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Decreased Use of Anti-Inflammatory Medications in Autoimmune Connective Tissue Disease Patients Following Breast Implant Removal: A National Analysis

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Abstract

Background. Recent case studies demonstrate resolution of rheumatologic symptoms following implant explantation, raising concern around breast implant illness and associated inflammatory symptomatology. In patients with connective tissue disorders (CTD) and breast implants, we quantified the number of anti-inflammatory medications as a proxy for inflammation and disease burden before and after implant removal.

Methods. Using the Clinformatics Data Mart Database, adult female patients from 2003 to 2021 were queried. *Current Procedural Terminology* codes were used to identify patients who underwent implant-based reconstruction and subsequent implant removal. *International Classification of Diseases, Ninth* (ICD-9) and *Tenth Revision* (ICD-10) codes identified patients with CTD. Filled prescriptions of anti-inflammatory drugs were quantified for each patient during the preoperative, perioperative, and postoperative windows surrounding breast implant removal.

Results. Of 1015 patients meeting criteria (mean age 56 ± 12 years), 821 (81%) filled prescriptions during the preoperative window, 753 (74%) filled during the perioperative window, and 735 (73%) filled during the postoperative window. Patients filled significantly fewer postoperative prescriptions than preoperative prescriptions ($P < .001$). Statistically significant predictors of the number of anti-inflammatory prescriptions filled in the postoperative window included additional anti-inflammatory prescriptions filled in the preoperative ($P < .001$) and perioperative ($P < .001$) windows. Experiencing a complication was not associated with the number of prescriptions filled in the postoperative window ($P = .935$).

Conclusions. We found a significant decrease in filled anti-inflammatory prescriptions in patients with known CTD following implant removal, suggesting that breast implant removal may help diminish inflammatory symptomology in predisposed patients.

Introduction

Autoimmune connective tissue disorders (CTD) comprise a spectrum of diseases with variable presentation and epidemiology. These conditions include rheumatoid arthritis (RA), systemic lupus erythematous (SLE), Sjögren's syndrome, systemic sclerosis, dermatomyositis, vasculitis, and many other disorders that implicate unregulated inflammation within connective tissue infrastructure.[1,2] Collectively, autoimmune CTD are prevalent and notably affect women much more often than men.[3]

With a similarly disproportionate impact on women, breast cancer is the most common cause of cancer mortality in women around the world.[4] As such, consideration of the impact of comprehensive breast cancer care on CTD symptomology in women afflicted by both breast cancer and CTD is essential. Breast implants continue to be the mainstay of post-mastectomy breast reconstruction, comprising 81% of all breast reconstruction procedures in 2019.[5] However, surgeons and regulatory entities, including the US Food and Drug Administration, have engaged in discourse about the safety of breast implants, citing reports of breast implant illness (BII) entailing systemic symptoms including joint pain, fatigue, and dermatologic findings.[6] Within this landscape, prior research has reported new autoimmune CTD onset following implant-based reconstruction as well as exacerbation of CTD symptomology in patients with prior CTD history following implant-based reconstruction.[7-11] For example, a landmark 2019 study concluded that patients with silicone breast implants demonstrated CTD rates almost double that of the general population.[12,13]

While the symptomatology of BII is poorly understood, removal of breast implants has been shown to reverse BII in some cases.[11,14-17] Likewise, previous research has speculated that removal of implants in patients with autoimmune CTD may ameliorate disease burden.[18] Amidst controversy about the safety and potentially inflammatory nature of breast implants, the present study utilizes a national claims repository to examine anti-inflammatory prescription patterns of patients with known autoimmune CTD diagnoses undergoing implant removal following implant-based breast reconstruction. We aimed to utilize the quantity of anti-inflammatory medications as a proxy for disease burden prior to and following implant explantation to examine the relationship between breast implants and autoimmune CTD symptomatology on a national scale.

Methods and Materials

Data Source and Study Cohort

Following a previous study involving assessment of breast reconstruction outcomes in patients with autoimmune CTD conducted by a subset of the present paper's authors, an additional retrospective investigation was performed utilizing the ClinformaticsData Mart Database.[19] We used this de-identified claims database to assess demographic and postoperative characteristics of autoimmune CTD patients who underwent implant-based breast reconstruction and subsequent implant removal between January 1, 2003 and March 31, 2021 using *Current Procedural Terminology* (CPT) codes (**Table 1**). The Clinformatics Data Mart Database contains inpatient and outpatient claims, as well as demographic and prescription data, comprising 8,140,311,544 claims involving 69,067,157 unique patients. From this dataset, adult female patients continuously enrolled for 6 months or more prior to and after the index procedures were identified.

Procedure	CPT
Implant-based breast reconstruction	19357, 11970, 19340, 19342
Implant removal	19328, 19330, 19370, 19371
Incision and drainage, deep abscess or hematoma, soft tissues of neck or thorax	21501
Image-guided fluid collection drainage by catheter (eg, abscess, hematoma, seroma, lymphoma, cyst)	10030
Incision and drainage of hematoma, seroma, or fluid collection	10140
Incision drainage of complex wound infection	10180
Secondary closure of surgical wound or dehiscence	13160
Tissue debridement	11042, 11045
Muscle debridement	11043
Bone debridement	11044

Table 1. CPT Codes Used to Identify Procedures in the Clinformatics Database

Diagnosis Claims

Insurance claims data were used to identify the year in which the index procedure was performed, patient age at the time of surgery, patient demographics, comorbidities, CTD diagnoses, and postoperative nonsurgical and surgical complications. As in our previous study, CTD diagnoses were identified using *International Classification of Diseases, Ninth* (ICD-9) and *Tenth Revision* (ICD-10) codes, including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, sarcoidosis, spondyloarthritides, antiphospholipid syndrome, psoriatic arthritis, dermatomyositis, polymyositis, and large, medium, or small vessel vasculitides (**Table 2**).[19] The Elixhauser Comorbidity Index, using ICD-9 (included only if no existing ICD-10 codes) and ICD-10 codes, evaluated comorbidity levels. As in our previous study, the postoperative complications assessed included nonsurgical complications (hematoma, seroma, wound dehiscence, deep vein thrombosis [DVT] or vascular complication, breast reconstruction deformity, postoperative infection, fat necrosis, tissue necrosis, and nonspecified complications of surgical care) and surgical complications (evacuation of hematoma, evacuation of seroma, other fluid collection or drainage, secondary closure of surgical wound or dehiscence, revision of breast reconstruction, tissue debridement, muscle debridement, or bone debridement) (**Tables 1** and **3**).[19,20]

Diagnosis	ICD-9	ICD-10
Rheumatoid arthritis	7140, 7141, 7142	M050, M051, M052, M053, M054, M055, M056, M057, M058, M059, M060, M068, M069
Systemic lupus erythematosus	7100	M320, M321, M3219, M328, M329
Raynaud phenomenon	4430	I7300, I7301
Anti-phospholipid syndrome	28981	D6861, D6862
Systemic sclerosis	7101	M340, M349, M3481, M341, M3482, M3483, M3489
Sjögren's syndrome	7102	M3500, M3501, M3502, M3503, M3504, M3505, M3506, M3507, M3508, M3509
Sarcoidosis	1350	D860, D861, D862, D863, D864, D865, D866, D867, D868, D869
Psoriatic arthritis	6960	L4050, L4051, L4052, L4053, L4054, L4055, L4056, L4057, L4058, L4059
Ankylosing spondylitis	7200	M450, M451, M452, M453, M454, M455, M456, M457, M458, M459
Other spondyloarthritides	7201, 7202, 7208, 7209	M460, M461, M462, M463, M464, M465, M468, M469
Dermatomyositis	7103	M3310, M3311, M3312, M3313, M3314, M3315, M3316, M3317, M3318, M3319
Polymyositis	7104	M3320, M3321, M3322, M3323, M3324, M3325, M3326, M3327, M3328, M3329
Other specified diffuse diseases of connective tissue	7105, 7108, 7109	M351, M352, M358, M359, M368, L948, L949
Large vessel vasculitis (polymyalgia rheumatica, GCA, Takayasus disease)	7250, 4465, 4467	M353, M315, M316, M314
Small/medium vessel vasculitis (Wegener, MP, Goodpasture, Kawasaki, PAN, Churg-Strauss)	4460, 44620, 44621, 44629, 4464	M3130, M3131, M317, M300, M301, M302, M303, M304, M305, M306, M307, M308,
Other vasculitis (TTP, Bechet's disease, HSP, unspecified arteritis)	4466, 1361, 2870, 4476, 4461	M311, M352, D690, I776

Table 2. ICD-9 and ICD-10 Codes Used to Identify Connective Tissue Disorders in the Clinformatics Database

Diagnosis	ICD-9	ICD-10
Hematoma or Hemorrhage	998.12	M79.81, R58, T79.2XXD, T79.2XXXS, T79.2XXA, L76.02, L76.22
Seroma	998.13	M70.98, L76.34, T79.2XXD, T79.2XXS, T79.2XXA
Deep vein Thrombosis or other vascular complication	4510, 4511, 45111, 45119, 4512, 45181, 45189, 4519, 4531, 4532, 4534, 45341, 45342, 45350, 45350, 45351, 45352, 4536, 4538, 45389, 4539, 99779, 9972	T81718D, T81718S, T81718A, T8172XD, T8172XS, T8172XA, I80201, I80202, I80203, I80221, I80222, I80223, I80229, I80231, I80232, I80233, I80239, I80241, I80242, I80243, I80251, I80252, I80253, I80291, I80292, I80293, I80299, I80209, I80249, I80259, I808, I82401, I82402, I82403, I82409, I82431,I82432, I82433, I824Y1, I824Y2, I824Y3, I82439, I824Y9, I82441, I82442, I82443, I82451, I82452, I82453, I82461, I82462, I82463, I82491, I82492, I82493, I824Z1, I824Z2, I824Z3, I82449, I82459, I82469, I82499, I824Z9, I8010, I8011, I8012, I8013, I82411, I82412, I82413, I82419, I80211, I80212,I80213, I80219, I82421, I82422, I82423, I82429,I82621, I82622, I82A11, I82A12, I82A13, I82A19, I82B11, I82B12, I82B13, I82B19, I82C11, I82C12, I82C13, I82C19
Breast reconstruction deformity	8750, 8751, 8790, 8791, 9983, 99832x	T8130XD, T8130XS, T8130XA, T8132XD, T8132XS, T8132XA, T8131XD, T8131XS T8131XA, T8183XD, T8183XS, T8183XA, T8189XD, T8189XS, T8189XA, T8133A, T8133D, T8133S, S21002A, S21001A
Wound dehiscence	875.0, 875.1, 879.0, 879.1, 998.3, 998.32	T81.30XD, T81.30XS, T81.30XA, T81.32XD, T81.32XS, T81.32XA, T81.31XD, T81.31XS, T81.31XA, T81.83XD, T81.83XS, T81.83XA, T81.89XD, T81.89XS, T81.89XA, T81.33A, T81.33D, T81.33S, S21.002A, S21.001A
Postoperative infection	998.5, 998.50–998.59	T81.40XA, T81.40XD, T81.40XS, T81.41XA, T81.41XD, T81.41XS, T81.42XA, T81.42XD, T81.42XS, T81.43XA, T81.43XD, T81.43XS, T81.44XA, T81.44XD, T81.44XS, T81.49XA, T81.49XD, T81.49XS, N61.1, T86.822
Fat necrosis	611.3, 567.82	N641, K654
Tissue necrosis	998.83	T81.89XA
Non-specified complication of surgical care	611.89	T88.8XXD, T88.8XXS, T88.8XXA, N64.89

Table 3. ICD-9 and ICD-10 Codes Used to Identify Complications in the Clinformatics Database

Prescription Data

Pharmaceutical data identified filled anti-inflammatory prescriptions during the study period using generic names (**Table 4**). Patients who filled 1 or more anti-inflammatory prescriptions during the preoperative (180 to 8 days before surgery), perioperative (7 days before to 7 days after surgery), and postoperative (8 to 180 days after surgery) periods were discerned and reported by mean (± standard deviation [SD]).

Generic name
Acetylsalicylic acid, indomethacin, phenylbutazone, meloxicam, piroxicam, tenoxicam, salicylate, nimesulide, celecoxib, rofecoxib, valdecoxib, lumiracoxib, parecoxib, etoricoxib, methotrexate, leflunomide, sulfasalazine, azathioprine, cyclophosphamide, antimalarials, D penicillamine, cyclosporine, hydroxychloroquine, chloroquine, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, infliximab, adalimumab, etanercept, golimumab, certolizumab pegol, diflunisal, acetaminophen, mefenamic acid, meclofenamate, flufenamic acid, ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, tocilizumab, abatacept, anakinra, ustekinumab, rituximab

Table 4. Generic Drug Names Used to Identify Anti-Inflammatory Medications in the Clinformatics Database

Outcomes

The following outcomes were investigated in this study population: (1) filling at least one anti-inflammatory prescription in the preoperative period (180 to 8 days before the index surgery), and (2) the number of anti-inflammatory prescriptions filled in the postoperative period (8 to 180 days following the index surgery).

Covariables and Statistical Analysis

Wilcoxon signed-rank testing was used to assess if individual patients' preoperative anti-inflammatory prescription fills matched, exceeded, or fell short of their postoperative anti-inflammatory prescription fills.

Multivariable logistic regression calculated adjusted odds ratios (OR) for at least 1 anti-inflammatory prescription fill in the preoperative period for each independent variable included in the model with the following covariates: (1) age at surgery (modeled continuously); (2) Elixhauser index (0 or 1, 2, 3, 4+); (3) surgery year (2003-2007, 2008-2012, 2013-2016, 2017-2020); (4) education level (high school diploma or less, less than bachelor's degree, bachelor's degree or more); and (5) race and ethnicity (White, Black, Hispanic, Asian).

Multivariable linear regression calculated average differences in the number of anti-inflammatory prescription fills in the postoperative period attributable to each independent variable in the model with the following covariates: (1) age at surgery (modeled continuously); (2) number of preoperative prescription fills (modeled continuously); (3) number of perioperative prescription fills (modeled continuously); (4) the presence or absence of at least 1 complication associated with the index procedure; (5) Elixhauser index (0 or 1, 2, 3, 4+); (6) surgery year (2003-2007, 2008-2012, 2013-2016, 2017-2020); (7) education level (high school diploma or less, less than bachelor's degree, bachelor's degree or more); and (8) race and ethnicity (White, Black, Hispanic, Asian).

Schapiro-Wilk testing was used to determine whether continuous variables were normally distributed. Wilcoxon signed-rank and multivariate regression testing were used for statistical analysis. *P* values of <.05 were considered statistically significant. All analyses were completed using Stata, version 16.1 (StataCorp LLC).

Results

Utilizing a Wilcoxon signed-rank test, we found that preoperative counts of anti-inflammatory prescription fills significantly exceeded postoperative counts ($z = 4.54$; $P < .001$) (**Figure**). **Table 5** describes the demographic characteristics of the study cohort. The mean age of the cohort was 56 (± 12) years, with 85% of patients identified as White. The mean number of fills for the preoperative, perioperative, and postoperative periods were 59 (± 167), 15 (± 37), and 56 (± 178), respectively. Most patients (58%) experienced 1 or more complications. There were high levels of comorbidities, with 84% of patients having an Elixhauser index score of 4 or higher. Most patients (76%) held less than a bachelor's degree, and 19% of patients held a high school diploma or less. Patients most often came from households with a collective income of $100,000 or higher (42%), whereas 19% of patients belonged to a household with an annual income under $40,000.

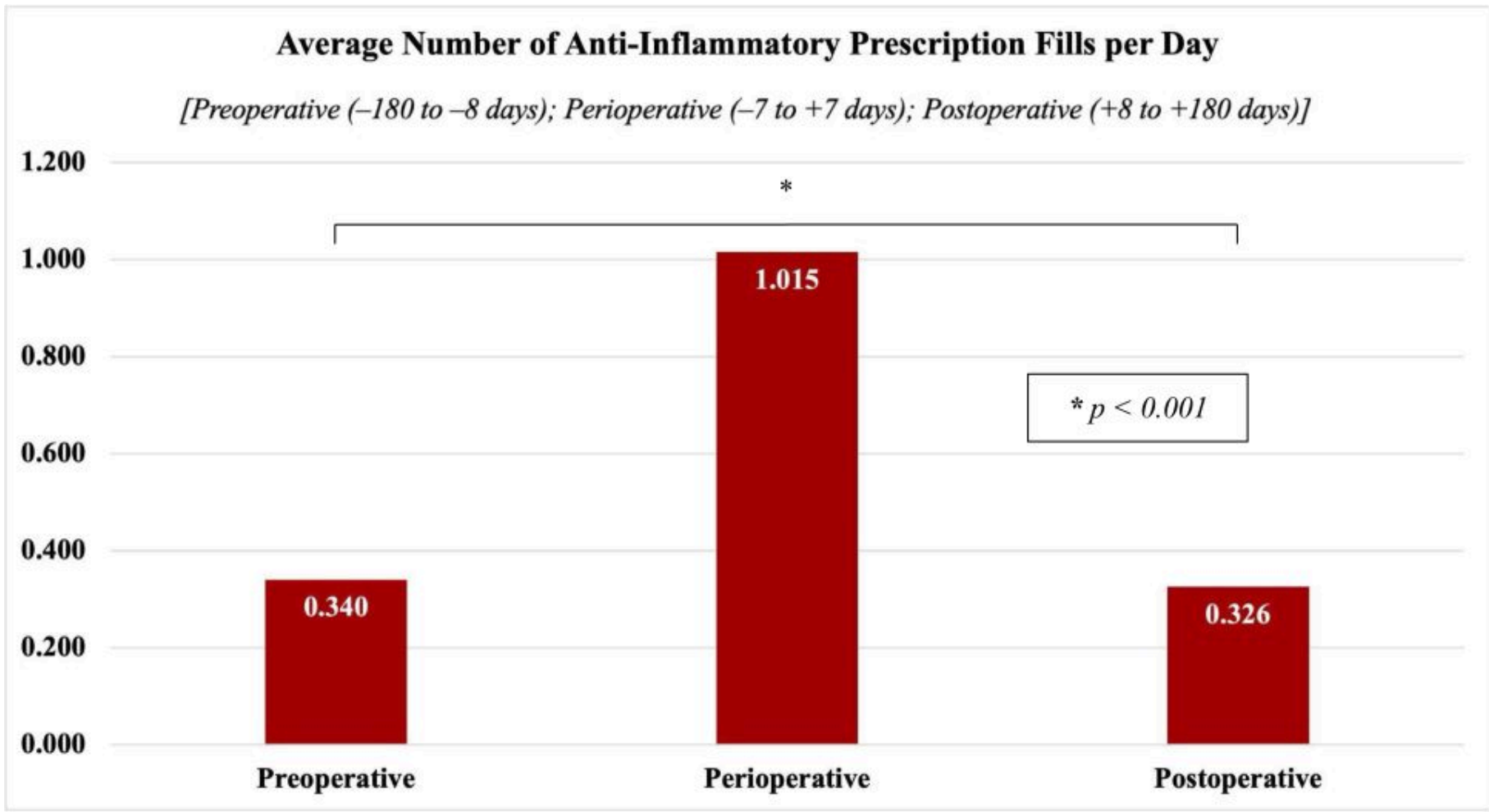

Figure. Average number of anti-inflammatory prescription fills per day in the preoperative period (-180 to -8 days), the perioperative period (-7 to +7 days), and the postoperative period (+8 to +180 days). A Wilcoxon signed-rank test determined that preoperative counts of anti-inflammatory prescription fills significantly exceeded postoperative counts ($z = 4.54$; $P < .001$).

Characteristic	No. (%)
Age at surgery	
Mean (± SD)	56.45 (± 11.56)
Number of preoperative prescription fills	
Mean (± SD)	58.54 (± 166.69)
Number of perioperative prescription fills	
Mean (± SD)	15.23 (± 36.46)
Number of postoperative prescription Fills	
Mean (± SD)	56.02 (± 178.41)
1+ complications associated with the index procedure	
No	465 (42)
Yes	640 (58)
Elixhauser Index	
0 or 1	50 (5)
2	58 (5)
3	71 (6)
4+	926 (84)
Surgery year	
2003-2007	252 (23)
2008-2012	388 (35)
2013-2016	275 (25)
2017-2020	190 (17)
Education Level (n = 1104)	
High school diploma or less	214 (19)
Less than bachelor's degree	625 (57)
Bachelor's degree or more	265 (24)
Household income (n = 430)	
< $40,000	82 (19)
$40,000-$49,000	27 (6)
$50,000-$59,000	30 (7)
$60,000-$74,000	51 (12)
$75,000-$99,000	61 (14)
$100,000+	179 (42)
Race (n = 888)	
White	914 (85)

Black	79 (7)
Hispanic	72 (7)
Asian	16 (1)

Table 5. Characteristics of the Study Cohort (n = 1105).

Patient factors associated with filling at least one prescription in the preoperative period among the patient cohort are described in **Table 6**. Older age was associated with lower odds of filling one or more preoperative prescriptions (OR 0.98; *P* < .001). Relative to those who underwent the index surgery in 2003-2007, those who underwent surgery in 2013-2016 were more likely to fill at least 1 preoperative prescription (OR 1.58; *P* = .028). Those of higher education levels (bachelor's degree or more) were less likely to fill at least 1 prescription preoperatively than those with a high school diploma or less (OR 0.53; *P* = .005). Relative to White patients, Asian patients were less likely to fill a preoperative prescription (OR 0.35; *P* = .040).

Characteristic	**Adjusted OR of filling 1+ prescriptions preoperatively (95% CI)**	***P* value**
Age at surgery		
Mean	**0.976 (0.963-0.989)**	< .001
Elixhauser Index		
0 or 1	1	–
2	1.651 (0.685-3.976)	.264
3	1.234 (0.545-2.797)	.614
4+	1.601 (0.836-3.063)	.155
Surgery year		
2003-2007	1	–
2008-2012	1.272 (0.881-1.836)	.200
2013-2016	**1.584 (1.052-2.385)**	.028
2017-2020	1.432 (0.910-2.252)	.120
Education level		
High school diploma or less	1	–
Less than bachelor's degree	0.819 (0.554-1.213)	.319
Bachelor's degree or more	**0.534 (0.344-0.829)**	.005
Race		
White	1	–
Black	1.192 (0.666-2.133)	.554
Hispanic	1.020 (0.572-1.819)	.947
Asian	**0.347 (0.126-0.951)**	.040

Table 6. Patient Factors Associated With Filling 1+ Prescriptions in the Postoperative Period

Variables associated with average differences in the number of filled postoperative prescriptions are delineated in **Table 7**. Increased postoperative prescription fillings were associated with greater preoperative and perioperative prescription fills (*P* < .001). However, among those patients who filled at least 1 prescription preoperatively, higher education levels (bachelor's degree or more) were associated with increased postoperative prescription fills (*P* = .035).

Characteristic	Average difference in postoperative prescription fills (95% CI)	*P* value
Age at surgery		
Mean	-0.174 (-0.686 to 0.339)	.506
Number of preoperative prescription fills		
Mean	**0.761 (0.711 to 0.812)**	< .001
Number of perioperative prescription fills		
Mean	**0.893 (0.660 to 1.127)**	< .001
1+ complications associated with the index procedure		
No	0	–
Yes	0.494 (-11.376 to 12.364)	.935
Elixhauser Index		
0 or 1	0	–
2	14.148 (-21.506 to 49.802)	.436
3	8.462 (-25.442 to 42.366)	.624
4+	24.647 (-2.428 to 51.723)	.074
Surgery year		
2003-2007	0	–
2008-2012	-5.790 (-21.299 to 9.720)	.464
2013-2016	-16.551 (-33.404 to 0.303)	.054
2017-2020	-2.274 (-20.742 to 16.194)	.809
Education level		
High school diploma or less	0	–
Less than bachelor's degree	11.578 (-3.125 to 26.281)	.123
Bachelor's degree or more	**18.590 (1.345 to 35.835)**	.035
Race		
White	0	–
Black	-0.469 (-22.022 to 21.084)	.966
Hispanic	-20.228 (-42.658 to 2.202)	.077
Asian	-1.967 (-47.897 to 43.963)	.933

Table 7. Patient Factors Associated With Quantity of Prescription Fills in the Postoperative Period

Discussion

Our national claims database study suggests that among patients with an established CTD, removal of breast implants preceded a decrease in postoperative prescription fills of anti-inflammatory medications and thus, by proxy, implant removal may be related to decreased disease burden. Our data elucidates that younger individuals as well as individuals who underwent surgery between 2013 and 2016 were more likely to fill a preoperative prescription. We hypothesize this is due to the increased exposure to social media and the impact advancing technology has on the field of aesthetic reconstructive surgery in recent years.[21] Likewise, our data shows elevated postoperative prescription fills for individuals with higher education levels possibly due to increased patient comprehension regarding symptom management postoperatively.

Breast Implant Illness in the Context of Connective Tissue Disorders

Symptoms relating to breast implant illness involve multiple body systems, including the musculoskeletal, immune, gastrointestinal, integument, psychological, cardiorespiratory, and nervous systems.[16,17] In the current literature, many of these symptoms arising from different body systems relate to CTD; these include arthralgia, arthritis, myalgia, sleep disturbances, autoantibodies onset, miscarriage, chronic fatigue, persistent infections, Raynaud phenomenon, and symptoms of autoimmune diseases such as scleroderma, Sjögren's syndrome, or rheumatoid arthritis.[10,22]

Reports of a relationship between BII and CTD have been documented for many decades, with one 1996 study demonstrating an increased relative risk of CTD in women with breast implants compared with women without breast implants.[15] More recently, this association has sparked renewed interest.[11,13,15,23] As of 2018, Watad et al showed in their

cross-sectional study a strong association between breast implants and CTD such as Sjögren's syndrome and systemic sclerosis.[24] Although multiple studies have investigated the relationship between BII and CTD, a consensus on the existence and strength of the association between these 2 conditions has not been achieved.[25,26]

Alternative views seem to support a more neutral relationship between the 2 variables. Sánchez-Guerrero et al demonstrated no relationship between breast implants and self-reported symptoms of CTD for women with breast implants.[27] This study utilized symptoms reported by the American College of Rheumatology for systemic lupus erythematosus, systemic sclerosis, Raynaud phenomenon, photosensitivity arthritis, morning stiffness, xerostomia, dry eyes, and positive rheumatoid-factor tests. Similarly, Singh et al studied 55,279 women with breast implants over a 5-year follow-up period and concluded no increased risk of CTD when compared with national norms.[28] While the impact of silicone-based implants on systemic inflammation has not been entirely elucidated, the general symptomatology of BII maintains relevance amidst preexisting CTD.

Literature Regarding Symptoms After Implant Removal

The topic of BII is largely limited to case reports, series, reviews, and retrospective cohort studies, which provide a limited level of clinical evidence regarding the relationship between implants and systemic symptoms. For instance, a consistent theme throughout the literature is that of the subjective symptomatology that women with BII experience. Some of the most commonly cited symptoms include fatigue, myalgia, arthralgia, morning stiffness, sicca, alopecia, and night sweats.[17,18,22,29-38] Objective clinical signs noted by physicians included ipsilateral axillary/cervical/inguinal lymphadenopathy, joint swelling/tenderness, and trapezius/paraspinal musculature tenderness.[30-32,39]

Following explantation, the literature appears to justify both the attenuation and persistence of symptomatology. However, the interpretation of these studies requires an understanding of the heterogeneous presentation of symptomatic patients to isolate confounders. On the one hand, vague systemic symptoms, such as those described above, can show overwhelming resolution with explantation, with persistence of results in 50% of explant patients in some cases.[18,22,29-39] Conversely, for those with a diagnosable autoimmune or rheumatologic condition, such as rheumatoid arthritis, systemic lupus erythematosus, or fibromyalgia, the effects of explantation tend to be transient and are difficult to ascertain given the concurrent usage of immunomodulators.[18,22,29,31,32,37] Furthermore, this lack of symptom resolution may relate to the persistence of silicone microparticles within the patient or to chronic sensitization by the immune system.[30-32,39]

Among patients with no history of CTD who report improved symptoms following explantation, duration of implant exposure may play an important role in assessing prognosis or response. Experiencing BII remains rare in the overall patient cohort undergoing implant-based reconstruction. However, in patients with a longer duration of implant exposure, studies demonstrate not only an increased severity of BII symptoms but a lower likelihood of resolution following explantation.[31,32,36] In effect, these findings make early recognition and explantation paramount in preventing progression and decreasing autoantibody sensitization.

Limitations

The Clinformatics Data Mart Database enables a powerful retrospective national depiction of CTD presentation amidst breast implant removal. Even so, we have several notable limitations. First, autoimmune CTD are assessed in this study collectively as a binary variable, but these conditions have important discrepancies in presentation, treatment, and outcomes. Future studies should assess CTD with more granularity to investigate the existence of relationships between breast implants and specific CTD conditions. Second, the Clinformatics warehouse includes information on prescriptions filled by patients, which do not necessarily represent the quantity of anti-inflammatory prescriptions consumed by the patient. Additionally, quantity of anti-inflammatory prescriptions is certainly an imperfect proxy for CTD disease burden. Third, there may be inherent heterogeneity regarding medication use and symptom relief following administration. Additionally, important factors relating to social determinants of health—such as insurance status, transportation, and medication costs—may influence a patient's ability to fulfill prescriptions. However, household income, education level, and race were reported.

Conclusions

Our study demonstrates a potential amelioration of autoimmune CTD disease burden following breast implant removal, given a decrease in filled anti-inflammatory prescriptions post-explantation, relative to pre-explantation quantities. While further research with greater granularity and more patient and physician perspectives is required, our findings may support additional pre-reconstruction consideration of the suitability of breast implants in patients with autoimmune CTD. Additionally, this study's results may substantiate expedited explantation in CTD patients with implants who develop new or worsening symptoms related to chronic inflammation.

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References

1. Fernandez AP. Connective tissue disease: current concepts. *Dermatol Clin.* 2019;37(1):37-48.

2. Sapkota B, Al Khalili Y. Mixed Connective Tissue Disease. In: *StatPearls*. Treasure Island, Florida: StatPearls Publishing; 2021.

3. Gaubitz M. Epidemiology of connective tissue disorders [published correction appears in rheumatology (Oxford) 2008;47(2):234-235]. *Rheumatology* (*Oxford*). 2006;45(Suppl 3):iii3–iii4.

4. Ferlay J, Héry C, Autier P, et al. Global burden of breast cancer. In: Li C, ed. *Breast Cancer Epidemiology*. Springer; 2010.

5. American Society of Plastic Surgeons. 2019 Plastic Surgery Statistics Report. Accessed December 21, 2023. https://www.plasticsurgery.org/documents/News/Statistics/2019/plastic-surgery-statistics-report-2019.pdf.

6. US Food and Drug Administration. Risks and Complications of Breast Implants. Accessed September 18, 2023. https://www.fda.gov/medical-devices/breast-implants/risks-and-complications-breast-implants

7. Levy Y, Rotman-Pikielny P, Ehrenfeld M, Shoenfeld Y. Silicone breast implantation-induced scleroderma: description of four patients and a critical review of the literature. *Lupus*. 2009 Nov;18(13):1226-1232. doi:10.1177/0961203309347795

8. Psarras A, Gkougkourelas I, Tselios K, Sarantopoulos A, Boura P. Systemic sclerosis and silicone breast implant: a case report and review of the literature. *Case Rep Rheumatol*. 2014;2014:809629. doi:10.1155/2014/809629

9. Wronski J, Bonek K, Stanislawska-Biernat E. Scleroderma-like syndrome in a woman with silicone breast implants - case report and critical review of the literature. *Reumatologia*. 2019;57(1):55-58. doi:10.5114/reum.2019.83241

10. Pavlov-Dolijanovic S, Vujasinovic Stupar N. Women with silicone breast implants and autoimmune inflammatory syndrome induced by adjuvants: description of three patients and a critical review of the literature. *Rheumatol Int*. 2017 Aug;37(8):1405-1411. doi:10.1007/s00296-017-3731-4

11. Balk EM, Earley A, Avendano EA, Raman G. Long-term health outcomes in women with silicone gel breast implants: A systematic review. *Ann Intern Med*. 2016 Feb 2;164(3):164-175. doi:10.7326/M15-1169

12. Nava MB, Catanuto G, Rocco N. Comment on "US FDA Breast Implant Post Approval Studies. Longterm Outcomes in 99,993 Patients". *Ann Surg*. 2019 Aug;270(2):e63. doi:10.1097/SLA.0000000000003294

13. Coroneos CJ, Selber JC, Offodile AC 2nd, Butler CE, Clemens MW. US FDA breast implant postapproval studies: long-term outcomes in 99,993 patients. *Ann Surg*. Jan 2019;269(1):30-36. doi:10.1097/SLA.0000000000002990

14. Edworthy SM, Martin L, Barr SG, Birdsell DC, Brant RF, Fritzler MJ. A clinical study of the relationship between silicone breast implants and connective tissue disease. *J Rheumatol*. 1998 Feb;25(2):254-260.

15. Hennekens CH, Lee IM, Cook NR, et al. Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. *JAMA*. 1996 Bef 28;275(8):616-621.

16. Wolfe F, Anderson J. Silicone filled breast implants and the risk of fibromyalgia and rheumatoid arthritis. *J Rheumatol*. 1999 Sep;26(9):2025-2028.

17. Maijers MC, de Blok CJ, Niessen FB, et al. Women with silicone breast implants and unexplained systemic symptoms: a descriptive cohort study. *Neth J Med*. 2013 Dec;71(10):534-540.

18 Suh LJ, Khan I, Kelley-Patteson C, Mohan G, Hassanein AH, Sinha M. Breast implant-associated immunological disorders. *J Immunol Res*. 2022 May 4;2022:8536149. doi:10.1155/2022/8536149

19. Rowley MA, Thawanyarat K, Shah JK, et al. A recent national analysis of breast reconstruction outcomes in patients with underlying autoimmune connective tissue diseases. *Eur J Plast Surg* 2023;46:551-561. .20. Shah JK, Lipman K, Pedreira R, Makarewicz N, Nazerali R. The impact of oncoplastic reduction on initiation of adjuvant radiation and need for re-excision. *Ann Plast Surg* 2022;89(6):e11-e17. doi: 10.1097/SAP.0000000000003313

21. Sergesketter AR, Lam S, Broadwater G, et al. Which factors are important to women when choosing a breast reconstruction surgeon? *Plast Reconstr Surg*. 2022 Jul 1;150(1):38-45. doi:10.1097/PRS.0000000000009194

22. de Boer M, Colaris M, van der Hulst R, Cohen Tervaert JW. Is explantation of silicone breast implants useful in patients with complaints? *Immunol Res*. 2017 Feb;65(1):25-36. doi:10.1007/s12026-016-8813-y

23. Magnusson MR, Cooter RD, Rakhorst H, McGuire PA, Adams WP, Jr., Deva AK. Breast implant illness: a way forward. *Plast Reconstr Surg*. 2019 Mar;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):74S-81S. doi:10.1097/PRS.0000000000005573

24. Watad A, Rosenberg V, Tiosano S, et al. Silicone breast implants and the risk of autoimmune/rheumatic disorders: a real-world analysis. *Int J Epidemiol*. 2018 Dec 1;47(6):1846-1854. doi:10.1093/ije/dyy217

25. Rohrich RJ, Kaplan J, Dayan E. Silicone implant illness: science versus myth? *Plast Reconstr Surg*. 2019 Jul;144(1):98-109. doi:10.1097/PRS.0000000000005710

26. Hortolam JG, Carvalho JF, Appenzeller S. Connective tissue diseases following silicone breast implantation: where do we stand? *Clinics (Sao Paulo)*. 2013;68(3):281. doi:10.6061/clinics/2013(03)e01

27. Sanchez-Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, Liang MH. Silicone breast implants and the risk of connective-tissue diseases and symptoms. *N Engl J Med*. 1995 Jun 22;332(25):1666-1670. doi:10.1056/NEJM199506223322502

28. Singh N, Picha GJ, Hardas B, Schumacher A, Murphy DK. Five-year safety data for more than 55,000 subjects following breast implantation: comparison of rare adverse event rates with silicone implants versus national norms and saline implants. *Plast Reconstr Surg*. 2017 Oct;140(4):666-679. doi:10.1097/PRS.0000000000003711

29. Cohen Tervaert JW, Colaris MJ, van der Hulst RR. Silicone breast implants and autoimmune rheumatic diseases: myth or reality. *Curr Opin Rheumatol*. 2017 Jul;29(4):348-354. doi:10.1097/BOR.0000000000000391

30. Vasey FB, Havice DL, Bocanegra TS, et al. Clinical findings in symptomatic women with silicone breast implants. *Semin Arthritis Rheum*. 1994 Aug;24(1 Suppl 1):22-28. doi:10.1016/0049-0172(94)90106-6

31. Peters W, Smith D, Fornasier V, Lugowski S, Ibanez D. An outcome analysis of 100 women after explantation of silicone gel breast implants. *Ann Plast Surg*. 1997 Jul;39(1):9-19. doi:10.1097/00000637-199707000-00002

32. Spit KA, Scharff M, de Blok CJ, Niessen FB, Bachour Y, Nanayakkara PW. Patient-reported systemic symptoms in women with silicone breast implants: a descriptive cohort study. *BMJ Open*. 2022 Jun 9;12(6):e057159. doi:10.1136/bmjopen-2021-057159

33. Colaris MJL, de Boer M, van der Hulst RR, Cohen Tervaert JW. Two hundreds cases of ASIA syndrome following silicone implants: a comparative study of 30 years and a review of current literature. *Immunol Res*. 2017 Feb;65(1):120-128. doi:10.1007/s12026-016-8821-y

34. Wee CE, Younis J, Isbester K, et al. Understanding breast implant illness, before and after explantation: a patient-reported outcomes study. *Ann Plast Surg*. 2020 Jul;85(S1 Suppl 1):S82-S86. doi:10.1097/SAP.0000000000002446

35. Cuellar ML, Gluck O, Molina JF, Gutierrez S, Garcia C, Espinoza R. Silicone breast implant--associated musculoskeletal manifestations. *Clin Rheumatol*. 1995 Nov;14(6):667-672. doi:10.1007/BF02207934

36. Misere RML, van der Hulst R. Self-reported health complaints in women undergoing explantation of breast implants. *Aesthet Surg J*. 2022 Jan;42(2):171-180. doi:10.1093/asj/sjaa337

37. Hoa S, Milord K, Hudson M, Nicolaidis SC, Bourre-Tessier J. Risk of rheumatic disease in breast implant users: a qualitative systematic review. *Gland Surg*. 2021 Aug;10(8):2557-2576. doi:10.21037/gs-21-266

38. Katsnelson JY, Spaniol JR, Buinewicz JC, Ramsey FV, Buinewicz BR. Outcomes of implant removal and capsulectomy for breast implant illness in 248 patients. *Plast Reconstr Surg Glob Open*. 2021 Sep 7;9(9):e3813. doi:10.1097/GOX.0000000000003813

39. Thomas WO 3rd, Harper LL, Wong SW, et al. Explantation of silicone breast implants. *Am Surg*. 1997 May;63(5):421-429.