acid secretion and lachrymal secretion) [27,28]. The binding of angiotensin II to its cognate receptor, angiotensin II type 1 receptor has a significant effect on sympathetic nervous system and mediates cardiovascular effects including: vasoconstriction, aldosterone and vasopressin secretion, enhancing peripheral noradrenergic activity, cardiac hypertrophy and contractility, decreased renal blood flow and renin inhibition and attenuates normal baroflex responses.

We previously reported an increase production of a broad range of classical autoimmune autoantibodies in both asymptomatic and symptomatic women with SBIs, a finding which supports the association of SBI with autoimmunity [29]. In the current study, we wished to understand the mechanisms of the autonomic-related manifestations associated with SBIs. Therefore, we examined the potential appearance of auto-antibodies against GPCRs of the autonomic nervous system such as: adrenergic receptors (α1, α2, β1, β2), muscarinic receptors (M1-M5), endothelin receptor type A and angiotensin II type 1 receptor in the sera of 93 women with SBIs as compared with 36 aged matched healthy control women.

## 2. Methods

### 2.1. Patients recruitment

The manuscript was written and edited according to the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration' [30]. The present study was designed as a single-center, prospective cohort study. All women were recruited from the Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel. They arrived at our clinic since they were symptomatic, suffering from clinical manifestations that they associated with their implants. Control blood samples from healthy women (median age of 40.5 years, IQR 28.5–51) were provided by the Magen David Adom, Israel's National Emergency Pre-Hospital Medical and Blood Services Organization. For all cases, recruitment was systematic: Inclusion criteria were the following: being symptomatic with a history of a breast augmentation procedure (either for cosmetic or reconstruction purposes). Exclusion criteria included having a SBI removed/explanted. One hundred twenty-nine women were eligible and were, as such, enrolled: 93 were with SBIs (72.1%) and 36 were healthy, age-matched controls (27.9%). Among cases, 19 underwent implant for reconstruction (20.4%) and 74 for cosmetic purposes (79.6%),. No dropouts were reported.

Clinical data were collected following an extensive structured interview conducted by a specialist in rheumatology and autoimmunity (HA and YS). The following data were obtained: medical history, age, time from implantation to symptoms, whether the subject had an underlying autoimmune disease, familial history of autoimmune diseases and occurrence of clinical manifestations.

### 2.2. IRB approval/Ethical clearance

The study was approved by the Ethical Committee of the Sheba Medical Center with an approval number of 6619–19-MSC, located at the Sheba Medical Center, Israel. The patients signed a written, informed consent.

### 2.3. Quantification of circulating auto-antibodies levels

Whole blood samples from each subject were allowed to clot at room temperature, and then centrifuged at 2,000 g for 15 min in a refrigerated centrifuge. Serum was purified and stored at −35 °C. The anti-adrenergic receptors (α1, α2, β1, β2), anti-muscarinic receptors (M1-M5), anti-endothelin receptor type A and anti-angiotensin II type 1 receptor autoantibodies were measured in serum samples using a sandwich ELISA kit (CellTrend GmbH Luckenwalde, Germany). The microtiter 96-well polystyrene plates were coated with GPCR. To maintain the conformational epitopes of the receptor, 1 mM calcium chloride was added to every buffer. Duplicate samples of a 1:100 serum dilution were incubated at 4 °C for 2 h. After washing steps, plates were incubated for 60 min with a 1: 20,000 dilution of horseradish-peroxidase–labeled goat anti-human IgG used for detection. In order to obtain a standard curve, plates were incubated with test serum from an anti-GPCR autoantibody positive index patient. The ELISAs were validated according to the FDA's "Guidance for industry: Bioanalytical method validation". The optimal cut-off level for each anti- GPCR autoantibody tests was analyzed using the receiver operating characteristic (ROC) analysis as described previously [31].

### 2.4. Statistical analysis

Normality was assessed by the Shapiro Wilk's test. Continuous variables were presented as median (IQR) and compared using the Mann-Whitney *U* test. For antibody levels, p-values of the differences were adjusted for multiple comparisons using the Bonferroni correction. Categorical variables were presented as count (%) and compared using a

chi-square test. Correlations were calculated using the Spearman's method. All tests used were two-tailed, and $p < 0.05$ was considered statistically significant. Data analysis was performed using R version 4.0.2 (R Core Team, Vienna, Austria).

## 3. Results

### 3.1. Imbalance in circulating level of autoantibodies against autonomic receptors in women with SBIs as compared with healthy women

We wanted to measure changes in the levels of autoantibodies against GPCRs of the autonomic nervous system in women with silicone breast implants as compared to healthy female controls. ELISA tests for a panel of 11 autoantibodies were used: against adrenergic receptors (α1, α2, β1, β2), muscarinic acetyl choline receptors (M1-M5), anti-endothelin receptor type A and anti-angiotensin II type 1 receptor, had been evaluated in the sera of 93 females with SBIs and in 36 aged matched healthy women without SBIs. Interestingly, we found a significant reduction in the sera level of anti-β1 adrenergic receptor ($p < 0.001$), anti-angiotensin II type 1 receptor ($p < 0.001$) and anti-endothelin receptor type A ($p = 0.001$) autoantibodies in women with silicone breast implants as compared with aged matched healthy women (Fig. 1). Notably, we also detected a trend for reduction in circulating level of anti-M2 and anti-M4 in women with SBIs as compared with healthy women controls, but this did not reach a statistical significance (Supp. Table 1).

### 3.2. Clinical symptoms reported by women with silicone breast implants (SBIs)

SBIs were implanted for cosmetic reasons in 74 out of 93 women (79.6%) and for reconstruction purposes in 19 out of 93 women (20.4%) (Supp. Table 2). The median time from SBI implantation to symptom onset in the cosmetic group was 12 (8.0–14.8) years, while median time following a reconstruction procedure was 5 (3.2–7.5) years (Supp. Table 2). The most common clinical symptoms reported by women with SBIs were chronic fatigue (84.7%), widespread pain (62.7%), memory impairment (57.2%), sleep disturbances (56.1%) and dry mouth (51.7%). In addition, 45.1% of patients reported subjective cognitive impairment, 50.6% palpitations, 39.6% depression, 41.8% dry eyes, 39.6% arthralgia, 40.7% hearing abnormalities (hearing loss or tinnitus), 20.9% myalgia, 27.5% vision abnormalities, 36.3% paresthesia, 26.4% hair loss, 16.5% diarrhea, 17.6% skin rash, 12.1% constipation and 24.2% excessive sweating (Supp. Fig. 1). Notably, 45.2% of women with SBIs had a positive familial history of autoimmune disorders.

### 3.3. Circulating anti-β1 adrenergic receptor autoantibody significantly correlated with autonomic-related manifestations in women with SBIs

We found that all the 11 antibodies against the autonomic nervous system highly correlated one with each other (Supp. Fig. 2). The most prominent correlation was found between anti-endothelin receptor type A and anti-angiotensin II type 1 receptor (Spearman's correlation = 0.88). Then, a group separation analysis showed that β1 adrenergic receptor autoantibody is the most important variable capable of separating the SBIs group (red dots) vs. the healthy control women group (blue dots), while all other antibodies were found to be less useful for this separation (Fig. 2). As shown in Fig. 3, correlation analysis revealed that anti-β1 adrenergic receptor autoantibody negatively correlated with a higher number of clinical manifestations compared with all the other autoantibodies. The strongest correlation was found between anti-β1 adrenergic receptor autoantibody and autonomic-related clinical manifestation such as depression (spearman's correlation of −0.3) and sleep disorders (spearman's correlation of −0.3). Interestingly, depression, as compared with the rest of clinical manifestations, was found to negatively correlate with almost all the autoantibodies (10 out of 11). Collectively, these results indicated that an imbalance of circulating level of anti-β1 adrenergic receptor autoantibody might be the strong and important indicator of dysautonomia in women with silicone breast implants.

## 4. Discussion

In the current study, we report for the first time, the appearance of dysautonomia in symptomatic women with silicone breast implants

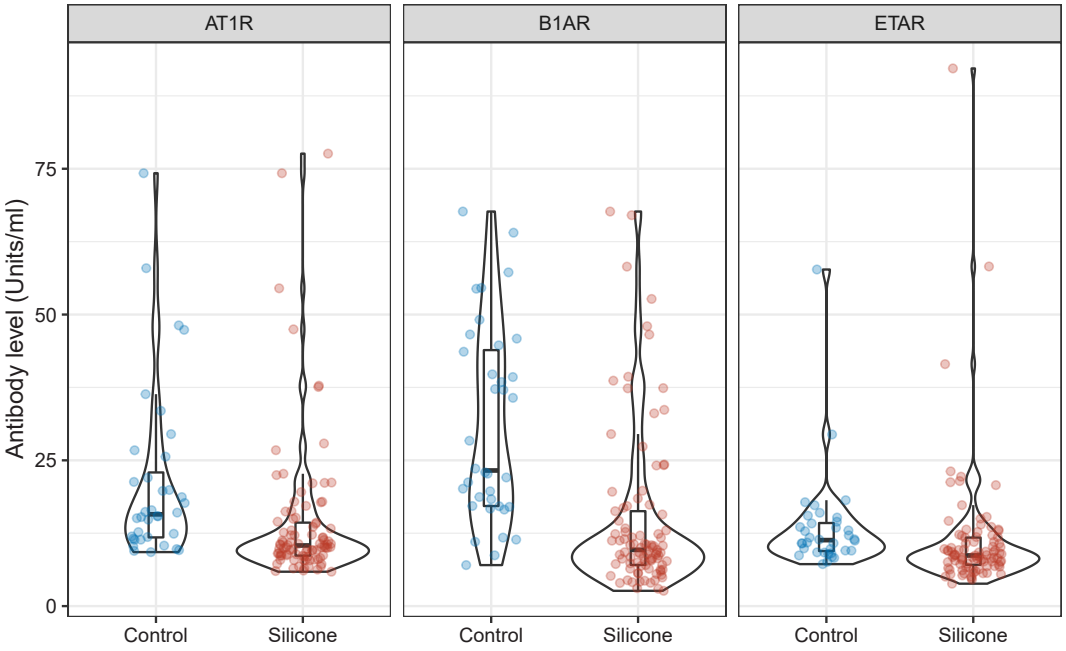


**Fig. 1.** Levels of circulating anti-GPCRs auto-antibodies that were found to be significantly different in women with silicone breast implants (SBIs) after adjusting for multiple comparisons. Individual measurements are shown as dots, summary data as boxplots, and the distributions as violin plots.

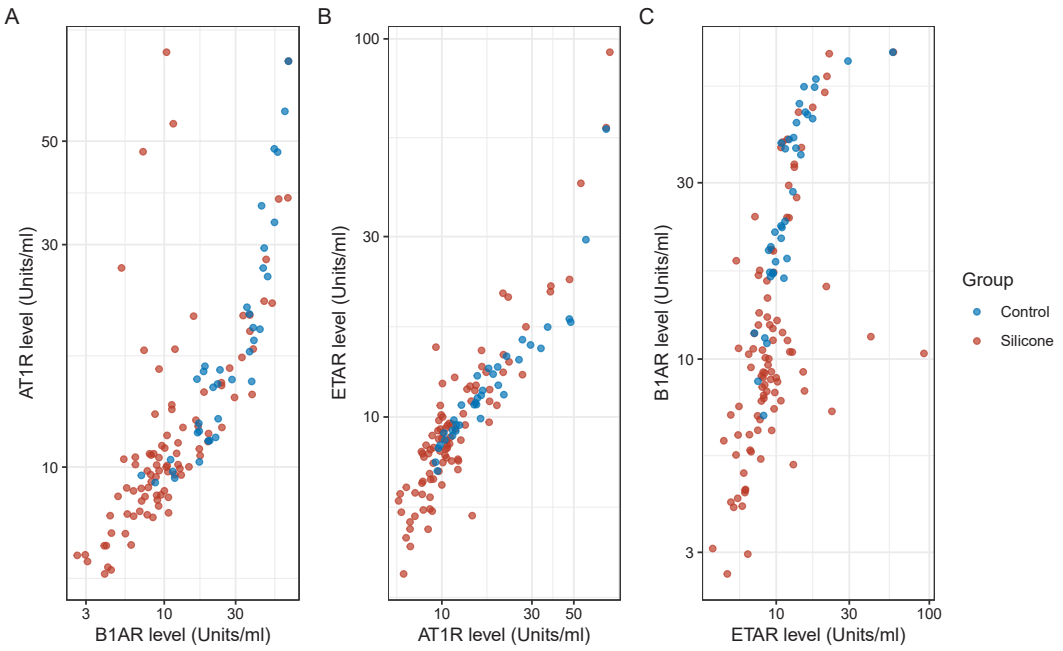


**Fig. 2.** Group separation analysis revealed the importance of anti-β1 adrenergic receptor antibody. Group separation analysis using antibodies titer level. Healthy (blue dots) and women with silicone breast implants (red dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(Supp Fig. 1), accompanied by imbalance in the circulating level of autoantibodies against GPCRs of the autonomic nervous system receptors such as: adrenergic, endothelin and angiotensin receptors (Fig. 1 and Supp. Table 1). Importantly, we found that anti-β1 adrenergic receptor autoantibody might be a strong and important indicator for dysautonomia in women with silicone breast implants (Figs. 1–3 and Supp. Table 1).

Silicone implants have been in use since the mid-twentieth century, especially in the field of reconstructive and cosmetic breast surgery, and have long been considered as biologically inert and harmless [7]. However, a growing body of evidence from the past two decades link silicone with dysregulated immunity and subsequent autoimmune-related complications in both animal and human studies [11–15,25,32–34]. Our group previously found a strong association between SBIs and the development of autoimmune diseases [25]. We also discussed, in a recent review article, the evidence for autoimmunity in women with SBIs and other suspected immune- and dysautonomic-related disorders such as: postural orthostatic tachycardia syndrome, chronic fatigue syndrome and complex regional pain syndrome (all of which are characterized by dysregulated levels of antibodies against GPCRs of the autonomic nervous system) [35]. We believe that chronic hyperstimulation of the immune system by the adjuvant activity of the non-self, silicone material, in a subgroup of potentially genetically susceptible women with SBIs – may lead to development autoimmune disease.

Human leukocyte antigen (HLA) polymorphism has been thoroughly examined and described to be associated with autoimmune diseases [36]. Some HLA alleles have been shown to be associated with autoimmune diseases mediated primarily by autoantigens [37]. Of note, HLA has been suggested to be used as a marker of individuals who are at risk for developing symptoms after exposure to silicone implants (32). Interestingly, the HLA gene was found recently to be associated with the production of antibodies against autonomic receptors such as: α1-AR and β2-AR [38,39].

In the last two decades, evidence has been accumulating indicating a role for functional auto-antibodies against GPCRs such as adrenergic, muscarinic, endothelin and angiotensin receptors (and gene defects in these receptors) in the development of autoimmune disease and other suspected immune- and dysautonomic-related disorders, both in experimental animal models [40,41] and in human patients [38,42–47]. For example, β2-AR signaling was reported to be involved in the pathogenesis and progress of various autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and myasthenia gravis [48], while auto-antibodies against muscarinic acetylcholine receptor M3 has been found to be involved in the progression of Sjögren's syndrome and corresponding mouse models [45,49]. Recently, it was demonstrated for the first time the *in-vivo* role of adrenergic autoantibodies in the pathophysiology of postural orthostatic tachycardia syndrome (POTS). In that study, co-immunization of rabbits with peptides of α1 and β1-adrenergic receptors, led to the production of functional α1AR and β1AR-autoantibodies, and to changes in cardiovascular responses to catecholamines, contributing to the POTS-like phenotypes. Moreover, the effect of these adrenergic autoantibodies was found to be reversed using selective decoy peptide inhibitors [50]. Of note, Scheibenbogen et al. [51], found that immunoadsorption can remove antibodies against β2 adrenergic receptor and lead to clinical improvement in chronic fatigue syndrome. Furthermore, it was found that therapeutic doses of intravenous immunoglobulin (IVIG) provided to patients with autoimmune diseases (Sjögren's syndrome, celiac disease and dermatomyositis) neutralize anti-M3R activity *in-vivo* and improve bladder and bowel symptoms [46,52]. Regarding our observations, we found a significant reduction in the titer of circulating auto-antibodies against adrenergic receptors (β1), anti-endothelin receptor (type A) and anti-angiotensin II (type 1) receptor in women with SBIs as compared with healthy women without SBIs (Fig. 1).

Autoantibodies against the β-1 adrenergic receptors were first described in 1980 to be associated with cardiomyopathy, heart failure and ischemic heart diseases. Imbalance of circulating level of anti-β1 adrenergic receptor autoantibody have been reported in acute coronary syndrome patients. We have preliminary results showing that out of 93 women with SBIs, 47 of them are complain of palpitations and more interestingly few autoantibodies against the autonomic nervous systems receptors in these women have been significantly reduced as compared to women with SBIs who do not suffer from this manifestation (personal manifestations, manuscript in preparation). Importantly, lowered titers of anti-β1 adrenergic receptor in the serum of ACS patients (as compared

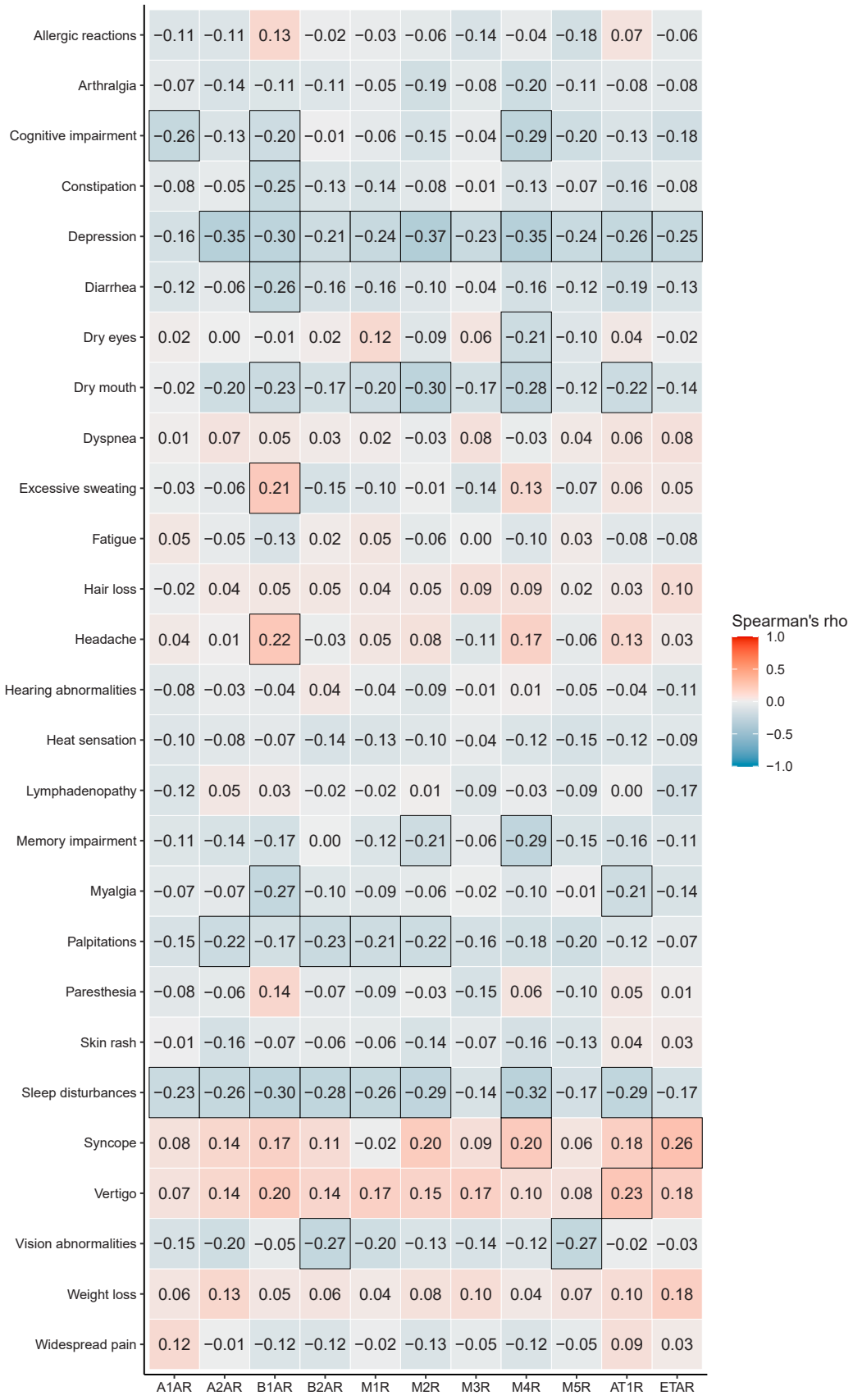


**Fig. 3.** Correlation analysis between clinical manifestation and autoantibodies titer level. Correlation analysis between titer level of every antibody with clinical manifestations reported by women with silicone breast implants (significant correlations are in black rectangle).

to healthy donors) may be associated with a higher risk for re-infraction and worse prognosis [53]. In that study, the authors hypothesized that higher expression of β1 adrenergic receptor in the tissues during and after an acute coronary syndrome, may lead to a high binding of the anti-β1 autoantibodies to these receptors and therefore a decreased level of these antibodies in the circulation. Moreover, recently it was demonstrated that autoantibodies targeting the endothelin receptor type A were significantly reduced in the sera of rheumatoid arthritis patients as compared with healthy donors [47]. Although these studies correlate well with our observations regarding the reduction in circulating level of autoantibodies against the autonomic nervous system in women with silicone breast implants, further mechanistic studies to explore the location of these autoantibodies (and the expression of their cognate receptors) in the tissues are needed. It is worth mentioning that autoantibodies can be found in healthy donors suggesting that they are part of a physiological immune system. Moreover, functional autoantibodies (agonistic or antagonistic antibodies) against GPCRs can activate or inhibit intracellular signaling pathways that are normally triggered by endogenous ligand such as catecholamines etc. Therefore, examination of the potential pathogenic or protective effect of autoantibodies against autonomic receptors *in-vivo* should be deciphered.

Our results showed a significant correlation between anti-β1 adrenergic receptor autoantibody and autonomic-related clinical manifestation such as sleep disturbance and depression (Fig. 3). Notably, β-adrenergic receptors were previously found to trigger melatonin synthesis [54] while beta-blockers have been shown to influence melatonin release by a specific inhibition of β1 adrenergic receptor [55]. These findings suggest that imbalance in the activity of β-adrenoreceptors can affect sleep disorders, a phenomenon which might explain the reported interrupted and unrefreshing sleep by women with SBIs (Supp. Fig. 1). Adrenergic receptors and muscarinic acetylcholine receptors, especially α2AR and M2R respectively, were found to be crucial components in pathologies such as depressive disorders [56,57]. These findings are in line with our correlation analysis showing that depression was found to significantly correlate with almost all the autoantibodies against the autonomic nervous system, especially with α2AR and M2 muscarinic acetylcholine receptors, among others such as anti-β1 adrenergic receptor and anti-M4 muscarinic acetylcholine receptor (Fig. 3).

We also found that the most debilitating manifestation reported by 90.9% of women with SBIs was severe fatigue (Supp. Fig. 1). Severe fatigue is the most common complaint reported among patients with autoimmune diseases, such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), type 1 diabetes, celiac disease and rheumatoid arthritis (RA) [58]. Physiological processes known to play a role in fatigue include oxygen/nutrient supply, metabolism, mood, motivation and sleepiness – all of which are affected by inflammation. It is worth to mention that acute and subsequent chronic inflammation has been already suggested to be associated with silicone breast implants patients [32], and might play a role in the appearance of chronic fatigue in these patients.

It is worth mentioning, that removal of SBIs in symptomatic women was found to improve the clinical pictures of subjects [59,60], while no improvement was found in other subjects, probably as a results silicone infiltration into lymph nodes and other tissues, as already been suggested by our group and others [14,61].

One limitation of our study is the small number of sera from healthy controls (n = 36) used for the measurement of circulating level of autoantibodies against the autonomic nervous system receptors.

## 5. Conclusions

We described here, an autoimmune dysautonomia-related clinical picture of symptomatic women with SBIs. We found significant differences in circulating levels of adrenergic, endothelin and angiotensin receptors autoantibodies in women with silicone breast implants as compared with women without silicone breast implants. In women with silicone breast implants, levels of autoantibodies against autonomic receptors were also correlated with autonomic-related symptoms. These findings suggest that autoantibodies against the autonomic nervous system might play a role in the development of autonomic-related clinical manifestations in women with silicone breast implants, but further studies are indicated. Even though the present study adopted a systematic recruitment from a single-center, we do not know what is the percentage of women who complain of these symptoms in the general healthy women population.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2021.102631.

## Author statement

Gilad Halpert: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Writing - Review & Editing. Abdulla Watad: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Writing - Review & Editing. Avishai M Tsur: Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Visualization, Writing - Review & Editing. Arad Dotan: Methodology, Software, Validation, Data Curation., Hector Enrique Quiros-Lim: Methodology, Software, Validation, Investigation, Resources, Data Curation. Harald Heidecke: Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Writing - Review & Editing. Boris Gilburd: Methodology, Validation, Writing - Review & Editing. Josef Haik: Resources, Investigation, Writing - Review & Editing. Yair Levy: Resources, Investigation, Writing - Review & Editing Miri Blank: Conceptualization, Validation, Visualization Writing - Review & Editing. Howard Amital: Conceptualization, Validation, Writing - Original Draft, Visualization, Supervision, Writing - Review & Editing. Yehuda Shoenfeld: Conceptualization, Validation, Writing - Original Draft, Visualization, Supervision, Funding acquisition, Writing - Review & Editing.

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