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The immune pathology of bursitis in rheumatic inflammatory diseases, degenerative conditions and mechanical stress: A systematic review

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ABSTRACT

Objective: To summarize current insights on the immune pathology of bursitis caused by rheumatic inflammatory diseases, degenerative conditions, or mechanical stress and identify knowledge gaps in this field. Data on tenosynovitis pathology was included for comparison.

Methods: We performed a systematic review encompassing an electronic database search of all published literatures in PubMed/MEDLINE from inception to February 13, 2023, investigating the immunological changes occurring in the bursa of patients with inflammatory rheumatic diseases, degenerative conditions or mechanical stress (e.g., impingement syndrome).

Results: Thirty-two articles provided data on the immune pathology of bursal tissue inflammation were identified. Histological and immunological perturbations included alterations of tissue morphology, infiltration of macrophages and some T cells, and enhanced expression of proinflammatory cytokines, such as interleukin (IL)-6, IL-1β and tumor necrosis factor alpha (TNF-α). These changes were described for all three underlying causes, although studies on bursitis associated with rheumatic inflammatory diseases were rare. Fibrosis was only reported in subacromial bursitis caused by mechanical stress within our included studies.

Conclusion: Current insights on bursitis were outdated and studies on bursitis associated with rheumatic inflammatory diseases are particularly lacking. Substantial overlap of enhanced expression of IL-6, IL-1β, TNF-α and infiltrating macrophages were found in bursitis irrespective of the underlying cause. In depth investigation on bursitis such as high throughput multi-omics are urgently needed to guide disease-specific therapeutic management.

Introduction

Rheumatic diseases characteristically present with pain and physical limitations. The burden of these conditions has increased globally [1]. The group of rheumatic diseases encompasses rheumatic inflammatory conditions and degenerative conditions. Rheumatic inflammatory diseases are characterized by autoimmune or autoinflammatory processes, the most prevalent of which being rheumatoid arthritis (RA), while degenerative conditions involve progressive tissue or organ deterioration over time due to factors like age or chronic mechanical stress. In addition to joint inflammation, these conditions may also cause inflammation of periarticular structures such as bursae and tendon sheaths. Subacromial and trochanteric bursitis is a hallmark feature of polymyalgia rheumatica (PMR) [2] but subacromial bursitis may also occur in other inflammatory rheumatic conditions such as RA. Although a vast number of studies have investigated the immune pathology of joint inflammation in rheumatic diseases, there remains a relative dearth of knowledge regarding the cellular and molecular pathobiology of bursitis and tenosynovitis.

Bursitis may be caused by a systemic rheumatic inflammatory disease or mechanical stress of surrounding structures. Bursae are sac-like structures covered by a synovial membrane which are normally filled with a small amount of synovial fluid that functions to reduce friction between different structures (e.g. tendons, muscles, bone) [3]. The subacromial subdeltoid bursa is the largest bursa in the body, located between the acromion, deltoid muscle, and the rotator cuff tendons [4]. This bursa may become inflamed due to a systemic rheumatic inflammatory disease, mechanical stress in the impingement syndrome [5], or

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secondary to rotator cuff pathology (e.g. rotator cuff tears and idiopathic frozen shoulder).

Inflammation of tendon sheaths, i.e., tenosynovitis, is also a common finding in rheumatic diseases such as RA and PMR [6]. Tendon sheaths consist of a fibrous membrane, made of tight collagenous tissue, and a synovial layer containing synovial fluid [7]. The tenosynovitis of RA may associate with an aggressive disease course and can lead to tendon adhesions or rupture in RA [8]. Similar to bursitis, tenosynovitis may also develop due to mechanical stress, as illustrated by the De Quervain tenosynovitis of the wrist [9].

Although a growing body of studies has reported on the cellular and molecular perturbations occurring in bursitis related to rheumatic inflammatory diseases, degenerative conditions or mechanical stress, a comprehensive understanding on immunopathology of bursitis is lacking. The aim of this systematic review was to summarize current knowledge on the immune pathology of bursitis caused by different conditions and identify knowledge gaps that warrant further research. For comparison we included tenosynovitis as another form of peri-articular inflammation.

Methods

Data source and search strategy

A systematic review was performed according to the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist [10]. A review plan was established beforehand but not registered. A search was performed in PubMed/MEDLINE from inception to February 13, 2023. The keywords (MeSH terms) included terms such as *'Polymyalgia Rheumatica', 'Arthritis, Rheumatoid', 'Shoulder Impingement Syndrome', 'Rotator Cuff', 'Bursa, Synovial', 'Tenosynovitis', 'Macrophages', 'Matrix Metalloproteinases', 'Inflammation mediators'*. Full research strategy is available in Supplementary material 1. The references of the selected papers were also screened to identify additional relevant publications. No ethical approval or informed consent was required for this study. An additional search for other rheumatic diseases was performed, and this search strategy is provided in Supplementary material 2.

Study screening and selection

A web-based software platform Covidence [11] was used for title, abstract, and full-text screening. Two authors (A.Z., K.S.M.G.) performed the screening independently. In case of any discrepancies between the two reviewers, consensus was sought. If no consensus could be obtained, a third reviewer (E.B.) made the final decision. Our inclusion criteria encompassed (a) studies reporting original data relevant to the topic, (b) more than 5 patients in the study, (c) English language only. We excluded articles that were (a) outside the scope of the current review, (b) letters, review articles, comments, editorials, study protocols, (c) case reports (5 or fewer patients), and (d) non-English articles.

Data extraction

All data extraction was performed by two independent reviewers (A.Z., K.S.M.G). The data extraction was performed in a standard template. The following data was collected: authors, year of publication, country, study design (prospective, retrospective), type of disease, sex, age of the study group, location of bursitis (e.g., subacromial bursa), location of tenosynovitis (e.g., wrist). If available in the study, data on immunosuppressive treatment and immunological changes in joint synovium were also collected (A.Z., K.S.M.G.). The authors were not contacted to retrieve unpublished data.

Results

Study selection

In total, 312 unique studies were retrieved, with eventually 32 studies selected as eligible for this systematic review [12–41] (Fig. 1). Ten additional studies were selected as comparison that did not contain data on bursa tissue: seven studies on tenosynovium [8,42–47] and three studies on bursa fluid [48–50] (Fig. 1). In the additional search for other rheumatic diseases, no eligible studies were found (Supplementary Figure S1).

Qualitative analysis (systematic review)

Study and patient characteristics

Most studies were carried out after the year of 2000. Geographically, studies were relatively more distributed in Asia than Europe and Northern-America. The majority of the studies had a prospective design, while only one study was retrospective by design, and nearly 30 % of the studies were unclear on study design. The main disease categories associated with bursitis in the included studies were gout, shoulder instability, rotator cuff disease, impingement syndrome, PMR, shoulder dislocation, and frozen shoulder (Table 1). These conditions were collectively classified into categories of rheumatic inflammatory diseases, degenerative or mechanical conditions, or others. Over half of the selected studies included control subjects, including patients undergoing surgery for shoulder instability or acute trauma (Table 1). Eleven studies on bursa explicitly commented on the use of immunosuppressive treatments, as shown in Supplementary Table S1. Whereas nearly one third of papers presented no data regarding the sex of patients, the remaining studies showed a slight male predominance. Approximately 85 % of studies recruited subjects with an average age older than 50 years.

Methodology aspect

Bursa biopsies were performed in 32 studies. Data were also collected from the joint synovium, seven of them compared joint inflammation to bursa inflammation. Immunohistochemistry and polymerase chain reaction were the most used method in tissue studies, applied in half of the studies. Haematoxylin and Eosin staining was applied in over a third of the studies. Four studies performed enzyme-linked immunosorbent assay on supernatant of isolated cells. The characteristics of sample selection and methodology are summarized in Table 1.

Main findings

Tissue morphological description

Twenty studies on bursa tissue investigated the immunohistological changes [13–15,17,18,20,22,24,26,29–34,36,37,40,41,51]. The cellular infiltrates and tissue characteristics in the bursa are summarized in Table 2. Most studies focused on subacromial bursa (SAB) tissue from patients with rotator cuff disease. Twelve out of twenty studies reported the presence of infiltrating leukocytes [15,18,22,24,26,30,32–34,37,41,51]. In contrast, two studies on shoulder instability [17] and impingement [20] reported no or sparse infiltrating inflammatory cells in the SAB, respectively. Infiltrating immune cells in SAB primarily consisted of macrophages [26,32,41,51], and some reported moderate amounts of T cells [32,51]. In SAB biopsies of PMR patients, some CD4+ and rare CD8+ Tcells were observed [51]. In conditions such as rotator cuff tendinitis or impingement syndrome, the majority of T cells present predominantly belong to the CD4+ T cell subset rather than the CD8+ T cell subset [32]. Five studies demonstrated synovial hyperplasia in the obtained SAB samples [13,14,26,31,36]. Fibrosis in the inflamed SAB was reported in five studies on impingement syndrome [13,14] and rotator cuff pathology [20,26,29].

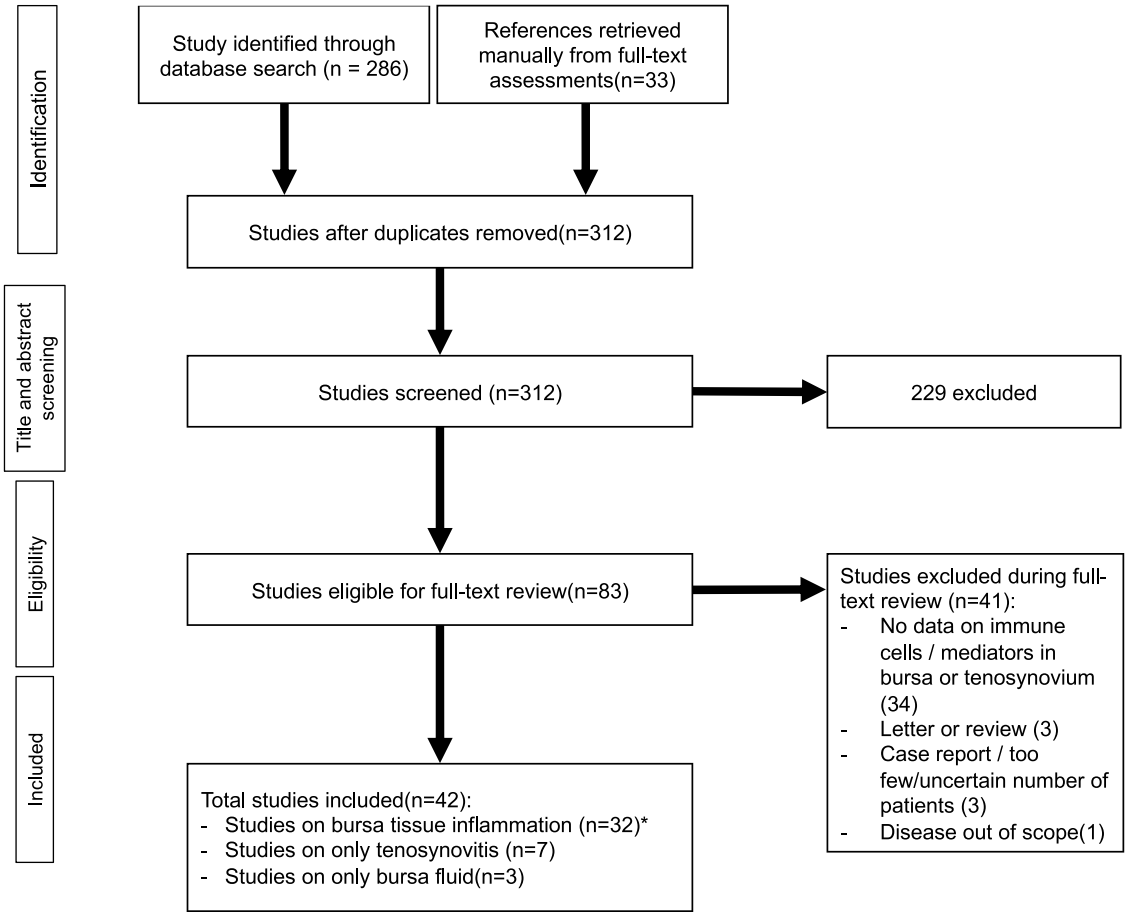

Fig. 1. Flow chart of the systematic search.
* One study also contained data on tenosynovitis, and two studies reported on bursa fluid.

Cytokines, enzymes, and neurotransmitter

The majority of studies focused on SAB inflammation in the context of rotator cuff disease [13-15,22,24,27,30,31,33–38,41,52]. Pro-inflammatory cytokines interleukin (IL)−6 and IL-1β were detected in bursa tissue in nearly all studies [12,15,18,24-26,28,30,31,33,37,38,52]. Cytokines and biomarkers reported by ≥ 3 studies on SAB are summarized in Table 3, and markers reported by two studies in Supplementary Table S2. Eight studies demonstrated the expression of matrix metalloproteinases (MMPs) in bursa, as shown in Table 4 [12,15,26,28,30,33,37,38], with MMP-1 and MMP-9 being the most commonly found MMPs. Six studies reported the expression of all cyclooxygenases (COX) in the SAB [12,25,26,30,33,37]. Substance P is a neurotransmitter associated with inflammatory processes and can be produced by inflammatory cells such as macrophages. It was identified in three studies in the SAB [15,16,21]. Overall, expression of IL-6, IL-1β, Tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), substance P and MMPs was observed in the tissues, irrespective of the underlying etiology (i.e., rheumatic inflammatory disease, degenerative or mechanical disease).

Expression of cytokines in subgroups of one disease

Expression of cytokines did not differ in subgroups of one disease. Similar mRNA expression of IL-12 was found in complete RCT with shoulder stiffness and without stiffness [24]. Also, two studies found no difference of TNF-α expression in the bursa in partial thickness tear(PTh) and full thickness tear(FTh) [33], as well as in healed and non-healed RCT groups[30]. In line with these results, no significant difference was detected in IL-6 expression between FTh and PTh patients [26,33]. However, substance P was more elevated in the patients with PTh compared to FTh [16].

Comparison of histological findings between inflammatory and non-inflammatory groups

Histological changes in tissues from patients with rheumatic inflammatory disease and degenerative or mechanical disease were compared to those in non-inflammatory controls in seven studies (Table 5) [15,18,20,29,31,37,41]. These studies focused on RCT, RCD or impingement syndrome. The non-inflammatory controls were included by several criteria in these studies. For instance, adult patients who underwent shoulder stabilization surgery were included, but patients who had any pain-related symptoms in the shoulder area, or any other diseases in the shoulder were excluded. In patients with degenerative or mechanical diseases, bursa tissue has been reported to display a trend of increased leukocyte infiltration [15,18,20,31,37], increased vascularity [15,18,20,31,41], and fibroblast proliferation [15,18,31]. Only one study investigated hyperplasia of the fibroblasts and blood vessels in the bursal tissue in RCT groups compared with that in non-inflammatory controls, and found no significances [31].

Comparisons of cytokines, MMPs and cox expression between inflammatory and non-inflammatory groups

Inflammation-related cytokines, MMPs and COX in bursal tissues that were investigated in more than 2 studies were compared between inflammatory and non-inflammatory groups in seven studies, as summarized in Table 6 [12,15,18,25,28,31,37]. The non-inflammatory controls were patients who underwent surgery for indications other than inflammatory bursitis and synovitis. All studies illustrated significantly enhanced expression of proinflammatory cytokines within the

Table 1
Characteristics of included studies on bursa tissue inflammation.

	No. of studies (%)	No. of patients (%)
Total	**32**	**1209**
Year of publication		
Before 2000[1]	6(18.75 %)	185(15.30 %)
2000–2009[2]	12(37.50 %)	407(34.58 %)
2010-present[3]	14(47.35 %)	617(51.03 %)
Geographical region		
Asia[4]	15(46.88 %)	518(42.85 %)
Europe[5]	9(28.13 %)	475(39.29 %)
Northern-America[6]	8(25.00 %)	21,617.87 %)
Study design		
Prospective[7]	23(71.88 %)	862(71.30 %)
Retrospective[8]	1(3.13 %)	84(6.95 %)
Unclear[9]	8(25.00 %)	263(21.75 %)
Primary disease of interest in study		
- Rheumatic inflammatory conditions		
Polymyalgia rheumatica[10]	1(3.13 %)	19(1.57 %)
- Degenerative and mechanical conditions		
Calcifying tendinitis[11]	1(3.13 %)	63(5.21 %)
Frozen shoulder[12]	3(9.38 %)	61(5.05 %)
Impingement syndrome[13]	5(2.17 %)	204(16.87 %)
Rotator cuff disease[14]	8(25.00 %)	284(23.49 %)
Rotator cuff tear[15]	16(50.00 %)	624(51.61 %)
Rotator cuff tendinitis[16]	1(3.13 %)	12(0.99 %)
- Other		
Recurrent shoulder dislocation or proximal humeral fracture[17]	2(6.25 %)	23(1.90 %)
Peri-articular specimen of interest		
Biopsies from subacromial bursa[18]	32(100 %)	1209(100 %)
Comparator tissue		
Shoulder Joint synovium[a,19]	7(21.88 %)	189(15.63 %)
Experimental methods		
IHC[20]	18(56.25 %)	537(44.42 %)
H&E staining[21]	12(37.50 %)	578(32.77 %)
IF[22]	4(12.50 %)	77(4.37 %)
PCR[23]	16(50.00 %)	562(31.86 %)
Gene expression array[24]	3(9.38%)	59(4.88 %)
ELISA[25]	4(12.50 %)	124(7.03 %)
Radioimmunoassay[26]	1(3.13 %)	44(2.49 %)
Flow cytometry[27]	2(6.25%)	32(1.81 %)
Western blot[28]	1(3.13 %)	15(0.85 %)
Cell counting[29]	1(3.13 %)	38(2.15 %)
Control		
Patients having surgery for shoulder instability/dislocation[30]	10(31.25 %)	84(6.94 %)
Fresh cadavers with no shoulder pain before death[31]	4(12.50 %)	35(2.89 %)
Traumatic acromioclavicular joint dislocation[32]	1(3.13 %)	4(0.33 %)
Humerus fracture[33]	3(9.38 %)	11(0.91 %)
Patients with acute trauma under shoulder surgery[34]	1(3.13 %)	2(0.17 %)
Mean age of recruited patients		
<50[35]	5(15.63 %)	157(12.99 %)
50–60[36]	13(40.63 %)	445(36.81 %)
60–70[37]	8(25.00 %)	487(40.28 %)
Unclear[38]	6(18.75 %)	120(9.93 %)
Sex (% Female)		
≥75 %[39]	1(3.13 %)	65(5.38 %)
50–74 %[40]	6(18.75 %)	356(29.45 %)
<50 %[41]	13(40.63 %)	380(31.43 %)
Unclear[42]	12(37.50 %)	408(33.75 %)

[1]From 6 of the analyzed studies[16, 17, 21, 22, 29, 32].[2] From 12 of the analyzed studies[12, 18–20, 23, 24, 27, 31, 37, 39–41].[3] From 14 of the analyzed studies [13–15, 25, 26, 28, 30, 33–36, 38, 51, 52]. [4] From 15 of the analyzed studies [16–19,21,24,25,28,31,35,36,39–41,52]. [5] From 9 of the analyzed studies[13, 14, 20, 26, 27, 29, 32, 34, 51]. [6] From 8 of the analyzed studies[12, 15, 22, 23, 30, 33, 37, 38]. [7] From 23 of the analyzed studies[12, 14–16, 18, 22–28, 30, 31, 33–36, 38–40, 51, 52]. [8] From 1 of the analyzed studies[13]. [9] From 8 of the analyzed studies[17, 19–21, 29, 32, 37, 41]. [10] From 1 of the analyzed studies [51]. [11] From 1 of the analyzed studies[22]. [12] From 3 of the analyzed studies [25, 28, 40]. [13] From 5 of the analyzed studies[20, 22, 29, 32, 37]. [14] From 8 of the analyzed studies[12, 16, 18, 19, 23, 26, 39, 40]. [15] From 16 of the analyzed studies[13–15, 22, 24, 27, 30, 31, 33–38, 41, 52]. [16] From 1 of the analyzed studies[32]. [17] From 2 of the analyzed studies[17, 21]. [18] From 32 of the analyzed studies[12–41, 51, 52]. [19] From 7 of the analyzed studies[17, 25, 28, 30, 33, 35, 36]. [20] From 18 of the analyzed studies[12, 15–21, 24, 25, 31, 32, 34, 35, 37, 39, 51, 52]. [21] From 12 of the analyzed studies[13–15, 22, 26, 29–31, 33, 36, 37, 41]. [22] From 4 of the analyzed studies[15, 27, 41, 51]. [23] From 16 of the analyzed studies[15, 17–19, 23–28, 30, 33, 35, 39, 40, 52]. [24] From 3 of the analyzed studies[12, 23, 36]. [25] From 4 of the analyzed studies[24, 25, 38, 52]. [26] From 1 of the analyzed studies[16]. [27] From 2 of the analyzed studies[36, 51]. [28] From 1 of the analyzed studies[15]. [29] From 1 of the analyzed studies[41]. [30] From 10 of the analyzed studies[12, 15, 18, 23, 25, 28, 31, 35, 37, 41]. [31] From 4 of the analyzed studies[16, 20, 21, 29]. [32] From 1 of the analyzed studies[20]. [33] From 3 of the analyzed studies[23, 37, 41]. [34] From 1 of the analyzed studies [27]. [35] From 5 of the analyzed studies[17, 20, 28, 29, 32]. [36] From 13 of the analyzed studies[16, 18, 19, 21–24, 26, 27, 30, 31, 33, 38]. [37] From 8 of the analyzed studies[13, 14, 35, 36, 39, 40, 51, 52]. [38] From 6 of the analyzed studies[12, 15, 25, 34, 37, 41]. [39] From 1 of the analyzed studies[52]. [40] From 6 of the analyzed studies[13–15, 24, 30, 51]. [41] From 13 of the analyzed studies [17, 20–22, 26, 28, 29, 31, 32, 34–36, 38]. [42] From 12 of the analyzed studies [12, 16, 18, 19, 23, 25, 27, 33, 37, 39–41].

[a] Including glenohumeral joint synovium, supraspinatus tendon, subscapularis tendon, synovium, supraspinatus tendon, subscapularis tendon, synovium. ELISA: enzyme-linked immunosorbent assay; FS: frozen shoulder; H&E staining: haematoxylin and eosin staining; IF: immunofluorescence; IHC: immunohistochemistry; IS: impingement syndrome; PCR: polymerase chain reaction; PMR: polymyalgia rheumatica; RA: rheumatoid arthritis; RCT: rotator cuff tear; RCD: rotator cuff disease.

inflamed bursa compared to the controls [12,15,18,25,28,31,37]. Specifically, five studies demonstrated that IL-6 and TNF-α expressions are significantly enhanced in the diseased bursa compared to the non-inflammatory groups [12,15,25,28,37]. Two studies explicitly illustrated a significant increase of IL-1β expression in the inflamed bursa compared to the non-inflammatory control bursa samples [12,18], while other studies presented no significant changes of IL-1β between groups [15,25,28]. The expression of MMP-1 and MMP-9 significantly increased in impingement syndrome (IS) patients with inflamed bursa versus healthy controls [12,37].

Comparisons of joints and bursa

One study compared samples from joints and SAB [17], and reported significantly increased expression of IL-1β and greater immune cell infiltration in the glenohumeral synovium than in the paired SAB obtained from patients with anterior shoulder instability [17](Supplementary Table S3).

Immunological findings on bursa fluid

Five studies reported on bursa fluid [48–52]. Characteristics of studies reported on bursa fluid summarized in Supplementary Table S4. Even though the number of studies was very limited, similar pattern of infiltrating leukocytes were found in bursa fluid of patients with bursitis [48–51] (Supplementary Table S5).

Tenosynovitis

Immunological findings were comparable in tenosynovium compared to bursa tissue, even though data was even more scarce. Eight studies reported on tenosynovitis were also included [8,42–47,51], which mostly derived from wrist tendon sheath [8,42–47]. Characteristics of studies reported on tenosynovitis summarized in Supplementary Table S6. Three of studies on RA were performed while patients were being treated by medications (Supplementary Table S1). Three studies on tenosynovium investigated the immunohistological changes [8,47,51], summarized in Supplementary Table S7. Two studies reported infiltrating leukocytes and synovial hyperplasia in tenosynovium of patients with RA [8,47](Supplementary Table S7). VEGF, IL-6, TNF- α were the most reported cytokines in RA tenosynovium [8,43,45,47] (Supplementary Table S8), while MMP-1, MMP-3, MMP-9 and MMP-13 were also observed [8,43,45](Supplementary Table S9). Only one study on RA compared diseased group to non-inflammatory controls [47]

Table 2
Cellular infiltrates and characteristics in bursa (continue in the next page).

Study	Disease	Tissue	Method	Infiltrating leukocytes	Macrophage	T cell	Fibroblast	B cell	CD34	Hyperplasia	Fibrosis	Neoangiogenesis
Chillemi, C., et al.,2011 [13]	RCT	SAB	H&E staining							+	+	+
Chillemi, C., et al.,2016 [14]	RCT	SAB	H&E staining							+	+	+
Feng, H., et al.,2019 [15]	RCT	SAB	H&E staining/IHC	+		-(CD3)	+ (fibroblast-like cells)	-(CD20+)	+			+
Gotoh et al.,1999 [17]	Anterior shoulder instability	SAB	IHC	–								
Gotoh et al.,2001 [18]	RCD	SAB	IHC	+			+					
Hyvönen, P., et al.,2003 [20]	IS	SAB	IHC	–							+	
Ishii, H et al.,1997 [22]	RCT, IS, calcifying tendinitis	SAB	H&E staining	+		–	+					
Ko, J. et al.,2008 [24]	Complete RCT with shoulder stiffness	SAB	IHC/IF	+			+ (myofibroblasts)					
Minkwitz, S., et al.,2021 [26]	RCD	SAB	H&E staining	+ [a]	+ [a]					+ [a]	+ [a]	
Rahme, H et al.,1993 [29]	IS	SAB	H&E staining								+	
Reitsema, R., et al., 2022 [51]	Polymyalgia Rheumatica	SAB	IHC	+	+	+(CD4+, CD8+)		-(CD20+)				
Robertson, C. M., et al.,2012 [30]	RCT	SAB	H&E staining	+								
Sakai, H., et al.,2001 [31]	RCT	SAB	H&E staining				+			+		
Santavirta, S., et al.,1992 [32]	Rotator cuff tendinitis/IS	SAB	IHC	+	+ (CD11b+)	+(CD2, CD4)	+ (Fibroblast-like cells)	-(CD19+)				
Shindle, M. K., et al.,2011 [33]	RCT	SAB	H&E staining	+								
Steinert, A. F.,2015 [34]	RCT	SAB	IHC	+			+(CD90, fibroblast-like cells)					
Utsunomiya, H., et al.,2013 [36]	Full-thickness RCT	SAB	H&E staining				+		+	+		
Voloshin, I., et al.,2005 [37]	Impingement with full-thickness RCT	SAB	H&E staining	+								
Yoshida, H et al.,2003 [40]	FS or RCD	SAB	PCR						+			
Zhu, J., et al.,2004 [41]	RCT	SAB	H&E staining	–								
			Electronmicroscopy	+	+ (macrophage-like cells)		+ (fibroblast-like cells)					

+ Indicates certain cellular infiltrates and characteristics exist in the samples; - indicates none/rare/ undetectable in the tissue. [a] Insufficient patient sample. FS: frozen shoulder; H&E staining: haematoxylin and eosin staining; IS: impingement syndrome; RCD: rotator cuff disease; RCT: rotator cuff tears; SAB: subacromial bursa.

Table 3
Cytokine expression in diseased specimens in individual studies.

Study	Disease	Sample	Method	IL-6	IL-1β	IL-8	TNF-α	TGF- β	VEGF
Blaine et al.,2005 [12]	IS and RCD	SAB	Gene expression arrary	+	+		+		
			IHC	+	+(IL-1)		+		
Feng, H.,et al.,2019 [15]	RCT	SAB	PCR		+		+		+
			Western Blot	+	+				
			IF	+	+				
Gotoh et al.,1999 [17]	Anterior shoulder instability	SAB	PCR, IHC		–				
Gotoh et al.,2001 [18]	RCD	SAB	PCR		+				
			IHC		+				
Handa, A., et al.,2003 [19]	RCD with/without type II diabetes	SAB	PCR						+
			IHC						+
Ko, J. et al.,2008 [24]	Complete RCT with shoulder stiffness	SAB	PCR	+	+		+		
			IHC/IF	+	+		+		
Kuo, S. J., et al.,2018 [52]	RCT	SAB	IHC/PCR		+				
			ELISA		+				
Lho, Y. M., et al.,2013 [25]	FS	SAB	PCR	+	+		+		
Minkwitz, S., et al.,2021 [26]	RCD	SAB	PCR	+ [a]	+ [a]		+ [a]	-(TGF β1) [a]	
Neuwirth, J., et al.,2006 [27]	RCT	SAB	PCR		–		+	+	+
Nishimoto, H., et al.,2022 [28]	FS	SAB	PCR	+	+		+		
Robertson, C. M., et al.,2012 [30]	RCT	SAB	PCR	+	+		+		+
Sakai, H., et al.,2001 [31]	RCT	SAB	IHC		+		+	+	
Shindle, M. K., et al.,2011 [33]	RCT	SAB	PCR	+	+		+		+
Voloshin, I., et al.,2005 [37]	Impingement with full-thickness RCT	SAB	IHC	+	+(IL-1)		+		
Wellington, I., et al.,2022 [38]	RCT	SAB	ELISA	+	–		–		+
Yanagisawa, K., et al.,2001 [39]	RCD	SAB	PCR						+
			IHC						+
Yoshida, H et al.,2003 [40]	FS or RCT	SAB	PCR		–	+			

+ Indicates certain cytokines are present in the samples; - indicates none/rare/ undetectable in the samples. [a] Insufficient patient sample. ELISA: enzyme-linked immunosorbent assay; FS: frozen shoulder; IF: immunofluorescence; IHC: immunohistochemistry; IS: impingement syndrome; PCR: polymerase chain reaction; RCD: rotator cuff disease; RCT: rotator cuff tears; SAB: subacromial bursa.

Table 4
Enzymes (MMPs and COX) and neurotransmitter expression in diseased specimens in individual studies.

Study	Disease	Tissue	Method	MMP-1	MMP-3	MMP-9	MMP-13	COX-1	COX-2	Substance P
Blaine et al.,2005 [12]	IS and RCD	SAB	IHC	+		+		+	+	
Feng, H., et al.,2019 [15]	RCT	SAB	H&E staining	+			+			
			PCR	+			+			+
Gotoh et al., 1998 [16]	RCD	SAB	Radioimmunoassay/ IHC							+
Ide, K., et al.,1996 [21]	Recurrent shoulder dislocation or proximal humeral fracture	SAB	IHC							+
Lho, Y. M., et al.,2013 [25]	FS	SAB	PCR/IHC					–	+	
Minkwitz, S., et al.,2021 [26]	RCD	SAB	PCR	+[a]		- [a]			+ [a]	
Robertson, C. M., et al.,2012 [30]	RCT (versus. Healed)	SAB	PCR	+		+	+		+	
Nishimoto, H., et al., 2022 [28]	FS	SAB	PCR		+	+	+			
Shindle, M. K., et al.,2011 [33]	RCT	SAB	PCR	+		+	+		+	
Voloshin, I., et al.,2005 [37]	Impingement with full-thickness RCT	SAB	IHC	+		+		+	+	
Wellington, I., et al.,2022 [38]	RCT	SAB	ELISA	+	+		+			

+ Indicates certain enzyme or neurotransmitter was present in the samples; - indicates none/rare/undetectable in the samples. [a] Insufficient patient sample. ELISA: enzyme-linked immunosorbent assay; FS: frozen shoulder; H&E staining: Haematoxylin and Eosin staining; IHC: immunohistochemistry; IS: Impingement syndrome; PCR: polymerase chain reaction; RCD: rotator cuff disease; RCT: rotator cuff tears; SAB: subacromial bursa.

(Supplementary Table S10). Four RA studies suggested the expression of pro-inflammatory cytokines and MMPs was either comparable in both tissue compartments or perhaps increased in the joint synovium [8, 43–45] (Supplementary Table S11).

Discussion

To the best of our knowledge, this study is the first to systematically review the immunological perturbations in the bursitis in rheumatic inflammatory, degenerative and mechanical diseases. This systematic review identified a critical knowledge gap in understanding immune perturbations in bursal tissue inflammation cause by rheumatic inflammatory, degenerative diseases or mechanical stress. Studies on tenosynovitis and bursa fluid were even rarer. Data on tenosynovium was only from RA studies. However, generic pattern of inflammation was found, including hyperplasia and IL-6. The available data revealed a generic inflammation pattern characterized by altered tissue morphology, leukocytes infiltration and enhanced expression of proinflammatory cytokines in inflamed bursal tissue, irrespective of etiology.

We found a consistent pattern of inflammation in the bursa of

Table 5
Histomorphology in rheumatic inflammatory diseases in comparison with the non-inflammatory controls[a].

Study	Disease	Tissue	Method	Vascularity	Infiltrating leukocytes	Macrophage	Fibroblast	Fibrosis	Hyperplasia
Feng, H., et al.,2019 [15]	RCT	SAB	H&E staining	(↑)	(↑)		(↑) (fibroblast-like cells)		
			IHC		(↑)	(↑)			
Gotoh et al.,2001 [18]	RCD	SAB	PCR	(↑)	(↑)		(↑)		
			IHC		(↑)		(↑)		
Hyvönen, P., et al.,2003 [20]	IS	SAB	IHC	(↑)	(↑)			↑	
Rahme, H et al.,1993 [29]	IS	SAB	H&E staining					↑	
Sakai, H., et al.,2001 [31]	RCT	SAB	H&E	(↑)	(↑)		(↑)		(↑)
Voloshin, I., et al.,2005 [37]	Impingement with full-thickness RCT	SAB	H&E staining		(↑)				
Zhu, J., et al.,2004 [41]	RCT	SAB	H&E staining	(↑)	=				
			Electron microscopy		=	= (macrophage-like)	=		

↑ Indicates significant increase histomorphology changes compared to the non-inflammatory control; (↑) indicates trend for increase, unclear whether significant, or no statistical test shown; = indicates rare/no difference compared to the non-inflammatory control. [a] The controls include subjects undergoing surgery for shoulder instability, cadaver, patients with traumatic acromioclavicular joint dislocation, and patients with healed rotator cuff tear. FTG: full-thickness tear group; H&E staining: haematoxylin and eosin staining; IHC: immunohistochemistry; IS: impingement syndrome; PCR: polymerase chain reaction; RCD: rotator cuff disease; RCT: rotator cuff tears; SAB: subacromial bursa.

Table 6
Cytokines and enzymes expression in rheumatic inflammatory diseases in comparison with the non-inflammatory controls[a].

Study	Disease	Tissue	Method	IL-6	IL-1β	TNF-α	VEGF	MMP-1	MMP-9	MMP-13	COX-1	COX-2
Blaine et al.,2005 [12]	IS and RCD	SAB	Gene expression arrary	↑	↑	(↑)						
			IHC	↑	↑	↑		↑	↑		(↑)	(↑)
Feng, H., et al.,2019 [15]	RCT	SAB	PCR	↑	=	↑	↑	↑		↑		
			Western blot	(↑)	(↑)							
			IF	(↑)	(↑)							
Gotoh et al.,2001 [18]	RCD	SAB	PCR		↑							
			IHC		(↑)							
Lho, Y. M., et al.,2013 [25]	FS	SAB	PCR	↑	=	↑					=	↑
Nishimoto, H., et al., 2022 [28]	FS	SAB	PCR	↑	=	↑			=	↑		
Sakai, H., et al.,2001 [31]	RCT	SAB	IHC		(↑)	(↑)						
Voloshin, I., et al.,2005 [37]	Impingement with full-thickness RCT	SAB	IHC	↑	↑(IL-1)	↑		↑	↑		↑	↑

↑ Indicates significantly increased expression of certain cytokine or MMPs compared to the non-inflammatory control; (↑) indicates trend for increase, unclear whether significant, or no statistical test shown; = indicates rare/no difference compared to the non-inflammatory control. [a] The controls include subjects undergoing surgery for shoulder instability, cadaver, patients with traumatic acromioclavicular joint dislocation, patients underwent hand surgery for indications other than inflammatory synovitis, and patients with healed rotator cuff tear. ELISA: enzyme-linked immunosorbent assay; FS: frozen shoulder; H&E staining: haematoxylin and eosin staining; IF: immunofluorescence; IHC: immunohistochemistry; IS: impingement syndrome; PCR: polymerase chain reaction; RCD: rotator cuff disease; RCT: rotator cuff tears; SAB: subacromial bursa.

affected patients compared to non-inflammatory controls based on limited data. Biopsies from patients with bursitis displayed elevated expression of pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α, along with a wide expansion of infiltrating leukocytes, in contrast to non-inflammatory controls. The infiltrating leukocytes in these tissues might contribute to the pathogenesis and tissue damage observed in these diseases.

Surprisingly, a negligible difference was found in immunological perturbations across various disease conditions. Despite a limited number of studies, our results exhibit resemblances in tissue morphological and immunological alterations between mechanical stress associated diseases and rheumatic inflammatory diseases. This implies that a generic manifestation of inflammation occurs in bursitis regardless of the underlying cause of the disease (Fig. 2). The manifestation of inflammation includes leukocyte infiltration, synovial hyperplasia and fibrosis, consistent with previous studies regarding the associations between synovial histological changes and changes in the blood compartment [53,54]. As an exception, fibrosis was primarily reported in rotator cuff diseases or impingement syndrome.

Therapeutic targets were consistently expressed in bursitis across various diseases. IL-6, IL-1β and TNF-α were among the most frequently expressed cytokines in bursa of patients with rheumatic inflammatory diseases. The upregulation of these cytokines in active rheumatic diseases aligns with existing literature, particularly highlighting the pathogenic role of IL-6 in rheumatic diseases [55,56]. IL-6 (receptor) blockade is an established treatment for RA and has become a promising treatment modality in other rheumatic diseases[57]. Similarly, IL-1β blockers [58] and TNF-α inhibitors [59] have also been developed as successful immunosuppressive drugs. This study indicates that shared pro-inflammatory cytokines such as IL-6(receptor) may serve as promising therapeutic targets for bursitis caused by different types of conditions. However, current knowledge is mostly descriptive and far from enough for identifying effective disease-specific therapeutic targets.

This systematic review revealed that current insights on bursitis are

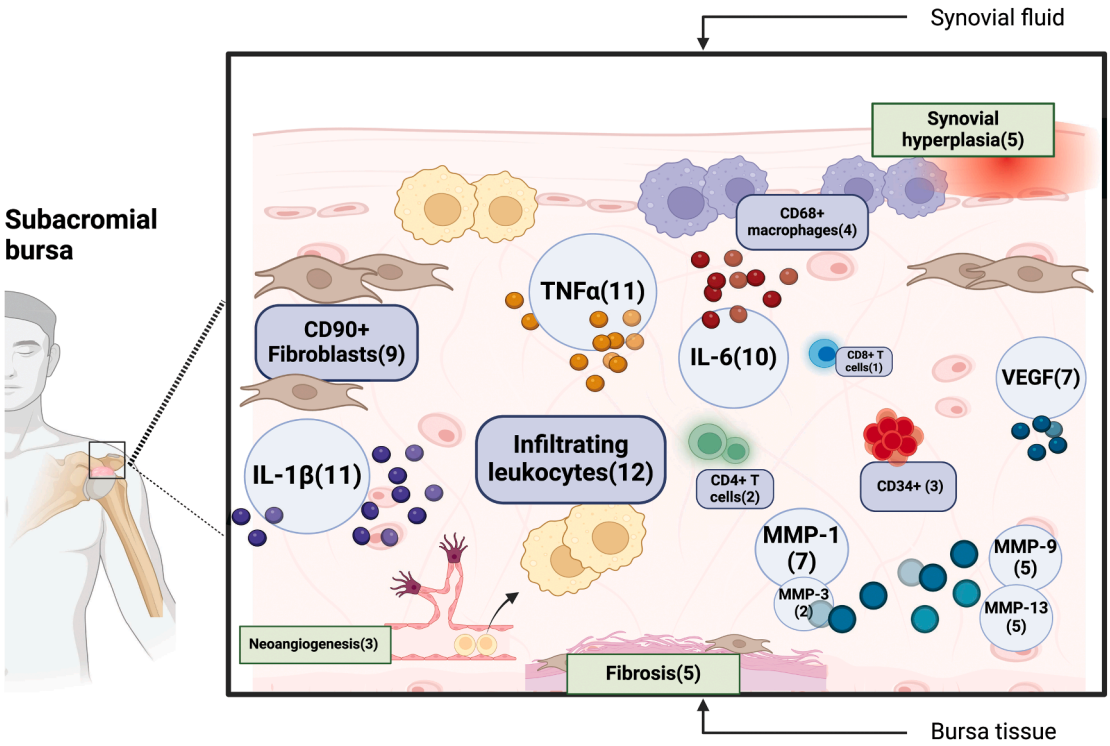

Fig. 2. Generic immunopathological features in bursitis.
*Numbers in the brackets represent the number of studies that reported this finding. Common morphological and immunobiological features of subacromial bursitis: infiltrating leukocytes in 12 studies [1–12], TNF-α in 11 studies [1, 4, 5, 7, 9, 11, 13–17], IL-1β in 11 studies [1, 2, 4, 5, 7, 9, 13, 14,16–18], IL-6 in 10 studies [1, 4, 5, 7, 9, 11, 13, 14, 16, 19], CD90+ fibroblast in 9 studies [1–4, 8, 10, 12, 17, 20], VEGF in 7 studies [1, 7, 9, 15, 19, 21, 22], MMP-1 in 7 studies [1, 5, 7, 9, 11, 13, 19], COX-2 in 6 studies [5, 7, 9, 11, 13, 14], MMP-9 in 5 studies [7, 9, 11, 13, 16], MMP-13 in 5 studies [1, 7, 9, 16, 19], synovial hyperplasia in 5 studies [5, 17, 20, 23, 24], fibrosis in 5 studies [5, 23–26], CD68+ macrophages in 4 studies [5, 6, 8, 12], CD34+ in 3 studies [1, 20, 27], COX-1 in 2 studies [11, 13], TGF-β in 2 studies [15, 17], MMP-3 in 2 studies [16, 19], CD4+ T cells in 2 studies [8, 26], CD8+T cells in 1 study [6]. Figure designed with Biorender®.

limited and outdated, particularly in rheumatic diseases. Firstly, most studies were published before 2010. Data on the immune pathology is based on studies applying traditional techniques such as immunohistochemistry, PCR and ELISA. Comprehensive immune cell profiling is missing in this field. Secondly, most data were presented descriptively and therefore expression levels were not summarized quantitatively in this review. Thirdly, much fewer studies on bursitis focused on rheumatic inflammatory diseases than degenerative and mechanical stress associated diseases. Although bursitis is a key feature in rheumatic diseases, only one relevant study could be retrieved investigating bursitis in PMR. Immunological perturbations of bursitis were also not reported for other rheumatic inflammatory diseases in our primary search. A supplemental search for bursitis in other rheumatic inflammatory disease (e.g., systemic lupus erythematosus and systemic sclerosis), also did not provide any relevant studies (Supplementary Figure S1). This could be majorly attributed to the limited access to bursa tissue samples from patients with rheumatic inflammatory diseases. However, the introduction of minimally invasive biopsies techniques, for instance through core needle biopsy guided by ultrasound, now makes this more feasible.

Limited understandings of local inflammation in this field would hinder the development of therapeutic management. Biopsies are taken regularly in oncology and play a critical role in guiding personalized treatment decisions, optimizing interventional procedures, validating histopathological classifications, and advancing biomarker discovery [60]. On the contrary, bursa biopsies from patients with rheumatic diseases associated bursitis were rare. The limited investigation of bursa biopsies in the field of rheumatic diseases limits opportunities for therapy development and disease stratification focused on this peri-articular inflammation that occurs commonly, and especially in polymyalgia rheumatica.

While the experimental methodology in the studies primarily relied on traditional techniques such as IHC and PCR, further in-depth analyses of biopsies are warranted to unravel the molecular pathways and mechanisms of bursitis. This includes multi-omics techniques such as spatial transcriptomics, single cell RNA sequencing and imaging mass cytometry. Such an approach would provide a clearer panoramic view on the immunological heterogeneity of bursitis.

Despite these insights, this systematic review has several limitations. Foremost, a quantitative meta-analysis was not possible due to the qualitative nature of the data. This also pinpoint the fact that quantitative studies and updates on rheumatic diseases related bursitis using state of art techniques are in dire need. Furthermore, studies on rheumatic inflammatory bursitis were very few. The only rheumatic inflammatory information comes from one study on PMR, while data on systemic lupus erythematosus, Sjogren's syndrome, scleroderma or vasculitis were not found. Besides, most data on bursa tissue focused on the subacromial bursa, while examination of other bursae was rare. It would be interesting to extend the analysis to other bursa, for example the olecranon bursa and trochanteric bursa, as distinct mechanical loading environments may affect the resulting biological responses. Notably, the tissue samples in selected studies may have a selection bias and reduced generalizability, since they were taken out probably at a later stage of the disease. The medication and treatments were not taken into consideration or not provided in most included studies. Also, the number of patients were relatively small in the majority of studies, which decreased the statistical power within studies. At last, there was substantial heterogeneity in the methods, which could have explained some of the discrepancies among the studies. The influential factors consist of subject selection and disease progression, complications, study design, and use of medications.

In conclusion, this review unraveled a significant knowledge gap in

immunopathology of bursitis caused by rheumatic inflammatory diseases. Current data only revealed a generic and aspecific pattern in immunological perturbations, such as elevated IL-6 expression, in bursitis associated with rheumatic inflammatory, degenerative, and mechanical stress-associated diseases. To identify disease-specific therapeutic markers, it is imperative to perform in depth comprehensive analysis of immune cells and pro-inflammatory cytokines by novel, high throughput multi-omics approaches in different rheumatic inflammatory diseases at the site of bursal inflammation.

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Ethics in publishing

No ethical approval was required for this systematic review as it included data from published studies.

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Author contributions

K.S.M.G. conceptualized the study. Literature search, screening and data collection were performed by A.Z. and K.S.M.G. The first draft of the manuscript was written by A.Z, and was critically revised by K.S.M.G. and E.B. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Kornelis van der Geest reports a relationship with Abbvie that includes: funding grants. Kornelis van der Geest reports a relationship with Roche that includes: speaking and lecture fees. Elisabeth Brouwer reports a relationship with Roche that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152527.

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