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The presence of gastroesophageal reflux disease increases the risk of developing postoperative shoulder stiffness after arthroscopic rotator cuff repair

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Background: Postoperative shoulder stiffness (SS) after arthroscopic rotator cuff (RC) repair has been reported with a variable incidence, and numerous preoperative risk factors have been described. This prospective study aimed to document the incidence of postoperative SS and to evaluate the role of preoperative risk factors in the development of this complication, with a special focus on the role of gastroesophageal reflux disease (GERD).

Methods: Preoperative risk factors for SS were prospectively evaluated in 237 consecutive patients undergoing arthroscopic single-row RC repair. The presence of GERD was evaluated with the GerdQ diagnostic tool. Postoperative SS was diagnosed according to the criteria described by Brislin et al in 2007.

Results: The incidence of postoperative SS was 8.02%. The presence of GERD was significantly associated with the development of postoperative SS (odds ratio [OR], 5.265; 95% confidence interval [CI], 1.657-1.731; $P = .005$). Older age (OR, 0.896; 95% CI, 0.847-0.949; $P < .001$), male sex (OR, 0.126; 95% CI, 0.0252-0.632; $P = .012$), and number of pregnancies (OR, 0.47; 95% CI, 0.228-0.967; $P = .040$) emerged as protective factors.

Conclusions: The presence of GERD significantly influences the development of postoperative SS after arthroscopic single-row RC repair. An underlying aspecific proinflammatory condition, characterized by increased expression of tumor necrosis factor α and transforming growth factor β, and disorders in retinoid metabolism are hypotheses that could explain this previously unknown association.

Informed consent was obtained from all participants included in the study. All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the regional ethical committee (no. 123/2017; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy).

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The documented incidence of postoperative SS falls within previously reported ranges, with women being significantly more affected than men.

Level of evidence: Level II; Prospective Cohort Design; Treatment Study

Keywords: Shoulder stiffness; arthroscopy; range of motion; complication; rotator cuff; gastroesophageal reflux disease

Shoulder stiffness (SS) is defined as a painful restriction in active and passive glenohumeral joint range of motion (ROM), and its occurrence after shoulder arthroscopy for rotator cuff (RC) repair has been reported with a variable incidence in the literature.[2,22] Numerous risk factors for both primary and secondary SS have been described, and different possible etiologies have been reported for postoperative SS, which is considered a subgroup of secondary SS.[13,20] However, few studies have been specifically designed to investigate how preoperative conditions may affect the incidence of postoperative SS.[4] Furthermore, a recent publication described, for the first time, a possible role of gastroesophageal diseases in increasing the risk of postoperative SS development—even though this study had a retrospective design, as well as an unspecific primary goal, and subsequently, limited statistical power.[14] This association was never reported in the literature before, and to confirm or deny it could have relevant clinical implications. The goals of this study were to document the incidence of postoperative SS in a cohort of consecutive patients who underwent shoulder arthroscopy for single-row RC repair and to evaluate the role of preoperative risk factors in the development of postoperative SS, with a special focus on evaluating whether the presence of gastroesophageal reflux disease (GERD) is associated with the development of postoperative SS.

Materials and methods

Study design

The primary aim of this study was to test the hypothesis that the presence of GERD would be associated with a higher rate of postoperative SS after arthroscopic single-row RC repair. The secondary goals were to document the incidence of postoperative SS and to evaluate the role of other previously described preoperative conditions as risk factors in the development of postoperative SS after arthroscopic RC repair.

Prior to study initiation, a literature review was performed to identify the preoperative risk factors possibly involved in the development of SS. After the literature review, the following factors were selected for investigation: age, body mass index, sex, dominant side, smoking habits, diabetes mellitus, hypertension, GERD, chronic obstructive pulmonary disease, anxiety or depressive disorders, hyperthyroidism, hypothyroidism, dyslipidemia, and hypercholesterolemia. For female patients, specific attention was paid to menarche age, menopausal age, pregnancies, miscarriages, and treatment with any hormonal therapy.

Furthermore, previous publications were consulted to select a suitable set of criteria to define the presence of postoperative SS among the numerous available criteria.[2] The criteria described by Brislin et al[5] were selected for this study because they refer to a fixed postoperative follow-up time point, provide a rigorous and reproducible definition of each item, and do not consider patient satisfaction as a rule-out criterion, which is expected to reduce the number of false-negative results. These criteria are reported in Table I.

Enrollment and preoperative evaluation

Patients referred to our institution to undergo surgery for arthroscopic RC repair of degenerative posterosuperior RC tears were assessed for eligibility. The preoperative exclusion criteria were a history of trauma and the presence of unequivocally diagnosed concomitant disorders of the shoulder, including glenohumeral arthritis, fracture, osteonecrosis, or infection. The intraoperative exclusion criteria were the presence of an isolated subscapularis tear and the use of a double-row repair technique.

The presence of the aforementioned risk factors was evaluated with a detailed and targeted patient medical history supported by evaluation of the clinical records. The preoperative presence of GERD was evaluated with a specific diagnostic tool, the GerdQ questionnaire.[23] This is a patient-centered, self-assessment questionnaire developed in a large international study performed in a primary care population presenting with upper gastrointestinal symptoms. The GerdQ tool has a diagnostic accuracy similar to that of a gastroenterologist supported by endoscopy and esophageal pH monitoring and is therefore recommended to diagnose GERD without initial specialist referral or endoscopy.[23]

Operative and perioperative procedures

Surgery was performed with the patient under sedation and a brachial plexus block in the lateral decubitus position, with the upper limb kept at about 30° of abduction and 30° of flexion. Diagnostic arthroscopy was performed from standard posterior, midglenoid, and lateral portals; the size of the tear was classified according to the Southern California Orthopedic Institute classification.[54] The tendon was repaired by use of double- or triple-loaded suture anchors (Super Revo FT and ThRevo FT; ConMed, Utica, NY, USA). A standard single-row suture anchor repair was performed in all included patients. Acromioplasty was performed with the Sampson cutting block technique in patients with type 2 or 3 acromial morphology according to the classification of Bigliani et al.[3] All the patients were operated on by a single surgeon (P.S.R.).

Pantoprazole (40 mg) was administered once a day postoperatively for 20 days to all patients, as part of the institution's

Table I Diagnostic criteria for postoperative shoulder stiffness, adapted from Brislin et al[5]

Presence of one of following deficits for ≥90 d postoperatively
Total passive external rotation with arm at side < 10°
Total passive external rotation with arm in 90° of abduction < 30°
Total passive forward flexion < 100°

standardized internal protocols. Patients were discharged the day after the operation wearing a sling (Ultrasling II; Don Joy, Carlsbad, CA, USA) and were instructed to wear the sling day and night for 28 days; they were allowed to remove the sling to eat and to perform personal hygiene and early self-assisted light passive ROM exercises, as well as mobilization of the elbow and scapulothoracic joint. From the 29th day, patients began formal passive rehabilitation assisted by a dedicated physical therapist to recover the full ROM of the shoulder joint and began active training once satisfactory passive ROM was reached. From the end of the second month, the main focus of physical therapy was to regain full muscle strength.

Postoperative evaluation

As part of the institution's standardized protocols after arthroscopic rotator cuff repair, routine clinical evaluation was scheduled 1, 3, and 6 months after surgery. Follow-up was extended beyond this time point only for symptomatic patients. Postoperative SS was diagnosed according to the criteria described by Brislin et al,[5] when one of the following was present (Table I): total passive external rotation with the arm at the side < 10°, total passive external rotation with the arm in 90° of abduction < 30°, or total passive forward flexion < 100°. The diagnosis of stiffness was made only when these motion deficits persisted for ≥90 days postoperatively.[5]

In patients in whom postoperative SS was diagnosed, recommendations to reduce pain-generating rehabilitation exercises were given, in addition to encouragement to perform physiotherapist-assisted mobilization, stretching, and exercises for deltoid and rotator cuff activation, always outside the pain range and associated with deep myofascial massage. Furthermore, according to SS severity and patients' comorbidities, cortisone therapy was initiated, either as up to 3 injections of 40 mg of triamcinolone acetonide or as oral therapy with methylprednisolone (8 mg/d for 4 days, followed by 4 mg/d for 15 days and then 4 mg every second day for 30 days, associated with the prolongation of pantoprazole coverage for 60 days).

Statistical analysis

A power analysis prior to study initiation indicated that a minimal sample size of 236 patients was sufficient to test the hypothesis that the prevalence of GERD is double among the patients in whom SS develops compared with those in whom SS does not develop, assuming a prevalence of GERD in the overall European population of 15%[46] and an incidence of postoperative SS of 10%.[5] Statistical analysis (A.M.) was performed using GraphPad Prism software (version 6.0; GraphPad Software, San Diego, CA, USA). Continuous variables were expressed as mean ± standard deviation or median (first quartile–third quartile) as appropriate. The Shapiro-Wilk normality test was used to evaluate the normal distribution of the sample, and if the null hypothesis of this test could not be rejected, the nonparametric Mann-Whitney test (U test) was applied for the analysis of the samples. Variables with a Gaussian distribution were analyzed with the Student t test. Categorical variables were expressed as numbers of cases and frequencies; their differences were tested using with the χ^2 test or Fisher exact test.

Variables significant on univariate analysis were inserted in a multivariate logistic regression model to correct for confounding, avoid multiple test correction, and estimate multivariate odds ratios (ORs) to evaluate the association between covariates and postoperative SS. For all analyses, the significance level was set at $P < .05$.

Results

Four hundred four patients were considered eligible, and 237 patients were included in the final analysis. A flow diagram illustrates the grouping and flow of patients in our clinical study (Fig. 1). Patient demographic characteristics are reported in Table II.

The incidence of postoperative SS in the study population was 8.02% (95% confidence interval [CI], 4.90%-12.24%), and all but 2 patients in whom postoperative SS was diagnosed were women ($P = .0005$) (Table II). Age at surgery was significantly lower in the population with postoperative SS ($P = .0051$).

Univariate analysis of the whole study population (Table III) revealed a significant association between the development of postoperative SS and the presence of GERD ($P = .0026$), as well as the presence of anxiety or depression ($P = .0305$). A multivariate logistic regression model could confirm GERD (OR, 5.265; 95% CI, 1.657-1.731; $P = .005$) and number of miscarriages (OR, 4.002; 95% CI, 1.154-13.887; $P = .029$) as significant risk factors associated with the development of postoperative SS, whereas older age (OR, 0.896; 95% CI, 0.847-0.949; $P < .001$, male sex (OR, 0.126; 95% CI, 0.0252-0.632; $P = .012$), and number of pregnancies (OR, 0.47; 95% CI, 0.228-0.967; $P = .040$) emerged as protective factors (Table IV, Fig. 2).

No statistically significant associations were found between the presence of any of the other examined potential risk factors and postoperative SS. Of the 19 patients in whom postoperative SS developed, only 5 (26%) presented with complete remission of the symptoms at 6 months postoperatively. At 1 year after surgery, all but 2 of the initially symptomatic patients fully recovered. SS was treated with appropriate modifications of the rehabilitation protocol combined with oral or intra-articular corticosteroid administration in 79% of the symptomatic cases.

Discussion

The most relevant finding of this study was that patients affected by GERD are at higher risk of postoperative SS

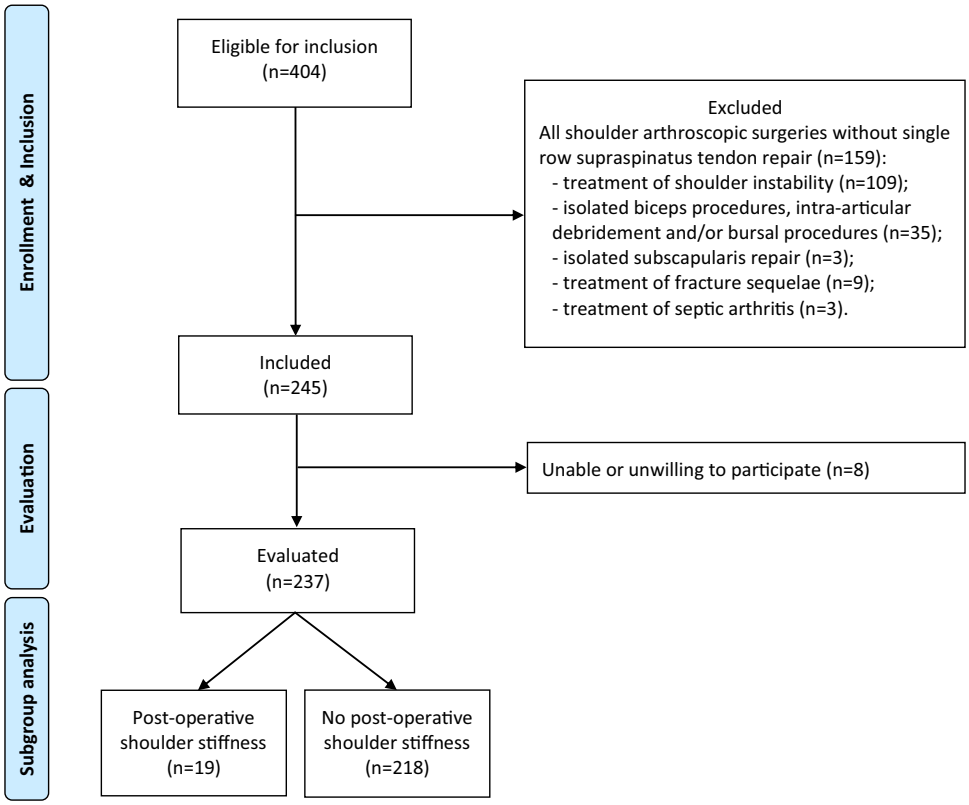

Figure 1 Flow diagram of study.

Table II Patient demographic characteristics

Characteristic	Overall	Postoperative SS	No postoperative SS	*P* value
Age, yr	59.5 (52.9-66.7)	53.3 ± 9.8	60.0 (53.2-67.2)	.0051*
BMI, kg/m^2	25.7 ± 3.6	24.3 ± 4.1	25.7 ± 3.6	.1144 (NS)
Sex: F-M ratio	0.51:0.49	0.89:0.11	0.48:0.52	.0005*
Dominant side: L-R ratio	0.04:0.96	0.05:0.95	0.04:0.96	.5737 (NS)
Lesion dimension: ratio of <1 cm to ≥1 cm	0.48:0.52	0.47:0.53	0.48:0.52	>.999 (NS)

SS, shoulder stiffness; *BMI*, body mass index; *NS*, not significant; *F*, female; *M*, male; *L*, left; *R*, right.
Continuous variables are expressed as mean ± standard deviation or median (interquartile range [ie, first quartile–third quartile]) as appropriate, whereas dichotomous variables are expressed as number of cases and frequency.
* Statistically significant ($P < .05$).

development after arthroscopic single-row RC repair. Furthermore, the results of this study confirm the data previously published on the incidence of postoperative SS and the association between female sex and the development of this complication. Finally, a previously unpublished association between postoperative SS and the presence of anxiety or depression emerged from this prospective cohort.

Codman[12] first used the term "frozen shoulder" to describe "many conditions which cause spasm of the short rotators or adhesions about the joint or bursae." More recently, the Upper Extremity Committee of the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine discouraged the generic use of the terms "frozen shoulder" and "adhesive capsulitis," recommending using etiology-based definitions: primary idiopathic SS, or frozen shoulder, which develops without any trauma or specific shoulder disease, and secondary SS, if a known cause is recognized.[22] Postoperative SS is a subgroup of secondary SS, for which various definitions have been proposed.[2] Historically, SS was considered one of the most devastating complications of shoulder surgery, especially after open procedures and after prolonged periods of immobilization.[18]

Table III Summary of main results of univariate analysis for study population

Factor	Overall	Postoperative SS	No postoperative SS	*P* value
No. of patients	237	19	218	
Surgery on dominant side	149 (62.9)	8 (42.1)	141 (64.7)	.0804 (NS)
Preoperative shoulder stiffness	9 (3.8)	1 (5.3)	8 (3.7)	.5350 (NS)
Relatives with shoulder stiffness	20 (8.4)	3 (15.8)	17 (7.8)	.2071 (NS)
Smoking	112 (47.2)	5 (26.3)	107 (49.1)	.0913 (NS)
DM	23 (9.7)	1 (5.3)	22 (10.1)	.7032 (NS)
Relatives with DM	78 (32.9)	5 (26.3)	73 (33.5)	.6177 (NS)
Hypertension	88 (37.1)	4 (21.1)	84 (38.5)	.1463 (NS)
GERD	44 (18.6)	9 (47.4)	35 (16.1)	.0026*
COPD	9 (3.8)	0 (0.0)	9 (4.1)	>.999 (NS)
Depression or anxiety	24 (10.1)	5 (26.3)	19 (8.7)	.0305*
Hyperthyroidism	2 (0.8)	1 (5.3)	1 (0.5)	.1542 (NS)
Hypothyroidism	33 (13.9)	3 (15.8)	30 (13.8)	.7243 (NS)
Dyslipidemia	24 (10.1)	2 (10.5)	22 (10.1)	>.999 (NS)
Hypercholesterolemia	57 (24.1)	5 (26.3)	52 (23.9)	.7835(NS)

SS, shoulder stiffness; *NS*, not significant; *DM*, diabetes mellitus; *GERD*, gastroesophageal reflux disease; *COPD*, chronic obstructive pulmonary disease. Dichotomous variables are expressed as number of cases with investigated condition (frequency of investigated condition in subgroup [as a percentage]).

* Statistically significant ($P < .05$).

Table IV Odds ratios and 95% CIs of significant risk factors for development of postoperative shoulder stiffness in study population and in subgroup of female patients (*) calculated by multivariate logistic regression model on variables significant on univariate analysis

	Odds ratio	95% CI	*P* value
Male sex	0.126	0.0252-0.632	.012†
Older age	0.896	0.847-0.949	<.001†
Presence of GERD	5.265	1.657-16.731	.005†
Depression or anxiety	2.085	0.561-7.743	.272 (NS)
No. of pregnancies*	0.470	0.228-0.967	.040†
No. of miscarriages*	4.002	1.154-13.887	.029†
Menopause*	1.375	0.259-7.300	.708 (NS)

CI, confidence interval; *GERD*, gastroesophageal reflux disease; *NS*, not significant.

* Multivariate analysis performed only in subgroup of female patients.

† Statistically significant ($P < .05$).

Nowadays, arthroscopic RC repair is accepted as the gold standard in the surgical treatment of most RC tears,[43] having proved to be effective and safe, with a high clinical success rate that is durable over time[45]; however, numerous possible complications have been described, including postoperative SS. The frequency of postoperative SS varies widely in the literature, partly depending on the selected study population and on the rehabilitation protocol and partly owing to the lack of common criteria used to define postoperative SS.[2,56] SS is a commonly reported complication after arthroscopic RC repair, with rates ranging from 1.5% to 11.1%.[44] Huberty et al[20] published the largest consecutive series available to date, indicating a rate of postoperative SS of 4.9%. The incidence of postoperative SS in our cohort was higher than that in the study by Huberty et al; this finding could be related to the fact that a stricter definition of SS was used in our study,[5] which encompasses both patients dissatisfied and satisfied with their ROM, as opposed to the less strict "patients' dissatisfaction with their range of motion" chosen by Huberty et al, which is likely to rule out patients who have stiffness but are satisfied.

Numerous risk factors have been related to the occurrence of primary and secondary SS; however, just a small number of publications have analyzed the role of preoperative risk factors in the development of postoperative SS after shoulder surgery.[4,10,33,51] A possible role of gastroesophageal diseases in increasing the risk of postoperative SS development was suggested in a recent study, however biased by its retrospective design and low statistical power.[14] Therefore, our study paid special attention to prospectively address the presence of GERD in a simple but effective way, using a validated diagnostic tool, the GerdQ. The diagnostic accuracy of this self-assessment

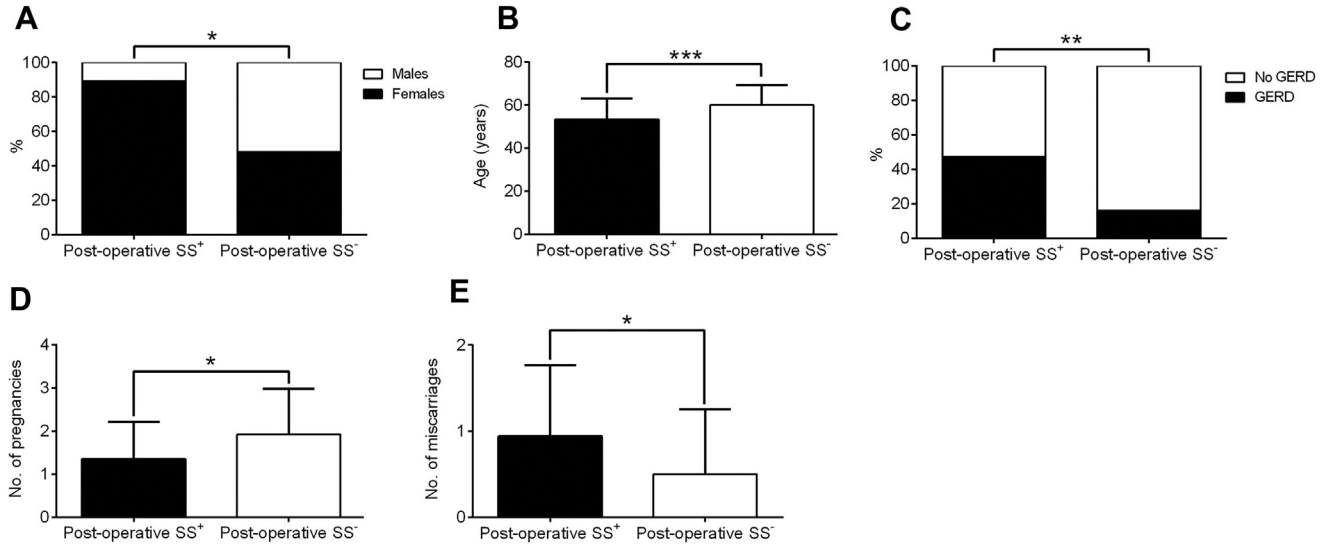

Figure 2 Relevant factors influencing development of postoperative shoulder stiffness *(SS)* after rotator cuff repair according to multivariate analysis. Risk factors are shown on the *left*: female sex **(A)**, gastroesophageal reflux disease *(GERD)* **(C)**, and number of miscarriages **(E)**. Protective factors are shown on the *right*: older age **(B)** and number of pregnancies **(D)**. For all analyses, the significance level was set at $P < .05$ *(*)*. **$P < .01$. ***$P < .001$.

questionnaire was tested in a large international study and appeared to be similar to that of a gastroenterologist supported by endoscopy and esophageal pH monitoring; as a result, the GerdQ questionnaire is recommended to diagnose GERD in a primary care population, without specialist referral or endoscopy.[23] As a consequence, our study could demonstrate that a significant association exists between the presence of GERD and the development of postoperative SS. However, the biological reasons for this association remain unknown.

An inflammatory cascade involving synovial cells and capsular fibroblasts and resulting in fibrosis is likely to lie behind the development of SS, with recent studies confirming the presence of several inflammatory mediators within the joints of patients with SS.[8,26,27,29] This inflammatory-fibrotic cascade is triggered by overexpression of transforming growth factor (TGF) β, tumor necrosis factor (TNF) α, and other cytokines[31,32] and leads first to fibroblastic hyperplasia of the synovium and then to a phenotypic shift of fibroblasts to myofibroblasts and an imbalance in matrix metalloproteinase homeostasis; this eventually leads to the alterations of the connective tissue in the glenohumeral capsule typical of the final stage of the disease.[31] In some clinical conditions associated with an increased risk of both primary and postoperative SS,[4] TGF-β and TNF-α are hyper-expressed: Diabetes mellitus is associated with increased TGF-β_1 and TNF-α serum concentrations,[7,24,42] and subclinical hypothyroidism is associated with high serum levels of TGF-β_1, markers of endothelial dysfunction[1] and, in experimental models, with high TNF-α serum concentrations.[21] Furthermore, gene polymorphisms of TGF-β_1, interleukin 6, and matrix metalloproteinases have been associated with increased susceptibility to SS and other fibrotic diseases.[33,34] Changes in proteins related to inflammation and tissue homeostasis also have been identified in patients affected by GERD.[9,25,41,53] This evidence supports the hypothesis that an underlying aspecific proinflammatory condition, characterized by increased expression of TNF-α and TGF-β, could represent a ''phenotypic pattern'' underlying multiple diseases and could itself represent a predisposing risk factor for the development of SS.[13,40]

Another possible hypothesis to explain the relation between GERD and SS is related to malabsorption and retinoid metabolism. Hagiwara et al[16] recently demonstrated that processes related to retinoid metabolism and lipid metabolism were downregulated in the inferior glenohumeral ligament of patients affected by primary SS. Because all-*trans*-retinoic acid has the potential to inhibit chondrogenic cell differentiation,[37] Hagiwara et al postulated that a decrease in retinoid metabolism could accelerate chondrogenesis and, subsequently, development of SS.[16] However, whether the presence of GERD is sufficient to negatively affect absorption of vitamin A in a way that can indirectly affect a metabolic pattern in a specific region of the shoulder joint is currently not proved, so this remains an intriguing hypothesis that requires further studies to confirm.

This newly described association between GERD and postoperative SS has important clinical relevance, and this finding suggests evaluating whether this condition is present prior to surgery. Considering that the GerdQ tool is a short and simple questionnaire, with high diagnostic accuracy, its use in the preoperative evaluation could easily help to identify patients at risk, for whom closer monitoring of postoperative rehabilitation would be recommended.

Furthermore, stratification of preoperative patient risk could help to differentiate physical therapy and pharmacologic treatment protocols in a preventive way between patients with a high risk of postoperative SS development and those with a low risk.

The role of perioperative prophylaxis with proton pump inhibitors was not addressed in this study because the administration of pantoprazole (40 mg once a day postoperatively for 20 days) already belonged to the institution's standardized postoperative protocols and the study design did not require changing this. The national recommendation for prescription of this medication, meanwhile, has been restricted to high-risk patients (age > 65 years, prior ulcers, aspirin use, high-dose nonsteroidal anti-inflammatory drugs [NSAIDs], combined use of different NSAIDs, or use of NSAIDs and antiplatelet or anticoagulant drugs), so routine administration is not considered necessary after arthroscopic shoulder surgery unless legal reasons guide this choice.[49,50]

Furthermore, in our hypothesis, it is the presence of GERD itself as a disease (with its underlying proinflammatory condition) that affects the development of postoperative SS, rather than the presence of its symptoms: therefore, it is regarded as unlikely that this medication could play a role in preventing postoperative SS because proton pump inhibitors act as a symptomatic treatment, blocking the final step of the pathologic events in GERD.[52]

Besides the main study goal, this study revealed that patients in whom postoperative SS developed were younger than those without postoperative SS, which is in accordance with the data reported by Huberty et al[20] but contrasting with other, more recent publications.[10,38,51] In our series, no significant difference in the incidence of postoperative SS was found between patients with and patients without diabetes mellitus, thyroid diseases, and lipid metabolism disorders, although all these diseases have been reported to be associated with primary and secondary SS.[4,6,19,30,36,47,57,59,62] Finally, a female predominance in the SS group, already described by numerous authors, was confirmed in our study, suggesting that sexual hormones may contribute to SS etiology.[17,36,60]

Rehabilitation plays an important role in regaining ROM and function after arthroscopic RC repair. Ideally, the most efficacious postoperative rehabilitation program is one that protects the repair and allows for optimal tendon-to-bone healing, simultaneously restoring motion and strength. Efforts to avoid stiffness led to 2 relevant advancements in current rehabilitation protocols: (1) postoperative positioning of the arm in a brace in light abduction, which can help to keep the inferior glenohumeral joint capsule stretched out, avoiding early contracture, and (2) encouragement of an early passive ROM protocol, which was believed to reduce the rate of postoperative SS.[15] Nevertheless, too rapid advancing-motion protocols could lead to an inflammatory response, increasing the risk of postoperative adhesions and producing strain on the RC with potential higher risk of retear,[38,39,55] and the clinical superiority of strict early passive ROM protocols is debated.[11,35,48] Therefore, current recommendations advise tailoring rehabilitation on the basis of intraoperative conditions as well as patients' pain during therapy.[28,58] The protocol in our study included the use of an abduction sling and patient-tailored rehabilitation.

This study has some limitations. First, it was primarily focused on the evaluation of preoperative risk factors in the development of postoperative SS; therefore, surgery-related variables and the role of rehabilitation in the development of postoperative SS were not investigated. Previous reports identified that tears <3 cm in diameter, partial articular-sided tears, calcific tendinosis, concomitant labral repair, single-tendon repair, and open surgery are potential risk factors for the development of SS after RC repair.[5,10,20,22,38,51]

Second, the diagnosis of SS was based on merely clinical criteria. Although this is widely accepted in the literature, the lack of common criteria to define SS makes comparison among outcomes from different studies difficult; imaging modalities could be used in the future to help to confirm the diagnosis.[61]

Conclusion

The presence of GERD is significantly associated with the development of postoperative SS after arthroscopic single-row RC repair. An underlying aspecific proinflammatory condition, characterized by increased expression of TNF-α and TGF-β and disorders in retinoid metabolism, could explain this previously unknown association. The incidence of postoperative SS encountered in this study falls within previously reported ranges, with women being significantly more affected than men.

Disclaimer

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