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SYSTEMATIC REVIEW

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Influence of the metabolic and inflammatory profile in patients with frozen shoulder – systematic review and meta-analysis

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Abstract

Background Frozen Shoulder (FS), also known as adhesive shoulder capsulitis, is characterized by a fibrotic inflammatory process of unknown origin, with the most prominent symptoms being pain, stiffness, and reduced joint mobility.

Methods The systematic review and meta-analysis presented herein provide insights into the pathogenesis of this condition, as well as common metabolic biomarkers potentially implicated in FS, such as glycated hemoglobin (HbA1c), and inflammatory biomarkers, including interleukins (IL-1, IL-6) and tumor necrosis factor alpha (TNF-α). Dyslipidemia and hormonal factors, such as thyroid dysfunctions, are also examined.

Results A total of 7,499 individuals were included in the meta-analysis, and one additional study collected 28,416 blood samples from individuals with FS from biobanks. The meta-analysis of metabolic variables showed that HbA1c was the most significantly elevated marker in FS, with a standardized mean difference (SMD) of μ^ = 0.3970 (95% CI: 0.0998 to 0.6943), indicating a moderate effect. Glucose showed a mean difference of -0.28 (95% CI: -0.60 to 0.05), which was not statistically significant, suggesting that short-term fluctuations in glucose levels may not be as relevant as long-term metabolic control. Cholesterol had a standardized difference of 0.278 (95% CI: 0.171 to 0.385), being significantly higher in FS. For triglycerides, the SMD was μ^ = 1.0318 (95% CI: -1.0027 to 3.0664), indicating high heterogeneity and preventing a clear conclusion. Hypothyroidism was also evaluated, with a total SMD of 0.067, a total variance of 0.0021, and a 95% confidence interval of -0.024 to 0.158, confirming no association between FS and thyroid function. Regarding inflammatory biomarkers, IL-1β was the most predominant, showing significantly higher levels in FS, with an SMD of μ^ = 2.2671 (95% CI: 0.5750 to 3.9591). TNF-α had a mean difference of μ^ = 0.7814 (95% CI: 0.1013 to 1.4615), reflecting a significant difference from zero ($z = 2.2520$, $p = 0.0243$). Finally, IL-6 did not show a significant association, with an SMD of μ^ = 1.6721 (95% CI: -0.9368 to 4.2810).

Conclusion This meta-analysis highlights the role of metabolic dysfunction and chronic inflammation in the pathogenesis of FS. HbA1c and cholesterol were the most associated metabolic biomarkers, while IL-1β and TNF-α showed a strong link to inflammation and fibrosis. The heterogeneity in triglycerides and IL-6 underscores the need for studies with standardized methodologies and subgroup analyses. Future research should focus on biomarker progression,

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patient stratification, and new therapeutic strategies targeting metabolic and immune modulation, considering FS within a broader metabolic-inflammatory framework to improve its classification and treatment.

Keywords Frozen shoulder, Metabolism, Biomarkers, Inflammation, Interleukins, Cytokines

Background

Adhesive capsulitis, or Frozen Shoulder (FS), is a condition characterized by stiffness and pain in the shoulder joint. Although its exact etiology is unknown, it has been associated with prolonged periods of immobilization, trauma, and systemic diseases such as diabetes and thyroid disorders [1, 2]. This condition has a prolonged clinical course, which can be frustrating for both patients and healthcare professionals [3]. FS is classified as primary when it occurs spontaneously and as secondary when it follows a prior event, such as trauma [4]. It is a relatively common disorder, affecting approximately 2% to 5% of the population [5]. However, despite its prevalence, FS remains one of the least understood shoulder conditions [6]. It is divided into three phases: the painful (freezing) phase, the stiff (frozen) phase, and the resolution (thawing) phase, typically resolving in most cases within a period of 1 to 2 years [7].

The pathophysiology of FS involves a complex interaction between inflammatory and metabolic processes within the joint capsule. Recent research has shown that both inflammatory and metabolic profiles play a key role in the development and progression of FS, influencing its clinical course and response to treatment [8, 9]. In this regard, several inflammatory markers and key cytokines have been identified in the progression of this condition. A significant increase in the levels of interleukin-1 (IL-1), IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) has been observed, playing a crucial role in fibroblast hyperactivation and excessive collagen production in the joint capsule, contributing to the characteristic stiffness of the disease [10, 11]. Additionally, matrix metalloproteinases (MMP-1, MMP-3, MMP-13) and their tissue inhibitors (TIMPs) regulate the remodeling of the extracellular matrix in the joint capsule; an imbalance in these mediators may promote fibrosis and capsular adhesion [12]. On the one hand, the overexpression of the ICAM-1 gene and the increase in TGF-β1 (Transforming Growth Factor Beta 1) have been implicated in the proliferation and differentiation of myofibroblasts, exacerbating fibrosis and restricting joint movement [13]. On the other hand, elevated levels of neuropeptides PGP9.5 (Protein Gene Product 9.5) and GAP43 (Growth Associated Protein 43) have been found in the synovial tissue of patients with FS, suggesting a significant role of neurogenic inflammation in pain perception and joint dysfunction [14]. These findings reinforce the importance of inflammatory processes in the pathogenesis of FS and open new avenues for therapeutic strategies aimed at modulating these biological responses.

In addition metabolic factors play a key role in the development and progression of FS. Several metabolic factors have been implicated in the onset and progression of this condition. Diabetes mellitus is one of the main risk factors, and elevated levels of glucose and glycated hemoglobin (HbA1c) have been shown to be associated with increased severity and duration of the disease [15]. Additionally, alterations in the lipid profile, such as increased triglycerides, total cholesterol, and low-density lipoproteins (LDL), as well as decreased high-density lipoproteins (HDL), have been associated with FS, especially in patients with diabetes [16]. A link has also been identified between thyroid dysfunction and FS, particularly hypothyroidism, where altered levels of thyroid-stimulating hormone (TSH) and free thyroxine (F-T4) may contribute to the inflammatory and fibrotic process characteristic of this condition [17, 18]. Moreover, recent studies have revealed a relationship between hepatic metabolism and FS, evidenced by a significant correlation between the levels of liver enzymes AST, ALT, and GGT with pain severity and joint dysfunction [19]. It has been also described that adipokines such as leptin and adiponectin modulate inflammation and fibrosis in the joint capsule, affecting the synovial microenvironment [20].

Given the crucial role of the interaction between inflammatory and metabolic processes in the progression of FS, this review aims to identify the predominant metabolic and inflammatory profiles associated with this condition. By elucidating these mechanisms, we seek to contribute to the development of more effective and personalized strategies for both prevention and treatment.

Material and Methods

Study design

A systematic review and meta-analysis were conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) standards [21]. All included studies were trials that analyzed metabolic and inflammatory profiles in FS, and only studies written in English were considered. The process was carried out using the PICOS strategy. The aim of this

search was to identify scientific evidence on the influence of the metabolic and inflammatory profile on pain and functionality in patients with adhesive capsulitis of the shoulder. PROSPERO registered: CRD42024569733.

Document sources consulted

The following electronic databases were consulted: MEDLINE, which is part of the PubMed platform; Cochrane Library; Web of Science Core Collection and Scielo, both part of the Web of Science platform; as well as LILACS and IBECS, which are part of the Virtual Health Library; and Scopus.

Search strategy

To develop the search strategy, keywords extracted from the Medical Subject Headings (MeSH) thesaurus were used:"Metabolism,""Lipids,""Glucose,""Cholesterol,""Biomarkers.", "cytokines", "Inflammation", Inflammation Mediators", "Interleukins", "TNF Receptor-Associated Factor 1″ Additionally, the following non-MeSH terms were used:"Frozen Shoulder","metabolite."and "TNF" These terms were combined using the boolean operators AND and OR. The terms had to appear in the title, abstract, and keywords.

To refine the search, the following filters were applied: English language and peer-reviewed publications published in the last 14 years.

The searches were carried out by three authors, as well as the risk assessment and article selection. To prevent disagreements, all search criteria, evaluations, and article selection were agreed upon before the study began. The final search was conducted on 23/10/2024.

Table A1. encompasses all the detailed search strategies (Supplementary Material 1).

Study selection

Studies were included in the systematic review if they met the following criteria: clinical studies that examined the impact of metabolic and inflammatory biomarkers on pain and functionality in patients with FS. Those studies that investigated biomarkers in patients with FS and cancer were excluded from the study.

The study selection process consisted on first, duplicate studies across the various databases were removed using the Rayyan QCRI program [22]. Then, the process of selecting and identifying studies was conducted through a selective reading of titles and abstracts. Subsequently, a full-text reading of the articles that apparently met the inclusion criteria was carried out.

The selection of studies was carried out independently by two researchers, following the previously established inclusion and exclusion criteria. Any disagreements were resolved through discussion, and if necessary, a third researcher was consulted. The final selection of included articles was made by consensus.

Data extraction and quality asessment

The PICOS strategy was used for data extraction. Details of the included studies were compiled, such as author names, year of publication, study design type, and location. Additionally, data on the sample were obtained, including age, size, sex, metabolic or inflammatory variables, as well as pain and functionality. The main results and assessment tools used were also recorded.

For assessing the risk of bias in systematic reviews of interventions [23], the risk of bias assessment tool recommended by the Cochrane manual was employed. This tool considers 7 domains, each evaluated across three categories:"high risk"(-),"low risk"(+), or"unclear risk"(?). The domains used to assess risk of bias include selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias where important unaddressed aspects can be noted.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system [24] was used to assess the quality of evidence from the reported study results. This system defines the quality of evidence as the level of confidence in the accuracy of effect estimation, necessary for making a recommendation. The assessment of evidence quality encompasses study bias risk, inconsistency, imprecision, publication bias, indirect outcomes, and other factors that may impact evidence quality.

Statistical analyses

The analysis was conducted using the JAMOVI program [25], specifically the MAJOR module, with the SMD as the outcome measure. A random-effects model was fitted to the data. The amount of heterogeneity (tau^2) was estimated using the restricted maximum likelihood estimator [26]. In addition to the tau^2 estimation, the Q test for heterogeneity and the I^2 statistic are reported. If any amount of heterogeneity is detected ($tau^2 > 0$, regardless of the Q test results), a prediction interval for the true outcomes is also provided. Studentized residuals and Cook's distances are used to examine whether studies may be outliers and/or influential within the model context. Studies with a studentized residual greater than the 100 x (1—0.05/(2 ×k)) percentile of a standard normal distribution are considered potential outliers (i.e., using a Bonferroni correction with a two-sided alpha =0.05 for k studies included in the meta-analysis). Studies with a Cook's distance greater than the median plus six times the interquartile range of Cook's distances are considered influential. The rank correlation test and the

regression test, using the standard error of the observed outcomes as a predictor, are employed to assess funnel plot asymmetry.

Subgroup and meta-regression analyses

A heterogeneity analysis was conducted for the biomarkers of triglycerides and IL-6, which showed the highest heterogeneity in the included studies. Key variables were extracted from each study, such as author, year of publication, country, measurement method, demographic characteristics, and triglyceride levels. The effect size was calculated using the SMD, and heterogeneity between studies was assessed using the Cochran Q statistic and Higgins'I^2 index. Given the high level of heterogeneity, a random effects model was applied in the meta-analysis, and subgroup analyses were performed based on country and measurement method.

Additionally, meta-regressions were carried out to explore the influence of moderator variables such as publication year, sample size, mean age, and the ratio between sample sizes of the compared groups. For IL-6 levels, further meta-regressions and subgroup analyses by tissue type and country were performed. All analyses were conducted using Python with the pandas, numpy, matplotlib, and scipy libraries, with a significance level of $\alpha = 0.05$.

Results

Study identification and selection process

During the article selection process, a total of 438 articles were identified in the various electronic databases. After removing duplicates, 109 articles were reviewed by their titles and abstracts to assess if they met the inclusion criteria. A total of 25 articles met these criteria and were then fully evaluated. After full-text reading, 10 articles were excluded because the patients in the studies had both FS and cancer. Finally, 15 studies were included in this systematic review [27–41].

Figure 1 shows the study selection flow.

General characteristics of the included studies

Table 1 encompasses the general characteristics of the included studies. Briefly, the studies included in this systematic review consisted of six case–control studies [27, 28, 33, 34, 37, 39], four basic science and molecular studies [29, 30, 32, 38], one Biology study [31], one Case series studies [35, 36], one cross-sectional study [40] and one Mendelian randomization study [41]. The publication period spanned from 2010 to 2024, with 2017 being

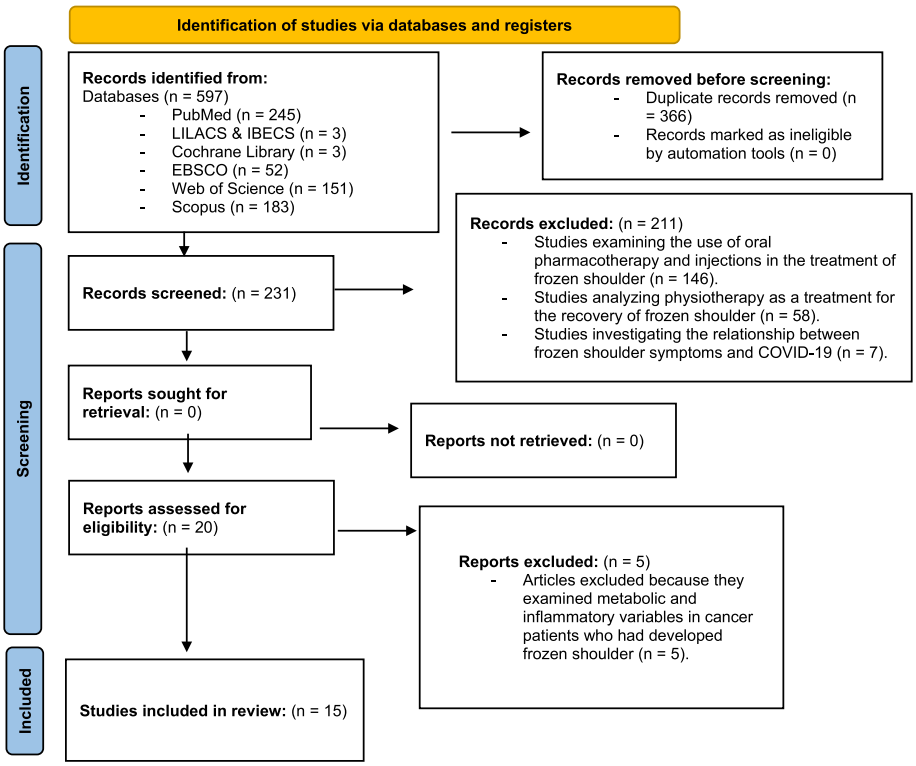

Fig. 1 Flow chart outlining the process for the selection and exclusion of the studies following the PRISMA statement

Table 1 General characteristics of the included studies

Author	Year	Study Design	Country	Biomarker	Sample	Gender	Age (years)
Salek et al. [27]	2010	Case-control	Dhakar	Metabolism	FSG = 30 CG = 30	Male and female	FSG = 56.77 ± 8.07 CG = 56.77 ± 8.07
Kabbabe et al. [28]	2010	Case-control	Australia	Inflammation	Gfs = 13 Gc = 10	Male and female	Not specified
Xu et al. [29]	2012	Basic science study, Molecular Biology	Australia	Inflammation	FSG = 8 RTCG = 10	Male and female	FSG = 58 ± 2.25 RTCG = 51 ± 12.5
Kim et al. [30]	2013	Basic science study, Molecular Biology	Korea	Inflammation	FSG = 13 CG = 6	Male and Female	FSG = 52.6 ± 7.25 CG = 40.1 ± 9.75
Lubis et al. [31]	2013	Biology	Indonesia	Inflammation	FSG = 50 CG = 50	Male AND female	FSG = 49.5 ± 10 CG = 53.5 ± 6
Lho et al. [32]	2013	Basic science study, molecular and cell	Korea	Inflammation	GFS = 14 GC = 7	Male AND female	Not specified
Sung et al. [33]	2014	Case-control	Korea	Metabolism	Fsg = 300 Gc = 900	Male AND female	FSG = 54.01 ± 8.4 CG = 54.01 ± 8.47
Schiefer et al.[34]	2017	Case-control	Brazil	Metabolism	FSG = 93 CG = 151	Male and female	FSG = 56.26 ± 8.61 CG = 52.32 ± 17.23
Safran et a l[35]	2017	Case series	Israel	Metabolism	GFS = 50	Male and Female	FSG = 51 ± 5.4
Chan et al. [36]	2017	Case series, prognosis	USA	METABOLISM	FSG = 197 CG = 4795	Male and female	FSG = 62.0 ± 18.8 CG = 62.0 ± 18.8
Chen A et al. [37]	2017	Case-control	UK	Inflammation	FSG = 42 CG = 50	Male and female	FSG = 53.86 ± 1.60 CG = 54.80 ± 2.58
Yano et al. [38]	2020	Basic Science; Molecular and Cell Biology	Japan	Inflammation	FSG = 33 RCTG = 25	Male and female	FSG: 62.0 ± 7.3 RCTG: 56.4 ± 5.8
Park et al. [39]	2020	Prognostic study: case and control	Korea	Metabolism	FSG = 151 CG = 453	Male and female	FSG = 52.1 ± 7.2 CG = 52.1 ± 7.2
Mertens et al. [40]	2024	Cross-sectional	Belgium	Metabolism	FSG = 35 CG = 35	Male and female	FSG = 53.40 ± 8.95 CG = 52.60 ± 6.93
Chen B et al. [41]	2024	Mendelian randomization	China	Metabolism	FSG = 28,416 (Biobank samples)	Male and Female	* As biobank samples, there is no age limit*

Abbreviations: FSG Frozen Shoulder Group, *CG* Control Group, *RTCG* Rotator Cuff, *RCTG* Rotator Cuff Tear. Age is expressed as mean ± standard deviation

the year with the highest number of published articles [34–37].

Among these 15 studies, one was conducted in Dhaka [27], two in Australia [28, 29], four in Korea [30, 32, 33, 39], one in Indonesia [31], one in Brazil [34], one in Israel [35], one in USA [36], one in the UK [37], one in Japan [38], one in Belgium [40] and finally, one in China [41].

The total sample size was 7,499 individuals, while the remaining article [41] collected 28,416 blood samples from individuals with FS from biobanks.

Regarding the study population, the age ranged from 18 and 65 years, and the experimental group consisted of patients with FS.

Risk of bias in the included studies

Studies with risk of bias in sequence generation, allocation concealment, and blinding of participants and personnel classified as"unclear"

The risk of bias for the included studies was evaluated using the Cochrane risk of bias tool [23]. In the studies by Yano et al. [38], Xu et al. [29], Schiefer et al. [34], Safran et al. [35], Park et al. [39], Lho et al. [32], Kim et al. [30], Kabbabe et al.[28], Chen B et al. [41], Chen A et al. [37], and Chan et al.[36], the risk of bias in these aspects was classified as unclear due to insufficient information provided in the studies. However, since the evaluator was aware of the group assignment, the risk of bias in this aspect was considered low. No patient loss was reported, and the risk of reporting bias was low.

Study with risk of bias in sequence generation, allocation concealment, and blinding of participants and personnel classified as"unclear", with additional bias in the control group size

In the study by Sung et al. [33], the risk of bias in these aspects was also unclear due to the lack of methodological details. Although no patient loss was reported, the control group was three times larger than the case group, leading to a high risk of bias in the results. However, the risk of reporting bias remained low.

Study with randomized sequence generation but not specifying whether the process was blinded

In the study by Salek et al. [27], sequence generation was randomized, but the study did not specify whether the randomization process was blinded. Since the evaluator was aware of the group assignment, this aspect was classified as low risk of bias. No patient loss was reported, and the risk of reporting bias was low.

Study with no allocation concealment or blinding of participants and personnel, but randomized sequence generation

In the study by Mertens et al. [40], allocation concealment and blinding of participants and personnel were not performed, resulting in a high risk of bias in these aspects. However, since the evaluator was aware of the group assignment, the risk of bias in this domain was considered low. No patient loss was reported, and the risk of reporting bias was low.

Study with proper sequence generation and allocation concealment but unclear blinding of participants and personnel:

In the study by Lubis et al. [31], sequence generation and allocation concealment were properly performed, leading to a low risk of bias in these domains. However, the blinding of participants and personnel was unclear, classifying this aspect as unclear risk of bias. The evaluator was aware of the group assignment, which was classified as low risk of bias, and no patient loss was reported. The risk of reporting bias was low.

Table 2 in the supplementary material provides a detailed summary of the risk of bias for the included studies. The table uses a color-coding system to represent the methodological quality of each study: unclear risk of bias (yellow), low risk of bias (green), and high risk of bias (red).

Quality of evidence

The quality of the evidence presented in this systematic review is low. The assessments have primarily been based on the risk of bias present in the trials and the lack of precision in their results. The quality of evidence is especially low in single-group studies. In this regard, Table A2 (Supplementary material) provides further details.

In particular, the quality of the studies included in this review is affected by several factors related to the risk of bias, such as the lack of key methodological details, including sequence generation, allocation concealment, and blinding of participants and personnel. Some studies have an unclear risk of bias, which limits the reliability of the results. Additionally, single-group studies have even lower quality due to the lack of appropriate controls, which impacts the internal validity of the results. Although no patient loss or reporting bias was reported, the lack of adequate blinding and limitations in the randomization methods increase the uncertainty in interpreting the results.

Intervention characteristics

This section presents a summary of the characteristics of the interventions related to the metabolic and inflammatory biomarkers studied in patients with FS.

Metabolic Biomarkers

Regarding metabolic biomarkers, various studies addressed different relevant aspects Salek et al. [27] conducted a case–control study comparing an experimental group and a control group, measuring fasting glucose levels, postprandial glucose (2 h after breakfast), glycated hemoglobin (HbA1c), and serum triglycerides in all participants. Sung et al. [33] analyzed serum lipid profiles, including total cholesterol, calculated and measured low-density lipoproteins, high-density lipoproteins, triglycerides, and non-HDL cholesterol. In another study, Schiefer et al. [34] compared serum levels of thyroid-stimulating hormone (TSH) and free thyroxine (T4) between patients with FS and those attending orthopedic consultation for other conditions. Safran et al. [35] evaluated fasting plasma glucose levels in patients with this condition, contrasting them with the prevalence of similar conditions in the general population. Chan et al. [36] conducted a retrospective analysis developing a variable called "cumulative HbA1c" to represent the prolonged impact of abnormal HbA1c values over time and used logistic regression to predict the development of adhesive capsulitis. Park et al. [39] studied metabolic variables such as lipid profiles, thyroid hormones, fasting glucose, HbA1c, and high-sensitivity C-reactive protein, classifying glucose levels both as continuous data and in categories. Mertens et al. [40] conducted a cross-sectional study analyzing blood glucose levels and using the A1 CNow + system to measure HbA1c from samples obtained through fingertip blood sampling. Finally, Chen B et al. [41] explored the causal relationship between diabetes and FS through Mendelian randomization analysis, identifying shared proteins in both conditions, with results validated through colocalization analysis and protein–protein interaction networks.

Inflammatory biomarkers

In the analysis of inflammatory biomarkers, both tissue and serum markers related to inflammatory and molecular processes were studied. Kabbabe et al. [28] compared synovial biopsies from patients with adhesive capsulitis with those from patients treated for subacromial bursitis,

Table 2 Risk of bias

	Salek et al. [27]	Kabbabe et al.[28]	Xu et al.[29]	Kim et al.[30]	Lubis et al. [31]	Lho et al.[32]	Sung et al. [33]	Schiefer et al. [34]	Safran et al. [35]	.Chan et al. [36]	Chen A et al. [37]	Yano et al. [38]	Park et al. [39]	Mertens et al. [40]	Chen B et al. [41]
Proper sequence generation (selection risk)	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Selection hiding (selection bias)	+	?	+	+	?	?	?	?	?	?	?	?	?	?	?
Blinding of participants and staff (implementation bias)	-	-	-	-	?	-	-	-	-	-	-	-	-	-	-
Blinding of outcome evaluators (detection bias)	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Incomplete results data (wear bias)	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Selective reporting of results (notification bias)	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Other sources of bias	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

evaluating RNA levels through quantitative PCR. Xu et al. [29] using immunohistochemistry to detect proteins related to neuronal and endothelial activity, such as PGP9.5, GAP43, the nerve growth factor receptor p75, and CD34. Kim et al. [30] analyzed the expression of ICAM-1 in capsular samples. Lubis et al.[31] measured serum levels of MMP-1, MMP-2, TIMP-1, TIMP-2, and TGF-β1 using the ELISA method in patients with the condition and healthy controls. Lho et al. [32] investigated the expression of cytokines such as IL-1α, IL-1β, IL-6, and TNF-α in capsular and subacromial bursa tissues, using techniques like RT-PCR, immunohistochemistry, and ELISA. Chen A et al. [37] evaluated single nucleotide polymorphisms (SNPs) associated with genes such as IL-1β, MMP-3, TGF-β1, and GDF5 in 42 patients with primary adhesive capsulitis and 50 healthy controls, as well as measuring serum levels of IL-1β. Finally, Yano et al. [38] analyzed cytokines such as IL-1β, IL-6, and TNF-α in samples from the coracohumeral ligament and anteroinferior glenohumeral ligament of 33 patients with severe stiffness from FS and 25 controls with rotator cuff tears, using real-time qPCR.

Tables 2 and 3 detail the biomarkers evaluated and the methods used in each study.

Results

Significant Metabolic Biomarkers and Their Relationship with FS

Several key metabolic biomarkers have been identified in FS patients. Regarding glucose metabolism, Salek et al. [27] found significantly higher fasting and postprandial glucose levels in FS patients ($p = 0.012$ and $p < 0.01$, respectively), while Park et al. [39] described a significant association between fasting glucose and adhesive capsulitis ($p < 0.030$). Safran et al. [35] reported that 8% of FS patients had prediabetes, with elevated fasting glucose levels and two-hour glucose measurements. Contrarily, Mertens et al. [40] did not observe differences in blood glucose between FS patients and controls, indicating the need for further research on metabolic profiles in FS.

Focusing on lipid metabolism, Salek et al. [27] reported significantly higher triglyceride levels in FS patients ($p < 0.001$). Additionally, Sung et al. [33] found a significant association between primary FS and elevated cholesterol, LDL, HDL, and non-HDL cholesterol levels (all $p < 0.001$), emphasizing the role of lipid profiles in FS development.

Table 3 Summary of Metabolic Biomarkers and Evaluation Methods in Patients with FS

Author	Study Design	Participants	Experimental Groups	Measured Biomarker	Sample Type	Analysis Method
Salek et al.[27]	Case-control	Not specified	Control group and experimental group	Fasting blood glucose, postprandial glucose, HbA1c, serum triglycerides	Blood	Not specified
Sung et al. [33]	Case-control	1,200 (900 control, 300 experimental)	FS group and control group	Total cholesterol, LDL, HDL, triglycerides, non-HDL cholesterol	Serum	Not specified
Schiefer et al. [34]	Case-control	Not specified	Patients with FS and other conditions	TSH, free T4	Serum	Not specified
Safran et al. [35]	Case study	Not specified	Patients with FS	Fasting plasma glucose	Plasma	Compared with prevalence in the general population
Chan et al. [36]	Case series	24,417	Retrospective	Cumulative HbA1c	Not specified	Logistic regression analysis
Park et al.[39]	Case–control	604 (151 experimental, 453 control)	FSG and control group	Lipid profile, thyroid hormones, fasting glucose, HbA1c, high-sensitivity C-reactive protein	Serum	Scale and categorical data analysis
Mertens et al. [40]	Cross-sectional	70 (35 experimental, 35 control)	Patients with and without FS	Blood glucose, HbA1c	Capillary blood	A1 CNow + system based on finger prick sampling
Chen B et al. [41]	Mendelian randomization	Not specified	Not specified	Proteins associated with diabetes and FS	Plasma	Protein–protein interaction networks, colocalization analysis

Abbreviations: HbA1c: Glycated hemoglobin, *LDL* Low-density lipoproteins, *HDL* High-density lipoproteins, *TSH* Thyroid-stimulating hormone, *T4* Thyroxine, *FSG* Frozen shoulder group

Contradictory results regarding hypothyroidism in FS patients have been reported. Schiefer et al. [34] highlighted a higher prevalence of hypothyroidism in FS patients ($p = 0.001$) and a link between elevated TSH levels and severe FS cases ($p = 0.05$), while Chan et al. [36] found no significant differences.

Additionally, Chen B et al. [41] found a causal link between diabetes and FS through Mendelian randomization.

A summary of these findings is provided in Table 4, which highlights the metabolic differences observed in FS patients.

Significant inflammatory biomarkers and their relationship with FS

Inflammatory biomarkers have been extensively studied in relation to FS, revealing significant alterations in cytokines and other markers associated with inflammation and fibrosis. Table 5 summarizes the key findings related to inflammatory biomarkers in patients with FS. Kabbabe et al. [28] identified elevated levels of inflammatory and fibrotic cytokines in the synovial membrane of FS patients compared to controls, although differences in MMP-3 ($p = 0.068$) and IL-6 ($p = 0.062$) did not reach statistical significance. Similarly, Xu et al. [29] observed increased cellular hyperplasia and fibroblast proliferation in FS samples, along with higher expression of the p75 nerve growth factor receptor and the CD34 marker. Additionally, the number of PGP9.5- and GAP43-positive nerves was significantly higher in FS tissue ($p < 0.01$). In line with these findings, Kim et al. [30] reported elevated ICAM-1 levels in the capsular tissue of patients with adhesive capsulitis, detected through oligonucleotide array analysis ($p = 0.001$) and real-time RT-PCR ($p < 0.05$). Conversely, Lubis et al. [31] found lower baseline levels of MMP-1 and MMP-2 in FS patients, whereas TIMP-1, TIMP-2, and TGF-b1 levels were significantly higher.

Further supporting the inflammatory component of FS, Chen A et al. [37] reported significantly higher serum IL-1β expression in FS patients ($p < 0.001$), while Lho et al. [32] documented increased IL-1, IL-1β, and TNF-α levels in the joint capsules, suggesting a key role of these cytokines in the transition from inflammation to fibrosis in the subacromial bursa. Gene expression analysis by Yano et al. [38] confirmed significantly elevated TNF-α, IL-6, and IL-1β levels in FS patients, reinforcing the importance of inflammatory and fibrotic processes in FS pathogenesis and highlighting potential therapeutic targets Table 6.

Statistical analysis results

Statistical analysis of prevalent biomarkers in patients with fs: meta-analysis by metabolic variable.

Studies were groping by metabolic variables to identify the most prevalent biomarkers y patients with FS

Table 4 Summary of Inflammatory Biomarkers and Evaluation Methods in Patients with FS

Author	Study Design	Participants	Experimental Groups	Measured Biomarker	Sample Type	Analysis Method
Kabbabe et al. [28]	Case-control	Not specified	FS vs subacromial bursitis	RNA levels	Synovial biopsy	qPCR
Xu et al. [29]	Molecular biology	18 (8 FS, 10 control)	FS vs rotator cuff tears	PGP9.5, GAP43, p75, CD34	Tissue	Immunohisto-chemistry
Kim et al. [30]	Molecular biology	26 (17 experimental, 9 control)	Patients with and without FS	ICAM-1	Tissue	Not specified
Lubis et al. [31]	Molecular biology	Not specified	FS vs control group	MMP-1, MMP-2, TIMP-1, TIMP-2, TGF-β 1	Serum	ELISA
Lho et al. [32]	Molecular biology	Not specified	Patients with and without FS	IL-1a, IL-1β, IL-6, TNF-α	Capsular and bursa tissue	RT-PCR, immuno-histochemistry, ELISA
Chen A et al. [37]	Case-control	92 (42 experimental, 50 control)	FS vs control group	SNPs in IL-1b, MMP-3, TGF-β1, GDF5, IL-1β levels	Serum	SNP analysis, IL-1b expression analysis
Yano et al. [38]	Molecular biology	58 (33 experimental, 25 control)	FS vs rotator cuff tears	IL-1β, IL-6, TNF-α	Capsular ligaments	qPCR

Abbreviations: PGP9.5 Protein Gene Product 9.5, *GAP43* Growth Associated Protein 43, *p75* Nerve growth factor receptor p75, *CD34* Cell surface antigen 34, *ICAM-1* Intercellular adhesion molecule 1, *MMP-1* Matrix metalloproteinase 1, *MMP-2* Matrix metalloproteinase 2, *TIMP-1* Tissue inhibitor of metalloproteinases 1,*TIMP-2* Tissue inhibitor of metalloproteinases 2, *TGF-β1* Transforming growth factor beta 1, *IL-1α* Interleukin 1 alpha, *IL-1β* Interleukin 1 beta, *IL-6* Interleukin 6, TNF-α: Tumor necrosis factor Alpha, SNPs in IL-1β: Single nucleotide polymorphisms in IL-1b, MMP-3: Matrix metalloproteinase 3, GDF5: Growth differentiation factor 5, qPCR: Quantitative polymerase chain reaction, RT-PCR: Real-time polymerase chain reaction, *SNP analysis* Single nucleotide polymorphism analysis

Table 5 Key Findings on Metabolic Biomarkers in Patients with FS

Author	Biomarker	FSG value*	CG value*	p value
Salek et al. [27]	Glucose	7.25 ± 0.96	6.67 ± 0.76	p = 0.012
	HbA1 C	7.15 ± 0.77	6.77 ± 0.51	p = 0.028
	Triglycerides	200.13 ± 21.26	144.03 ± 12.58	p < 0.001
Sung et al. [33]	Cholesterol	199.2 ± 37.2	186.5 ± 36.3	p < 0.05
	Triglyceride	100.0 (78.0 to 145.8)	101.0 (73.0 to 147.0)	p < 0.05
Schiefer et al. [34]	TSH	2.3 ± 1.5	2.2 ± 1.9	p = 0.124
	F-T4	1.2 ± 0.4	1.1 ± 0.2	p = 0.124
	Hypothyroidism	27.2 ± 25	10.7 ± 16	p = 0.001
Safran et al. [35]	Fasting Glucose	4.5 ± 0.7		p > 0.5
	Glucose after 2 h	5.5 ± 1.5		p > 0.5
Chan et al. [36]	Hypothyroidism	30.4 ± 6.4	10.7 ± 16	p = 0.29
	HBA1 C	7.75 ± 2.13	6.91 ± 1.98	p = 0.29
Park et al. [39]	Cholesterol	203.1 ± 36.2	198.1 ± 35.1	p < 0.022
	LDL	132.8 ± 32.1	129.7 ± 31.5	p < 0.022
	Triglycerides	122.0 ± 77.1	119.6 ± 61.2	p < 0.030
	HDL	59.6 ± 11.2	61.2 1 ± 6.8	p < 0.022
	Non-HDL	141.8 ± 28.6	137.6 ± 32.6	p < 0.022
	HbA1 C	5.48 ± 0.35	5.4 ± 0.33	p < 0.030
Mertents et al. [40]	HbA1 C	5.28 ± 0.68	4.86 ± 0.36	P = 0.0056
Chen B et al. [41]	Glucose	1.11	1.69	P = 0.003

Abbreviations: *FSG* Frozen shoulder group, *CG* Control group, *HbA1 C* Hemoglobin A1c, *TSH* Thyroid Stimulating Hormone, *F-T4* Free Thyroxine, *LDL* Low-Density Lipoprotein, *HDL* High-Density Lipoprotein, *Non-HDL* Non-High-Density Lipoprotein

* Data are expressed as mean ± SD (standard deviation)

Table 6 Key Findings on Inflammatory Biomarkers in Patients with FS

Author	biomarkers	FS value*	GC value*	P value
Kabbabe et al. [28]	IL 1β	154.0 ± 316.37	12.7 ± 16.61	P = 0.25
	IL 6	1679.2 ± 3328.08	1304.52.7 ± 874.28	P = 0.06
	TNF-α	484.8 ± 682.3	152.6 ± 47.48	P = 0.34
	MMP1	9369.4	235.4	P = 0.39
	MMP3	19,792.1	755.0	P = 0.07
	MMP13	29.7	1.6	P = 0.12
Xu et al. [29]	PGP9.5	2.8 ± 0.2	2.4 ± 0.4	P < 0.01
	GAP43	1.6 ± 0.3	1.3 ± 0.3	P < 0.05
Kim et al. [30]	gen ICAM-1	0.12 ± 0.01	0.09 ± 0.00	P < 0.05
Lubis et al. [31]	MMPs	26.6 ± 123.7	109.2 ± 297.2	p = o.oo1
	TIMPs	106.0 ± 82.1	313.7 ± 321.1	p = 0.001
	TGF-β1	65.9	288.4	p = 0.001
Lho et al. [32]	IL-1	1.5 ± 0.15	1.0 ± 0.01	p = 0.05
	IL-1β	4.3 ± 0.3	3.1 ± 0.2	p < 0.05
	TNF-α	16.0 ± 4.04	10.0 ± 1.76	P < 0.05
	IL-6	21.8 ± 4.63	3.7 ± 0.42	P < 0.05
Chen A et al. [37]	IL-1β	28.55 ± 2.58	20.12 ± 2.28	*P* < 0.001
Yano et al. [38]	IL-6	4.89 ± 14.43	1.59 ± 3.9	p = 0.044
	IL-1β	5.69 ± 6.63	1.41 ± 0.57	p = 0.011
	TNF-α	5.23 ± 12.51	1.31 ± 3.04	p = 0.016

Abbreviations: *IL-1β* Interleukin 1 beta, *IL-6* Interleukin 6, *TNF-α* Tumor Necrosis Factor Alpha, *MMP1* Matrix Metalloproteinase 1, *MMP3* Matrix Metalloproteinase 3, *MMP13* Matrix Metalloproteinase 13, *PGP9.5* Protein Gene Product 9.5, *GAP43* Growth Associated Protein 43, *ICAM-1 gene* Intercellular Adhesion Molecule 1 gene, *MMPs* Matrix Metalloproteinases, *TIMPs* Tissue Inhibitors of Metalloproteinases, *TGF-β 1* Transforming Growth Factor beta 1, *IL-1* Interleukin 1, *TNF-α* Tumor Necrosis Factor Alpha

* Data are expressed as mean ± SD (standard deviation)

(HbA1c, glucose, cholesterol, triglycerides, and hypothyroidism). Meta-analyses were performed for each subgroup using sample size, mean, and standard deviation data from the included studies and results are described below.

Hemoglobin A1c

Four studies -Salek et al. [27], Chan et al. [36], Park et al. [39], Mertens et al. [40] were included in the analysis. The overall standardized mean difference (SMD) was 0.3970 (95% CI: 0.0998 to 0.6943), indicating a significant difference in HbA1c levels between FS patients and controls ($z = 2.6180$, $p = 0.0088$). However, significant heterogeneity was observed ($I^2 = 79.91\%$, $Q = 13.8089$, $p = 0.0032$), suggesting that factors such as sample population, study design, or measurement methods may contribute to this variability.

Glucose

Two studies, (Salek et al. [27], Safran et al. [35] were analyzed, showing a combined Cohen's d of −0.28 (95% CI: −0.60 to 0.05). The Forest plot in Fig. 2 demonstrates the variability in the results, which may be influenced by differences in patient characteristics (e.g., age, comorbidities), as well as the method of glucose measurement.

Cholesterol

Two studies (Sung et al. [33], Park et al. [39])were included in the analysis, yielding a combined SMD of 0.278 (95% CI: 0.171 to 0.385), indicating a small effect size. Heterogeneity was low ($I^2 = 0\%$), suggesting that the variability between studies is minimal.

Triglycerides

Three studies (Salek et al. [27], Sung et al. [33], Park et al. [39]) were analyzed, revealing a high degree of heterogeneity ($I^2 = 99.61\%$) with an average SMD of 1.0318 (95% CI: −1.0027 to 3.0664). The significant heterogeneity ($Q = 65.7561$, $p < 0.0001$) could be attributed to differences in patient characteristics, study settings, or the methodology used in measuring triglycerides.

Thyroid Stimulating Hormone

Two studies (Schiefer et al. [34], Park et al. [39]) were included in the analysis, with a combined SMD of 0.067 (95% CI: −0.024 to 0.158). No significant effect was observed, and heterogeneity was minimal ($I^2 = 0\%$). This suggests that hypothyroidism may not be a major factor in FS development.

The results are presented in Fig. 2, which illustrates the variability in effect sizes and heterogeneity of all

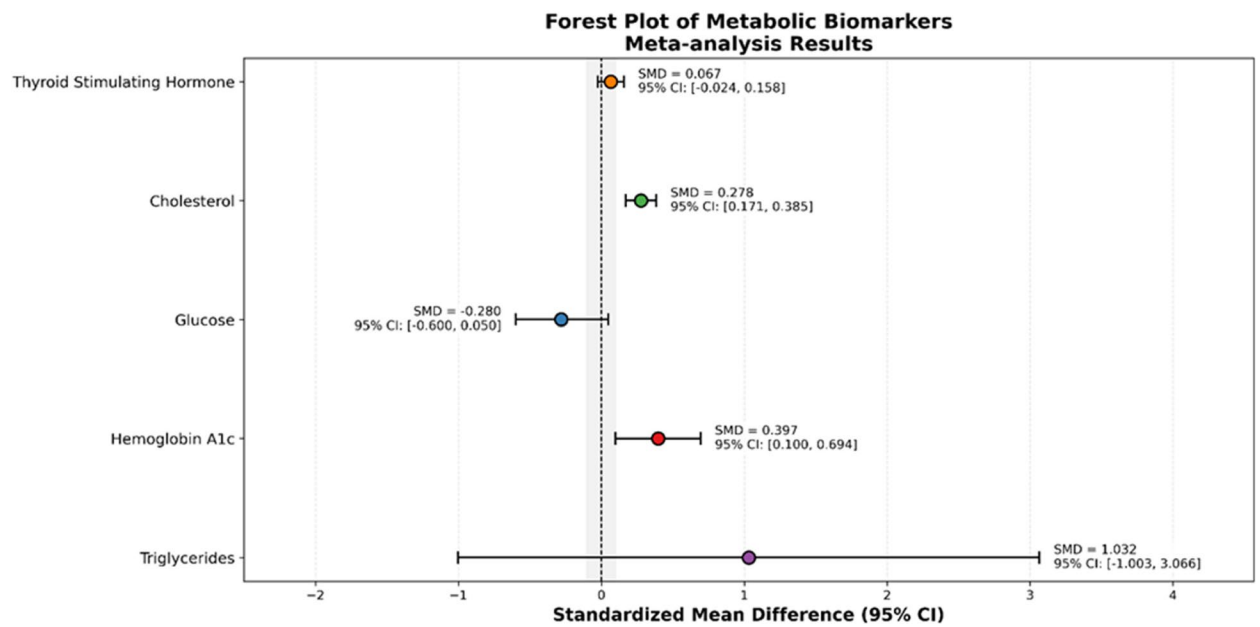

Fig. 2 Forest Plot of metabolic biomarkers

Standardized Mean Difference (SMD): The x-axis represents the standardized mean difference, which quantifies the size and direction of the effect for each biomarker. Positive values indicate higher levels in the study group compared to controls, while negative values indicate lower levels. Biomarkers Analyzed: Five key metabolic biomarkers are presented, ordered by the magnitude of their effect size Confidence Intervals: The horizontal lines extending from each point represent the 95% confidence intervals. When these intervals do not cross the vertical zero line, the result is considered statistically significant ($p < 0.05$)

metabolic variables analyzed (Hemoglobin A1c, glucose, cholesterol, triglycerides, and thyroid-stimulating hormone [TSH]). This graphical representation enables a visual comparison of effect sizes, confidence intervals, and the degree of heterogeneity among the different metabolic biomarkers. Additionally, it facilitates the identification of general trends, potential outliers, and patterns of variability across studies, providing a comprehensive overview of the associations between these metabolic markers and the studied condition.

Statistical analysis of prevalent biomarkers in patients with FS: meta-analysis by inflammatory variable

The results of the meta-analyses on the presence and significance of key inflammatory cytokines (IL-1b, TNF-α, and IL-6) in patients with FS are presented.

Interleukin 1 Beta

Four studies were included (Kabbabee et al. [28], Lho et al. [32], Chen et al. [37], Yano et al. [38]). The observed SMD ranged from 0.8308 to 4.2284, with most estimates being positive. The estimated mean SMD was 2.2671 (95% CI: 0.5750 to 3.9591), significantly different from zero (p = 0.0086). However, the results were heterogeneous (I^2 = 94.62%), suggesting contributing factors to this variability. Some studies could show a negative effect (prediction interval: −1.3935 to 5.9277). No outliers or influential studies were detected.

3.3.4.2.2. Tumor Necrosis Factor Alpha.

Three studies were included (Kabbabe et al. [28], Lho e t al. [32], Yano et al. [38]). The SMD values ranged from 0.4002 to 1.6526, with positive estimates in all studies. The mean SMD was 0.7814 (95% CI: 0.1013 to 1.4615), significantly different from zero (p = 0.0243). The results did not show significant heterogeneity (I^2 = 56.06%). Although the overall mean is positive, some studies might show a negative result (prediction interval: −0.3320 to 1.8949). No outliers or influential studies were identified.

Interleukin 6

Three studies were included (Kabbabe et al. [28], Lho et al. [32], Yano et al. [38]). The observed SMD ranged from 0.2906 to 4.5280, with positive estimates in all studies. The mean SMD was 1.6721 (95% CI: −0.9368 to 4.2810), but it was not significantly different from zero (p = 0.2090). The results showed high heterogeneity (I^2 = 96.17%), indicating variability among studies. Some studies could show negative results (prediction interval: −3.4323 to 6.7765). One study presented an outlier (residual > ± 2.3940). Additionally, the asymmetry analysis of the funnel plot indicated bias (p = 0.0009), suggesting an influence of study design quality.

The results are presented in Fig. 3, which shows the variability in effect sizes and heterogeneity of all

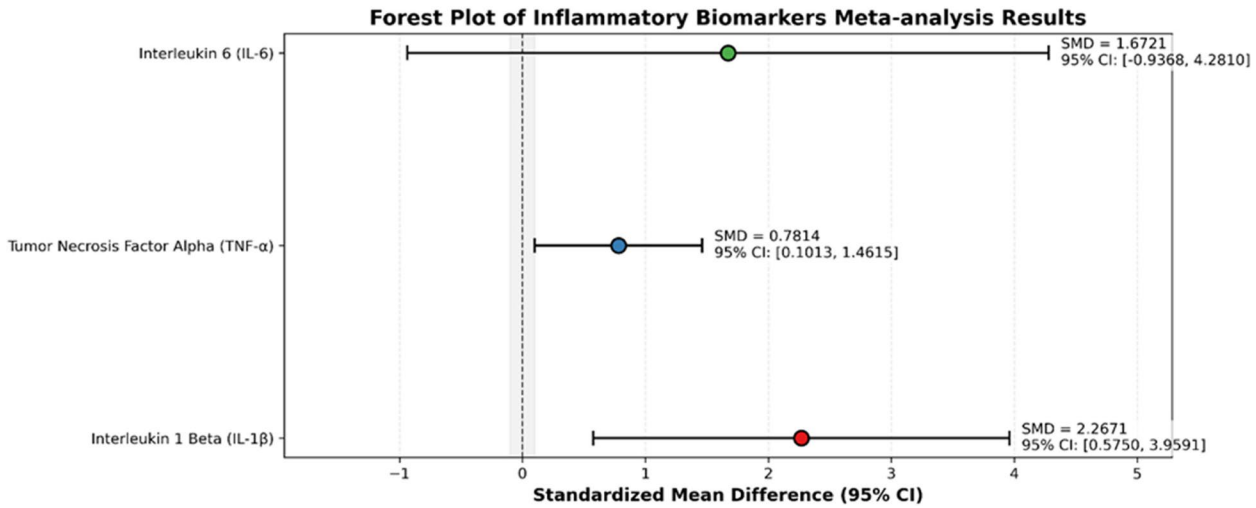

Fig. 3 Forest Plot of inflammatory biomarkers

Horizontal Axis (X): Represents the SMD, indicating the effect size. A vertical line at zero serves as a reference for the absence of effect. If the line of a study (or estimate) crosses this point, the effect is considered not statistically significant.. Vertical Axis (Y): Lists the different biomarkers included in the analysis (e.g., Interleukin 1 Beta, Tumor Necrosis Factor Alpha, Interleukin 6). Each horizontal line corresponds to a biomarker or study within the meta-analysis.Points and Horizontal Lines: Each point indicates the point estimate (SMD) for that biomarker, the horizontal lines extending from each point show the 95% confidence interval (95% CI),the range of the error (minimum and maximum) allows for the assessment of the precision of each estimate: wider intervals suggest greater uncertainty or heterogeneity between studies

inflammatory variables (IL-1b, TNF-α, and IL-6). This graphical representation allows for a visual comparison of effect sizes, confidence intervals, and the degree of heterogeneity among the different inflammatory biomarkers analyzed. Additionally, it facilitates the identification of general trends, the potential presence of outliers, and patterns of variability across studies.

Subgroup analysis and meta-regression

Given the high levels of heterogeneity observed in some outcomes, particularly triglycerides and IL-6, we performed subgroup analyses and meta-regressions to explore potential sources of variability. These analyses examined factors such as study location, sample type, publication year, and sample size to better understand the observed differences in effect sizes between studies.

Triglycerides analysis

Three studies [27, 33, 39] including 481 FS patients and 1,383 healthy controls were analyzed. The meta-analysis showed significantly higher triglyceride levels in FS patients, but significant heterogeneity was observed, leading to a subgroup analysis. The country-based analysis revealed a significantly higher effect in the Dhaka study (SMD = 3.21) compared to Korean studies, which showed no significant differences (SMD = −0.02). The sample type analysis indicated a larger effect in the study using total blood compared to those using serum. Meta-regressions showed that the ratio between FS and control group sizes had a trend toward significance ($p = 0.062$), suggesting that studies with a more balanced distribution report larger effects, while publication year, sample size, and mean age of participants showed no significant impact. The following information is detailed in Figs. 4, 5, 6, and 7.

IL-6: The meta-analysis of IL-6 included three studies with high heterogeneity. No significant relationship was found with the year of publication ($p = 0.452$) or sample size ($p = 0.378$), although larger studies tended to report smaller effects. The study by Lho et al. [32] showed the largest effect (SMD = 4.53), while those by Kabbabe et al. [28](SMD = 0.29) and Yano et al.[38] (SMD = 1.67) showed smaller effects. Subgroup analysis revealed differences between studies using synovial biopsy (SMD = 0.29) and those using capsular/bursa tissue (SMD = 3.10). Additionally, the country-based analysis showed geographic variations, with higher effects in Korea (SMD = 4.53) and lower effects in Australia (SMD = 0.29), suggesting that both methodological and regional factors contribute to the observed heterogeneity. The following information is detailed in Figs. 8,9,10,11 and 12.

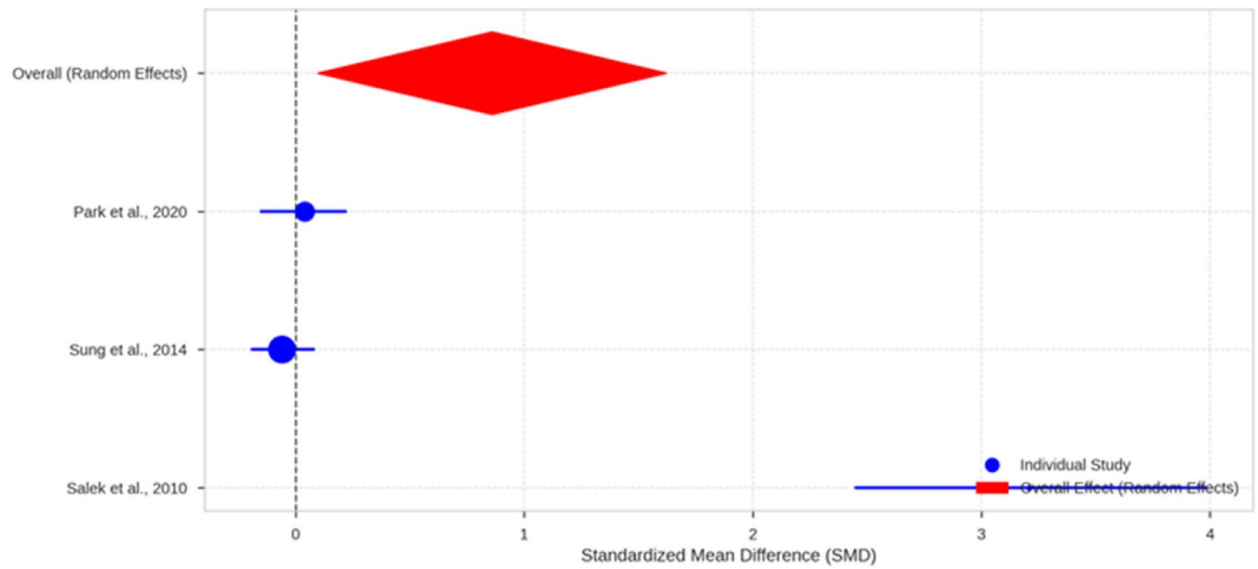

Fig. 4 Forest Plot of SMD in triglyceride levels between patients with FS and healthy controls

Forest plot of SMD in triglyceride levels between patients with frozen shoulder and healthy controls for each included study. Blue dots represent individual studies with horizontal lines showing 95% confidence intervals. The size of each dot is proportional to the study's weight in the meta-analysis. The red diamond at the bottom represents the combined overall effect using a random effects model. The vertical dashed line at zero indicates no difference between groups. The plot shows considerable heterogeneity, with Salek et al. [27] showing a large positive effect, while Korean studies show effects closer to zero

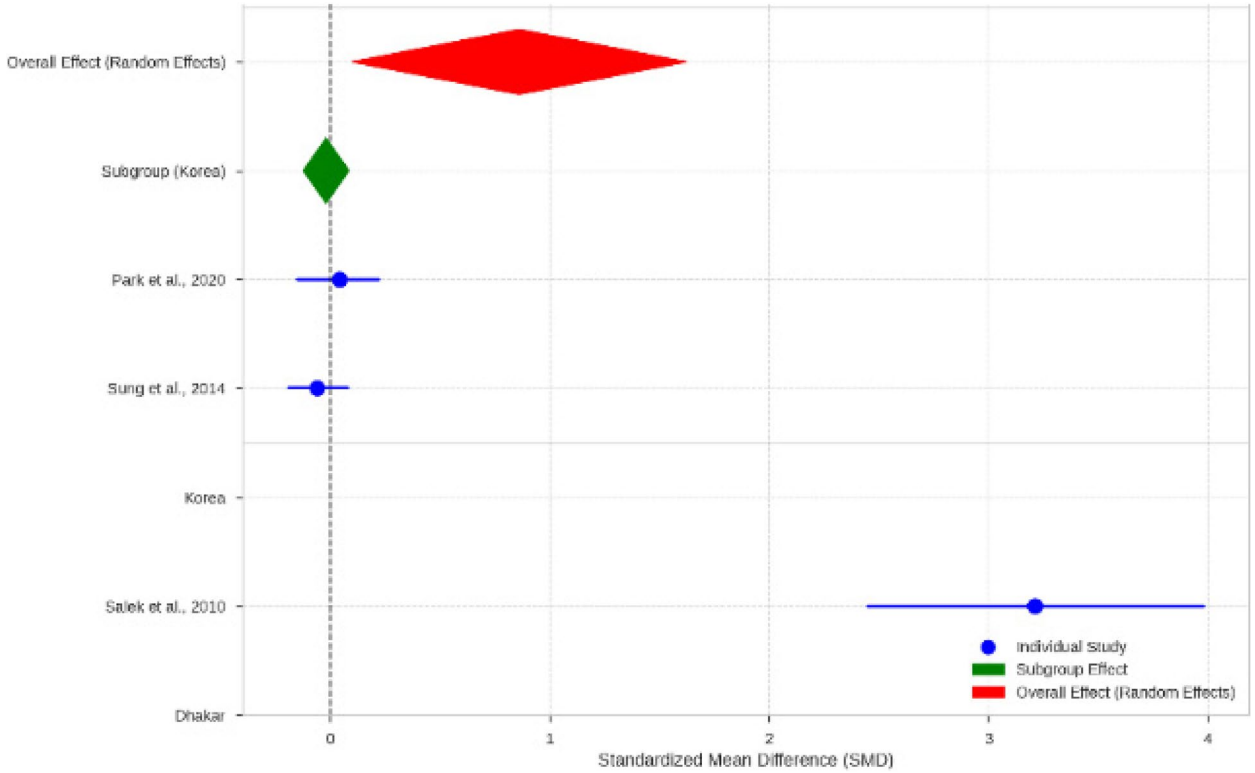

Fig. 5 Subgroup analysis of SMD in triglyceride levels by country

Individual studies are represented by blue dots with horizontal lines showing 95% confidence intervals. Green diamonds represent subgroup effects (e.g., for Korean studies), while the red diamond shows the combined overall effect. The plot reveals substantial differences between the Dhakar study [27], which shows a large positive effect, and Korean studies [33, 39], which show effects close to zero. This geographical variation suggests that regional factors, such as genetics, diet, or diagnostic criteria, may influence the relationship between frozen shoulder and triglyceride levels

Discussion

Summary of meta-analysis findings

This meta-analysis evaluated the association between metabolic and inflammatory biomarkers and FS. Our results revealed that HbA1c was the most consistently elevated metabolic biomarker in FS patients, with a significant SMD (0.397, $p = 0.0088$), indicating that chronic dysregulation of glucose metabolism may contribute to FS pathogenesis. However, fasting glucose levels did not show significant differences compared to controls (SMD $= -0.28$, $p > 0.05$), suggesting that long-term glycemic alterations (as reflected by HbA1c) may be more relevant than acute fluctuations in glucose levels.

Regarding lipid metabolism, cholesterol was significantly higher in FS patients (SMD $= 0.278$, $p < 0.001$), while triglyceride levels exhibited considerable heterogeneity, preventing definitive conclusions.

For thyroid function, our analysis showed no significant association between TSH levels and FS (SMD $= 0.067$, $p > 0.05$), suggesting that while some studies have reported a link between thyroid dysfunction and FS, our meta-analysis did not confirm this relationship.

Among inflammatory biomarkers, IL-1β showed the strongest association with FS (SMD $= 2.267$, $p = 0.0086$), indicating a robust link between chronic inflammation and FS development. TNF-α also demonstrated a significant association with FS (SMD $= 0.781$, $p = 0.0243$), reinforcing its role in pro-inflammatory pathways and fibrosis. However, IL-6 levels were highly variable across studies (SMD $= 1.672$, $p > 0.05$), possibly due to differences in patient populations, disease stages, or assay methodologies.

These findings highlight a strong metabolic-inflammatory interplay in FS, warranting further investigation into the mechanisms linking chronic metabolic dysfunction and immune dysregulation to FS progression.

Exploration of Heterogeneity

In the sensitivity analysis, subgroup analyses and meta-regressions were conducted to assess the influence of potential factors contributing to the heterogeneity

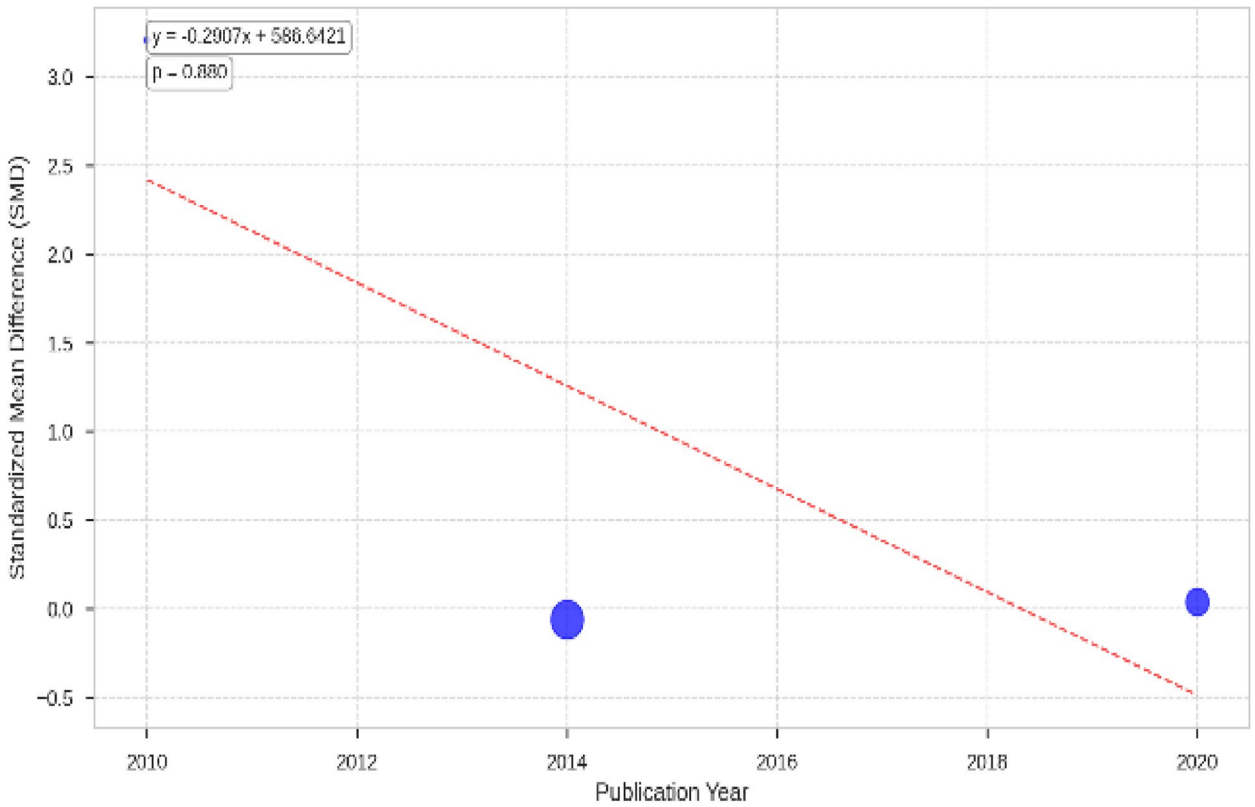

Fig. 6 Meta-regression of SMD by publication year

This meta-regression plot illustrates the relationship between publication year and effect size (SMD). Each blue circle represents a study, with the circle size proportional to the study's weight in the meta-analysis. The red dashed line shows the regression trend. The plot reveals a decreasing trend in effect size over time, suggesting that more recent studies tend to report smaller differences in triglyceride levels between patients with frozen shoulder and controls. However, this relationship is not statistically significant (p = 0.880), likely due to the limited number of studies included in the analysis

observed in some biomarkers. The biomarkers that exhibited the highest heterogeneity, such as triglycerides and IL-6, were subjected to more detailed analysis. In the case of triglycerides, the subgroup analysis revealed that geographic location and sample type (whole blood vs. serum) were relevant factors for variability between studies. For IL-6, the analysis identified that tissue type and geographical differences between studies were significant sources of heterogeneity. Additionally, meta-regressions suggested that the distribution of sample sizes between the study and control groups could influence the effect size, with more balanced studies reporting larger effects. These analyses highlight the importance of considering methodological and regional factors when interpreting the results of the most heterogeneous biomarkers.

Metabolic Biomarkers in FS

Glycemic Dysregulation and FS

Our results align with previous studies reporting a strong association between glycemic control and FS. Chronic hyperglycemia leads to the accumulation of advanced glycation end-products (AGEs), which trigger oxidative stress and chronic low-grade inflammation, ultimately promoting fibroblast activation and excessive collagen deposition in the shoulder capsule [17, 42]. The meta-analysis confirmed that elevated HbA1c levels are frequently observed in FS patients, consistent with reviews by Struyf et al. [43] and Dyer et al. [44], which documented a high prevalence of shoulder dysfunctions in diabetic patients. However, Yian et al. [45] found no association between HbA1c and FS prevalence in diabetic populations, suggesting that additional factors such as insulin resistance and inflammatory responses may play a role.

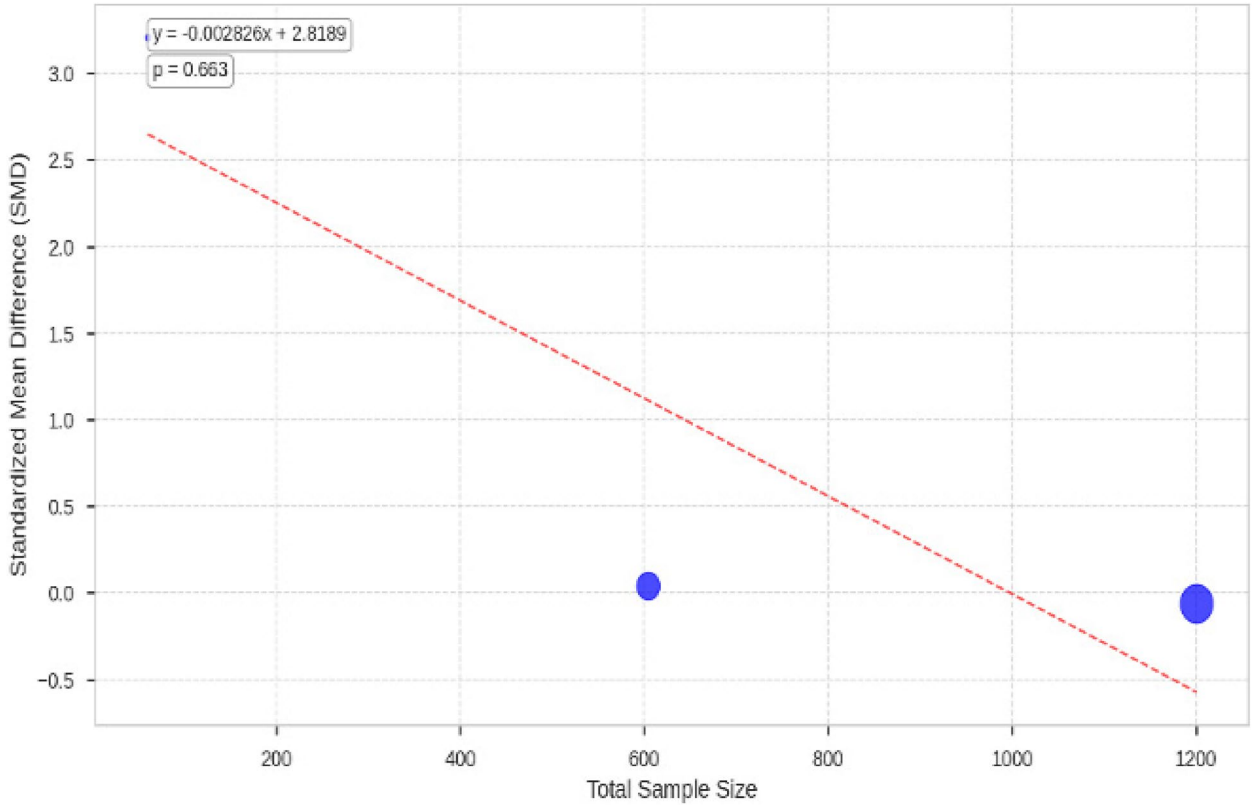

Fig. 7 Meta-regression of SMD by total sample size

Each blue circle represents a study, with the size proportional to the study's weight in the meta-analysis. The red dashed line indicates the regression trend. The plot suggests a slight negative association between sample size and effect size, with larger studies reporting smaller differences in triglyceride levels. However, this relationship is not statistically significant (p = 0.663), indicating that sample size alone does not explain the observed heterogeneity among studies

Recent research further supports this hypothesis, indicating that insulin resistance may be a stronger predictor of FS than HbA1c alone [41]. Pérez-Montilla et al. [46] found that higher HOMA-IR values were associated with increased pain, disability, and reduced shoulder mobility in FS patients, underscoring the need to consider insulin resistance in FS pathogenesis. Hyperinsulinemia promotes fibroblast proliferation and extracellular matrix remodeling through the activation of the TGF-β/Smad signaling pathway, a key driver of fibrosis in various musculoskeletal disorders [41]. This suggests that FS may share pathophysiological mechanisms with systemic fibrotic diseases, reinforcing the metabolic basis of the condition.

Lipid Metabolism and FS

The meta-analysis also revealed a significant association between FS and dyslipidemia, particularly elevated cholesterol and triglycerides. These findings align with studies by Park et al. [39] and Sung et al. [33], which linked hypercholesterolemia to FS. Hyperlipidemia has been implicated in musculoskeletal disorders due to its role in chronic inflammation, vascular dysfunction, and impaired tissue repair [47, 48]. In the study by Abboud et al. [49], patients with rotator cuff tears were more likely to have hypercholesterolemia, supporting the notion that altered lipid metabolism contributes to shoulder pathology. Klemp et al. [50] further demonstrated an association between musculoskeletal manifestations and hyperlipidemia, highlighting the systemic effects of lipid dysregulation. Additionally, Piras et al. [51] proposed that alterations in lipid profiles influence pain perception, suggesting a metabolic-inflammatory link in FS. This is further supported by recent studies indicating that hyperlipidemia induces systemic inflammation by increasing pro-inflammatory cytokines such as TNF-α and IL-6, both of which are elevated in FS patients [41]. These findings suggest that lipid abnormalities may exacerbate FS through inflammatory and

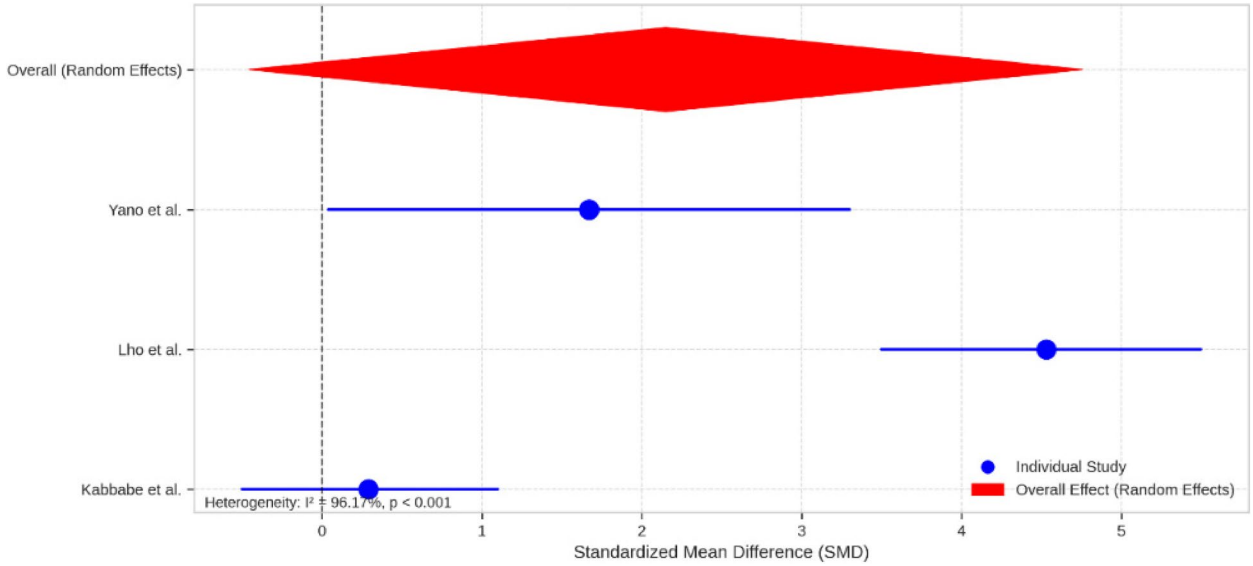

Fig. 8 Forest plot of SMD in IL-6 levels between patients with frozen shoulder and controls for each included study

Blue dots represent individual studies with horizontal lines showing 95% confidence intervals. The size of each dot is proportional to the study's weight in the meta-analysis. The red diamond at the bottom represents the combined overall effect using a random effects model. The vertical dashed line at zero indicates no difference between groups. The plot shows considerable heterogeneity ($I^2 = 96.17\%$), with Lho et al. [32] showing a large positive effect (SMD = 4.53), while Kabbabe et al. [28] shows a much smaller effect (SMD = 0.29)

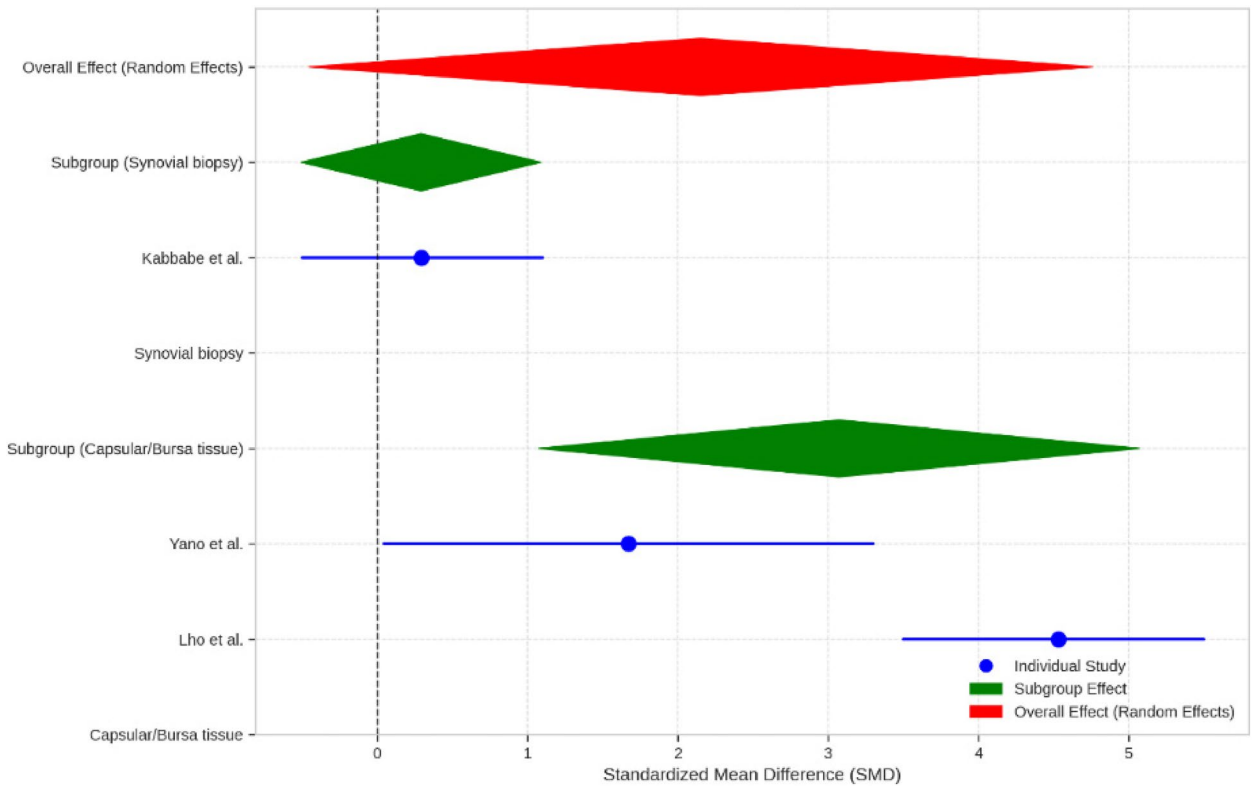

Fig. 9 Subgroup analysis of IL-6 SMD by tissue type

This subgroup analysis shows substantial differences between studies using synovial biopsy (Kabbabe et al., 2010) [28], which reported a small positive effect, and those using capsular/bursa tissue (Lho et al., 2013 [32]; Yano et al., 2020 [38]), which reported larger effects. This tissue-specific variation suggests that the type of tissue analyzed may significantly influence the measured IL-6 levels

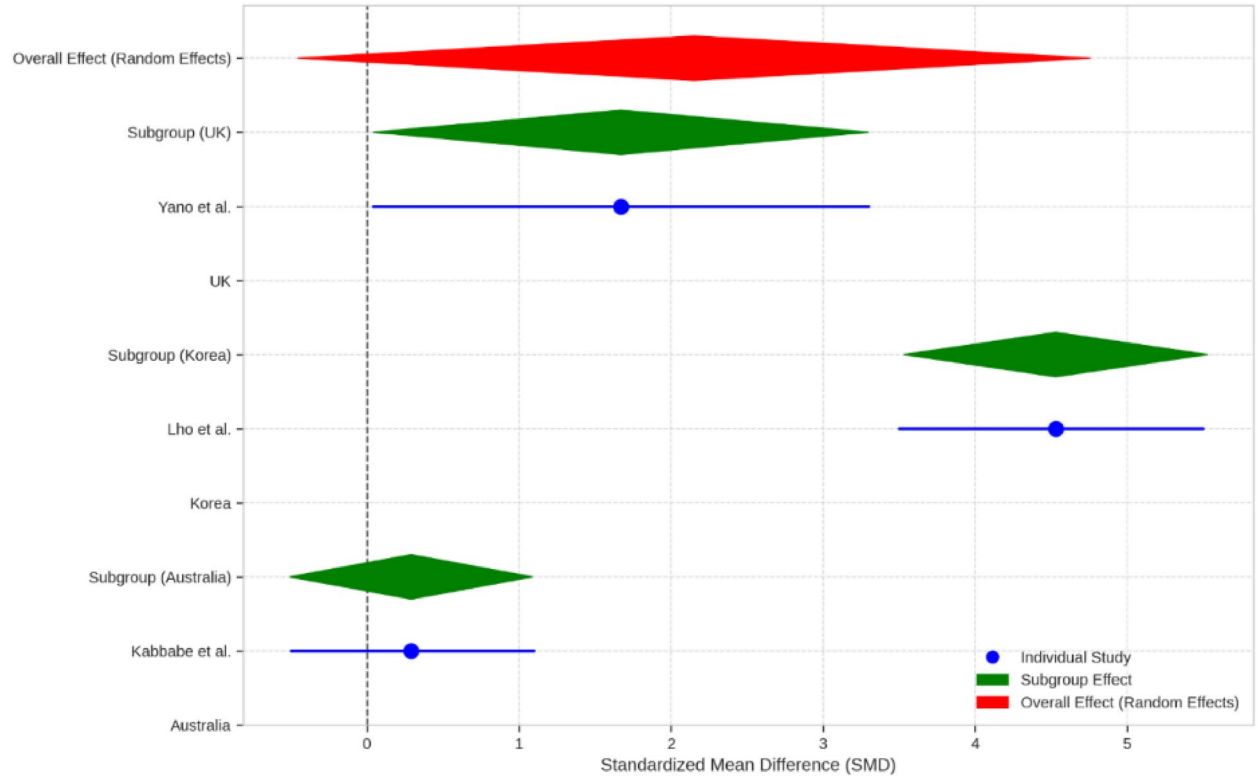

Fig. 10 This forest plot for subgroup analysis shows the SMD in IL-6 levels grouped by country

Individual studies are represented by blue dots with horizontal lines showing 95% confidence intervals. Green diamonds represent subgroup effects, while the red diamond shows the combined overall effect. The plot reveals substantial geographical variations, with the Korean study [32] (Lho et al., 2013) showing the largest effect size (SMD = 4.53), followed by the UK study [38] (Yano et al., 2020, SMD = 1.67), and the Australian study [28] (Kabbabe et al., 2010, SMD = 0.29) showing the smallest effect. This geographical variation suggests that regional factors, such as genetics, environmental influences, or differences in clinical protocols, may significantly contribute to the observed heterogeneity in IL-6 levels

vascular mechanisms, supporting the need for metabolic interventions targeting lipid homeostasis.

Thyroid Function and FS

The relationship between thyroid dysfunction and FS remains controversial. While Schiefer et al. [34] reported a higher prevalence of hypothyroidism in FS patients, Chan et al. [36] found no significant difference between groups. The meta-analysis confirmed the heterogeneity in TSH-related findings, suggesting that thyroid hormone alterations may influence FS in a subset of patients rather than serving as a universal biomarker.

Thyroid hormones regulate connective tissue integrity and fibroblast activity, potentially contributing to the fibrotic changes observed in FS [34]. Hyperthyroidism induces a hypermetabolic state that can enhance systemic inflammation, which may predispose patients to inflammatory musculoskeletal conditions, including FS. However, the mechanisms linking thyroid dysfunction to FS remain unclear, necessitating further investigation to determine whether thyroid hormone modulation could be a viable therapeutic target. Recent findings further support the role of thyroid dysfunction in FS. Our previous study [19] demonstrated a significant negative correlation between TSH levels and pain ($r = -0.556$, $p = 0.017$) and functional impairment ($r = -0.511$, $p = 0.039$) in FS patients. Notably, multiple regression analysis indicated that TSH was one of the strongest predictors of pain ($\beta = -0.298$, $p = 0.014$). These results highlight a potential role for thyroid dysregulation in FS symptomatology, suggesting that lower TSH levels may be linked to increased pain perception and shoulder disability.

These findings challenge the traditional perspective that hypothyroidism is the primary thyroid disorder associated with FS. While earlier studies have suggested that hypothyroidism contributes to FS pathogenesis by promoting extracellular matrix accumulation and fibrosis [34], the data from Hamed Hamed et al. [19] suggest that hypermetabolic states—characterized by lower TSH

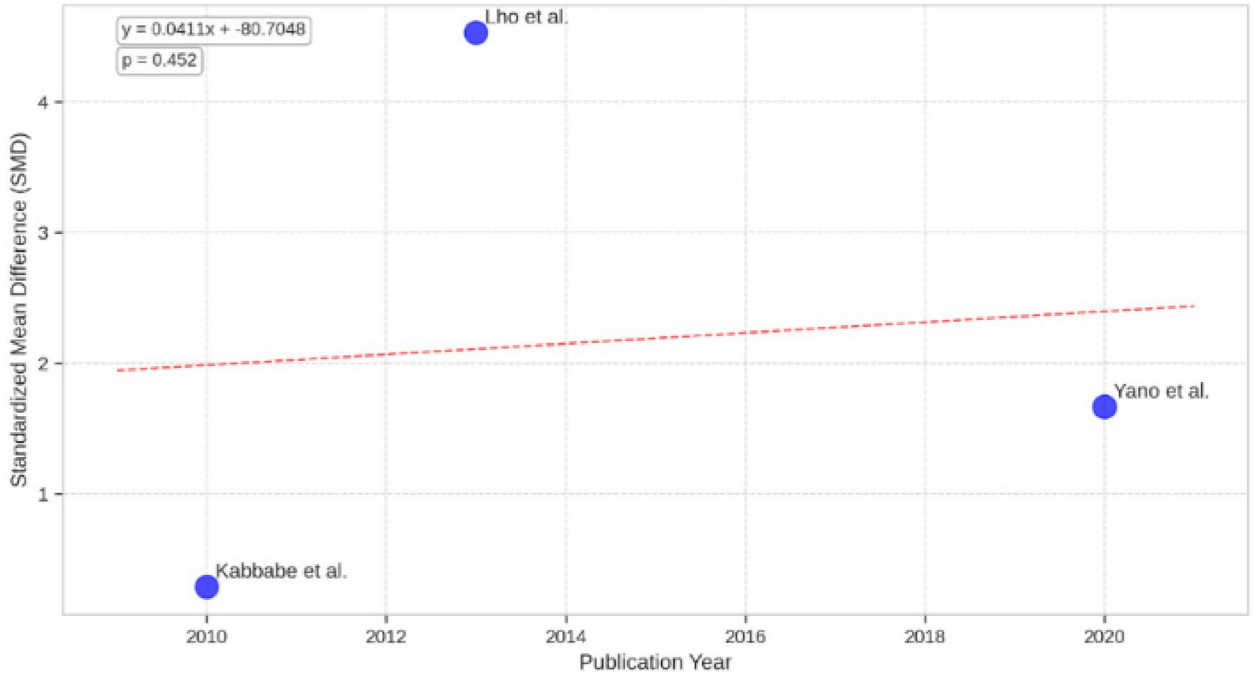

Fig. 11 Meta-regression of IL-6 SMD by publication year. This meta-regression analysis shows the relationship between publication year and effect size (SMD) for IL-6 levels. The regression trend line (dashed red line) suggests no significant linear relationship between publication year and effect size ($p = 0.452$). This indicates that temporal factors alone do not account for the observed heterogeneity

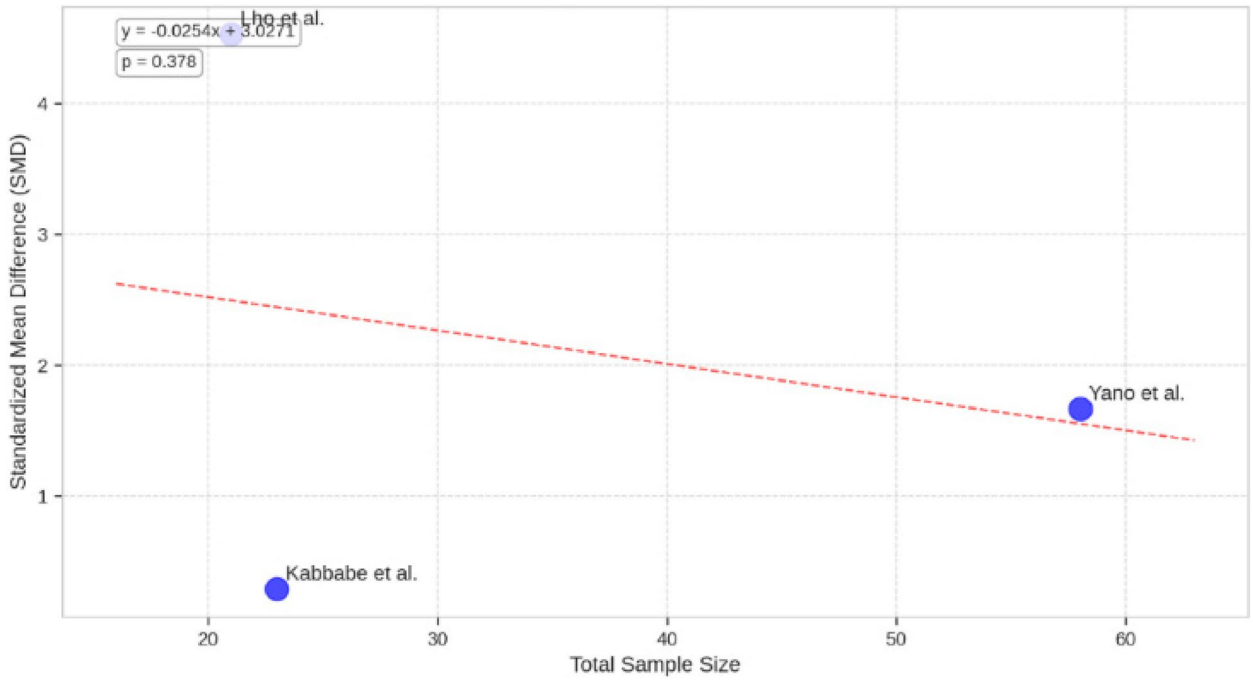

Fig. 12 Meta-regression of IL-6 SMD by total sample size. This meta-regression analysis examines the relationship between total sample size and effect size (SMD) for IL-6 levels. A negative trend is observed, suggesting that studies with larger samples report smaller effects. However, this relationship is not statistically significant ($p = 0.378$), indicating that sample size alone does not fully explain the observed heterogeneity

levels—may also exacerbate pain and functional impairment in FS patients.

Expanding the metabolic perspective

While our meta-analysis did not specifically evaluate leptin and insulin resistance, recent studies suggest that these metabolic factors play a crucial role in FS. Pérez-Montilla et al. [46] found that elevated leptin levels correlated with increased pain, disability, and reduced shoulder range of motion. Leptin is a key immunometabolic regulator that interacts with pro-inflammatory cytokines such as IL-6 and TNF-α, sustaining chronic inflammation and fibrosis. Additionally, leptin resistance impairs macrophage polarization, preventing effective tissue remodeling and fibrosis resolution [41]. These findings align with Navarro-Ledesma et al. [14], who proposed that leptin resistance contributes to FS pathogenesis by perpetuating inflammation through JAK-STAT signaling. This pathway plays a central role in immune and fibrotic responses, and its dysregulation in FS may create a pathological loop of persistent inflammation and tissue stiffness. Given the growing evidence supporting leptin's role in FS, future studies should investigate whether targeting leptin signaling could serve as a therapeutic approach.

Similarly, the association between insulin resistance and FS has gained attention. The study by Pérez-Montilla et al. [46] highlighted that higher HOMA-IR levels were linked to increased pain and disability, reinforcing the hypothesis that insulin resistance contributes to FS pathophysiology. Insulin resistance induces systemic inflammation and fibroblast proliferation, promoting tissue fibrosis through mechanisms similar to those observed in diabetic complications [43]. These findings suggest that metabolic interventions aimed at improving insulin sensitivity could have therapeutic potential in FS management.

Moreover, emerging evidence suggests that vitamin D status may play a role in upper extremity impairments, including FS, particularly in diabetic patients. A recent study by Arnqvist et al. [52] explored the relationship between vitamin D levels and musculoskeletal complications in type 1 diabetes, finding a higher prevalence of FS and other upper extremity disorders in this population. Although their results did not establish a direct link between vitamin D deficiency and FS, the immunomodulatory properties of vitamin D warrant further exploration in FS pathogenesis. Given its known effects on inflammation and fibrosis, vitamin D regulation could be an important factor influencing metabolic-inflammatory interactions in FS patients.

Additionally, metabolic syndrome has been increasingly recognized as a risk factor for various musculoskeletal disorders, including FS. The study by Park et al. [53] identified metabolic syndrome as a significant risk factor for subscapularis tendon pathology, which shares pathophysiological features with FS. Their findings suggest that obesity, dyslipidemia, and insulin resistance contribute to tendon degeneration and fibrosis, supporting the notion that metabolic dysfunction may play a key role in FS development. These findings further reinforce the importance of metabolic profiling in FS research and highlight the need for targeted metabolic interventions in at-risk populations.

Inflammatory Biomarkers in FS

IL-1β, TNF-α and IL-6.

Our findings confirm that IL-1β and TNF-α are strongly associated with FS, supporting their potential role as key inflammatory mediators in the disease [28, 32, 37, 38]. IL-1β is involved in synovial inflammation, fibroblast activation, and extracellular matrix remodeling, all of which contribute to capsular fibrosis and joint contracture [54]. This aligns with histopathological studies showing increased IL-1β expression in FS tissue, correlating with greater fibrosis and reduced range of motion [55]. TNF-α was also significantly elevated in FS patients [28, 32, 38], and is known to promote fibroblast proliferation, synovial thickening, and collagen deposition—mechanisms implicated in joint stiffness and pain [54]. These effects mirror its role in other fibrotic conditions such as systemic sclerosis and idiopathic pulmonary fibrosis [56].

Supporting this, Navarro-Ledesma et al. [57] highlighted IL-1β and TNF-α as master regulators of inflammation and fibrosis in FS, emphasizing that they may perpetuate a cycle of chronic synovial inflammation and remodeling. Their work suggests these cytokines could be valuable therapeutic targets, especially in early disease phases where inflammation predominates.

IL-6 also appeared elevated in several FS studies [28, 32, 38], though our meta-analysis revealed high variability, likely due to differences in disease stage, sample collection, and patient comorbidities. Despite consistent findings of elevated IL-6 in FS patients, the wide range of effect sizes implies IL-6 may not be a universal biomarker, but one that varies with disease progression. It has been implicated in the inflammatory-to-fibrotic transition via activation of the JAK/STAT3 pathway, which regulates fibroblast differentiation and matrix production [41, 57]. IL-6 may also mediate interactions between metabolic and inflammatory pathways in FS, further supporting the view that this condition arises from a complex interplay between systemic inflammation and metabolic dysfunction.

Expanding the Inflammatory Perspective

Beyond traditional pro-inflammatory cytokines, adipokines such as leptin have been implicated in FS pathogenesis. Pérez-Montilla et al. [46] demonstrated that elevated leptin levels were associated with increased pain, disability, and restricted range of motion in FS patients, suggesting that leptin-mediated inflammation plays a key role in disease progression.

Leptin is an immunomodulatory adipokine that enhances the production of IL-6, TNF-α, and IL-1β, creating a self-perpetuating cycle of chronic inflammation and fibrosis [41, 57]. Additionally, leptin resistance impairs macrophage-mediated tissue remodeling, leading to prolonged synovial inflammation and increased collagen deposition in FS [43, 57]. Another emerging concept is the role of neuroimmune interactions in FS. Recent studies have found that capsular tissue from FS patients exhibits increased expression of nerve growth factor (NGF) receptors, which are linked to pain sensitization and synovial fibrosis [14, 29]. Xu et al. [29] reported an increase in nerve fiber density within FS capsules, suggesting that neurogenic inflammation contributes to pain and fibrosis. Furthermore, Navarro et al. [14] highlighted that psychological stress, anxiety, and depression may exacerbate FS symptoms via the neuroimmune axis, supporting a biopsychosocial model of FS.

Strengths and limitations of the study

This study provides a comprehensive meta-analysis evaluating both metabolic and inflammatory biomarkers in Frozen Shoulder (FS), offering a multifactorial perspective on its pathophysiology. One of the major strengths of this study is the integration of both metabolic and immune components, an approach that allows for a more holistic understanding of FS beyond its traditional classification as a mechanical disorder. Previous research has often analyzed these aspects in isolation; however, our results emphasize that chronic metabolic alterations (HbA1 C, cholesterol) interact with systemic inflammation (IL-1 β, TNF-α) to contribute to FS pathogenesis. This dual-pathway model aligns with recent findings highlighting metabolic-immune dysregulation in musculoskeletal fibrosis [41, 43].

Another important strength of this study is the inclusion of a broad range of biomarkers, allowing us to compare glucose metabolism, lipid dysregulation, thyroid function, and key inflammatory mediators. The analysis confirmed that HbA1 C and IL-1β are strongly associated with FS, suggesting that chronic hyperglycemia and persistent inflammation play a central role in disease progression. The identification of TNF-α as a significant contributor further supports the hypothesis that fibrotic remodeling in FS shares molecular mechanisms with other systemic fibrotic diseases. These findings provide valuable insights into potential therapeutic targets for future FS treatments.

However, despite these strengths, the study has several limitations that should be acknowledged. One of the main challenges encountered was the high heterogeneity observed in several biomarker analyses, particularly in triglyceride and IL-6 levels. The presence of substantial variability across studies can be attributed to differences in study design, patient characteristics, biomarker measurement methods, and disease stage at the time of sampling. Some studies included diabetic and non-diabetic FS patients, while others did not stratify based on metabolic comorbidities, potentially influencing the variability in metabolic biomarkers such as glucose and lipids. The diverse methodological approaches used to assess inflammatory biomarkers (e.g., ELISA, PCR, or multiplex assays) may also have contributed to inconsistencies in cytokine levels, particularly in IL-6 measurements, which exhibited the highest variability.

Another limitation of this study is the cross-sectional nature of most of the included studies, which limits the ability to establish causal relationships between biomarker alterations and FS progression. It remains unclear whether elevated HbA1 C, dyslipidemia, and inflammatory cytokines are primary drivers of FS or secondary manifestations of chronic disease. Longitudinal studies are needed to determine whether metabolic and inflammatory dysregulation precede FS onset and to evaluate whether biomarkers such as IL-1β or leptin can serve as early indicators of disease susceptibility.

Additionally, certain metabolic markers, such as insulin resistance, leptin, and adiponectin, were not extensively analyzed in this meta-analysis due to limited available data. Recent studies [41, 43, 57] suggest that these markers play a crucial role in linking metabolic dysfunction with fibrosis, and future research should aim to include them in FS biomarker panels.

Lastly, psychological and neuroimmune factors, which have recently been proposed as contributors to FS, were not widely assessed in the studies included in this meta-analysis. Neurogenic inflammation, stress-related cytokine alterations, and central sensitization mechanisms have been reported in FS patients, suggesting that biopsychosocial influences should be further explored in future research [14].

Despite these limitations, this study represents a significant step toward understanding FS as a systemic disorder with metabolic and immune underpinnings. The findings highlight key biomarkers that could be targeted in therapeutic interventions and underscore the need for

standardized methodologies in future research to reduce heterogeneity and improve reproducibility.

Clinical extrapolation of the results

This meta-analysis supports the conceptualization of FS as a systemic condition influenced by metabolic and inflammatory dysregulation, offering several actionable insights for clinical practice.

First, the significant association between elevated HbA1c levels and FS (SMD = 0.397, $p = 0.0088$), in the absence of differences in fasting glucose, supports incorporating routine assessment of long-term glycemic control—specifically HbA1c testing—into the initial evaluation of FS patients, particularly those with diabetes, prediabetes, or features of metabolic syndrome. These findings suggest that chronic glycemic dysfunction, rather than short-term glucose fluctuations, may be linked to persistent processes such as capsular fibrosis and progressive functional limitation.

Similarly, elevated cholesterol levels (SMD = 0.278, $p < 0.001$) underscore the value of lipid profile screening in patients with FS. Treating dyslipidemia through statin therapy or lifestyle modification may not only reduce cardiovascular risk but also help modulate fibrotic progression in FS, given the likely role of chronic inflammation.

From an inflammatory perspective, the significant elevations of IL-1β (SMD = 2.267, $p = 0.0086$) and TNF-α (SMD = 0.781, $p = 0.0243$) suggest an active contribution of these cytokines to FS pathogenesis. Although the studies included in this meta-analysis did not allow for direct correlation with clinical parameters such as pain severity, range of motion, or treatment response, these biomarkers are known to be associated with more severe symptoms and prolonged disease duration in other fibrotic and inflammatory conditions. They may therefore be relevant candidates for future research focused on clinical stratification or therapeutic response prediction. In clinical practice, adjunctive anti-inflammatory therapies, such as corticosteroids or emerging biologics targeting these cytokines, may be worth exploring in refractory cases, particularly in patients with systemic inflammatory features or autoimmune overlap.

Regarding IL-6, although elevated levels were observed, the findings showed high heterogeneity, and the sensitivity analysis indicated that tissue type and geographic location were significant contributors to this variability. This suggests that IL-6 may not serve as a universal biomarker, and its clinical utility could depend on contextual or methodological factors. The phase-dependent role of IL-6 remains plausible, but further studies with standardized protocols are needed before it can be reliably used to guide treatment timing or stratify patients.

In the case of triglycerides, although initial analyses indicated no significant association with FS, subgroup analyses identified geographic differences and sample type (whole blood vs. serum) as influential factors. These results point to the possibility that triglycerides may still have a role in specific subpopulations or settings, though more standardized and regionally diverse studies are necessary to clarify their contribution.

In contrast, the lack of a consistent association between TSH levels and FS suggests that routine thyroid screening is not warranted in all cases, though it may still be appropriate in individuals with suggestive symptoms or known thyroid disease.

Taken together, these findings support a multidisciplinary and individualized approach to FS management, incorporating metabolic and inflammatory profiling into diagnostic and therapeutic strategies. In the future, the integration of biomarker data with longitudinal clinical parameters could improve risk stratification and personalized treatment, expanding management beyond conventional orthopedic interventions.

Future research

The results of our meta-analysis reinforce the multifactorial nature of FS, highlighting the role of both metabolic dysregulation and chronic inflammation in its pathogenesis. However, several questions remain unanswered, needing further research to refine our understanding of the mechanisms linking metabolic and immune dysfunction to fibrosis and joint restriction in FS.

One of the key areas that future research should address is the longitudinal progression of metabolic and inflammatory biomarker alterations in FS patients. The cross-sectional nature of most studies included in this meta-analysis limits our ability to determine whether elevated HbA1c, dyslipidemia, and pro-inflammatory cytokines precede the onset of FS or whether these metabolic disturbances are consequences of reduced shoulder mobility and chronic pain. Longitudinal cohort studies are needed to evaluate how these biomarkers fluctuate over time and whether their modulation can influence disease severity and recovery. In particular, investigating whether IL-1β, TNF-α, or leptin levels can serve as early predictive markers for FS development is an important avenue of exploration.

Additionally, given the heterogeneity observed in triglyceride and IL-6 levels across studies, future research should focus on stratifying FS patients based on their metabolic and inflammatory profiles. Subgroup analyses based on diabetes status, lipid profiles, or immune dysregulation may help identify distinct FS phenotypes with different pathophysiological mechanisms. This stratification could enable personalized treatment

approaches, where metabolic interventions (e.g., glucose and lipid-lowering therapies) are prioritized in metabolically driven FS cases, while targeted immunomodulatory strategies are implemented in inflammation-dominant FS subtypes.

Another critical aspect that remains underexplored is the role of insulin resistance, leptin, and adiponectin in FS pathophysiology. Although our meta-analysis primarily focused on HbA1c and glucose metabolism, recent studies [41, 43, 57]suggest that insulin resistance may be a stronger predictor of FS than HbA1c alone, as it contributes to chronic low-grade inflammation and fibrotic remodeling through TGF-β/Smad activation. Likewise, leptin has emerged as a key immunometabolic modulator that exacerbates inflammatory cytokine production (IL-6, TNF-α) and impairs macrophage-mediated tissue remodeling, leading to persistent fibrosis [43, 57]. Future studies should investigate whether therapeutic strategies aimed at improving insulin sensitivity (e.g., metformin, GLP-1 receptor agonists) or modulating leptin signaling could mitigate FS severity.

The circadian regulation of metabolism and immune function is another emerging area that warrants further investigation in FS. Circadian rhythms regulate glucose metabolism, lipid homeostasis, and immune responses, and their disruption has been implicated in chronic inflammatory and fibrotic diseases. Studies have shown that circadian misalignment due to shift work, sleep disturbances, or metabolic disorders can lead to altered secretion of cortisol, melatonin, and pro-inflammatory cytokines, exacerbating fibrosis and joint stiffness [57]. In the context of FS, future research should explore how circadian disruption affects metabolic-inflammatory interactions and whether interventions aimed at restoring circadian homeostasis (e.g., timed feeding, light therapy, or chronotherapy) could improve disease outcomes.

Furthermore, the neuroimmune interactions in FS remain poorly understood, despite increasing evidence suggesting that capsular fibrosis may be influenced by autonomic nervous system dysregulation and stress-related immune alterations [14]. FS patients have been shown to exhibit increased expression of nerve growth factor receptors in capsular tissue, which may contribute to pain sensitization and chronic inflammation [29]. Future research should integrate biomarkers of neuroinflammation (e.g., substance P, neuropeptides) and autonomic function into FS studies to determine whether central nervous system dysfunction plays a role in disease progression.

A promising avenue for advancing FS research is the application of metabolomic and proteomic approaches to uncover novel biomarkers and mechanistic pathways involved in FS progression. Metabolomics allows for the comprehensive profiling of small molecules involved in metabolic processes, providing insights into the interplay between glucose metabolism, lipid homeostasis, and immune regulation in FS. Similarly, proteomic analyses can identify dysregulated proteins related to fibrosis, inflammation, and oxidative stress, offering potential targets for early diagnosis and therapeutic intervention. Given the strong metabolic-inflammatory component identified in this meta-analysis, future studies should incorporate untargeted metabolomic and proteomic analyses to explore new disease-specific signatures in FS patients. This systems biology approach could facilitate the discovery of novel therapeutic targets and improve disease classification by identifying distinct FS phenotypes based on metabolic and immune signatures.

Finally, standardization of biomarker measurement methodologies is crucial for improving reproducibility in FS research. The heterogeneity observed in IL-6 and triglyceride levels suggests that variations in assay techniques (e.g., ELISA vs. PCR) and patient selection criteria significantly impact study outcomes. Establishing uniform diagnostic and biomarker assessment protocols will be essential for future meta-analyses and clinical trials investigating targeted interventions for FS.

By addressing these research gaps, future studies will contribute to a more precise classification of FS phenotypes, the development of metabolic and immunomodulatory treatment strategies, and the identification of novel therapeutic targets, ultimately improving patient management and clinical outcomes in this debilitating condition.

Conclusions

This meta-analysis highlights an association between metabolic and inflammatory dysregulation and FS, suggesting that metabolic factors such as HbA1c and cholesterol, along with inflammatory markers IL-1β and TNF-α, may contribute to FS pathogenesis. However, the high heterogeneity observed in several biomarker analyses underscores the need for more standardized methodologies and subgroup analyses in future research. These findings suggest that FS should be considered within a broader metabolic-inflammatory framework, rather than solely as a localized musculoskeletal disorder. Future investigations should aim to refine FS classification based on metabolic and immune profiles, leading to more targeted therapeutic approaches.

Abbreviations

FS	Frozen Shoulder
HbA2c	Glycated hemoglobin
Il-1	Interleukins 1
IL6	Interleukins 6
TNF-α	Tumor necrosis factor alpha
SMD	Standardized Mean Difference
TGF-beta	Tumor necrosis factor beta
PCR	C-reactive protein
ESR	Erythrocyte sedimentation rate
AGEs	Advanced glycation end products
LDL	Low-density lipoproteins
AST	Liver enzymes aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transferase
SPADI	Shoulder Pain, and Disability Index
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
MeSH	Medical Subject Headings
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GFS	Frozen Shoulder Group
GC	Control Group
GRTC	Rotator Cuff
GRCT	Rotator Cuff Tear
HDL	High-density lipoproteins
TSH	Thyroid-stimulating hormone
T4	Thyroxine
PGP9.5	Protein Gene Product 9.5
GAP43	Growth Associated Protein 43
p75	Nerve growth factor receptor p75
CD34	Cell surface antigen 34
ICAM-1	Intercellular adhesion molecule 1
MMP-1	Matrix metalloproteinase 1
MMP-2	Matrix metalloproteinase 2
TIMP-1	Tissue inhibitor of metalloproteinases 1
TIMP-2	Tissue inhibitor of metalloproteinases 2
TGF-β1	Transforming growth factor beta 1
IL-1α	Interleukin 1 alpha
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
SNPs in IL-1β	Single nucleotide polymorphisms in IL-1β
MMP-3	Matrix metalloproteinase 3
GDF5	Growth differentiation factor 5
Qpcr	Quantitative polymerase chain reaction
RT-PCR	Real-time polymerase chain reaction
SNP analysis	Single nucleotide polymorphism analysis
Non-HDL	Non-High-Density Lipoprotein
F-T4	Free Thyroxine

Supplementary Information

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Supplementary Material 1. Table A1: Search strategies. Table A2: Grade System.

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Authors' contributions
Conceptualization, S.N.-L. and D.H.H.; methodology, D.H.H.; software, S.N.-L. validation, S.N.-L. and C.R-P.; formal analysis, D.H.H.; investigation, D.H.H., S.N.-L., C.R.-P., and L.P.; resources, D.H.H., S.N.-L., C.R.-P., and L.P.; data curation, D.H.H.; writing—original draft preparation, D.H.H., S.N.-L., C.R.-P., and L.P.; writing—review and editing, D.H.H., S.N.-L., C.R.-P., and L.P.; visualization, D.H.H., S.N.-L., C.R.-P., and L.P.; supervision, D.H.H., S.N.-L., C.R.-P., and L.P.; project administration, D.H.H., S.N.-L., C.R.-P., and L.P.; funding acquisition, D.H.H., S.N.-L., and L.P. All authors have read and agreed to the published version of the manuscript.

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Declarations

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