Calprotectin as a Marker

of Disease Activity In Spondyloarthritis

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Abstract

Introduction

Spondyloarthritis is a group of arthritic diseases that classically manifest as inflammation of the sacroiliac and limb joints, as well as the axial skeleton. Microscopic bowel inflammation is identifiable in over 50% of these patients. Calprotectin measured in the serum and stool is an emerging surrogate marker of disease activity and/or bowel inflammation in spondyloarthritis.

Objective

This article aims to review published literature to determine the accuracy of serum and faecal calprotectin levels for use in monitoring bowel inflammation and spondyloarthritis disease activity.

Methods

Boolean operator strategy was used to search two databases (Embase and PubMed) and 52 relevant articles were identified. Duplicate results were eliminated, inclusion and exclusion criteria were applied.

Results

Ten studies met the inclusion criteria and were summarized and analyzed. The EBL Validity questionnaire was applied to determine study quality. All research articles found calprotectin to be elevated in spondyloarthritis patients when compared to controls. Faecal calprotectin was superior in detecting disease activity and correlated with disease activity questionnaires, radiology and endoscopy results. Only one study assessed the effect of treatment on calprotectin and its correlation to bowel inflammation.

Conclusion

Faecal calprotectin shows promise as a surrogate marker for disease activity and bowel inflammation in spondyloarthritis. Future studies should focus on the effect of treatment on faecal calprotectin and whether some treatments are better at preventing the progression of bowel inflammation in addition to treating spondyloarthritis. Supplementary investigations are needed to identify whether faecal calprotectin is useful as a marker of disease activity in response to treatment.

Keywords

Spondyloarthritis, SpA, Disease Activity, Calprotectin, Bowel Inflammation

Introduction

Spondyloarthritis

Spondyloarthritis (SpA) encompasses several arthritic diseases: ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, and SpA with inflammatory bowel disease [1]. These diseases are grouped by similarities in pathophysiology; characteristically: progressive inflammation and structural joint damage. Clinical manifestations are common in: entheses, sacroiliac joints, and the axial skeleton. Extra-articular sites include: the gut, skin, eyes and aortic valve [1]. These diseases affect roughly 1% of the adult population [2], predominantly males. Though only a small portion of the population positive for the HLA-B27 haplotype develop spondyloarthritis, this genetic marker is in part responsible for genetic susceptibility [3] .

Bowel Inflammation

Over 50% of SpA patients have histopathology consistent with bowel inflammation in the absence of gastrointestinal symptoms [3]. The degree of bowel inflammation may be a marker of disease prognosis as it is associated with bone marrow oedema in sacroiliac joints and disease progression [4, 5]. Bowel inflammation is classically measured via colonoscopy. However, it is an expensive, invasive and unpleasant procedure. Calprotectin is emerging as a surrogate marker.

Calprotectin

Calprotectin is a pro-inflammatory calcium-binding protein released from monocytes and granulocytes [6]. Calprotectin levels are measurable in the stool and rise with increased bowel inflammation [7]. Often, faecal calprotectin (FC) is used to diagnose and monitor treatment in patients with inflammatory bowel disease (IBD) [7]. Alternatively, calprotectin can also be tested in the serum and is a useful marker of disease activity and joint inflammation in rheumatoid arthritis [8].

Inclusion	Exclusion
• Adults only (18 years plus) • English • 2010-2020 • Human only subjects • Full Text Access • Articles focusing on any/all Spondyloarthritis subtype(s)	• Inflammatory bowel disease as the primary disease • Focus on other rheumatic diseases • Any articles without original research (i.e. Review articles) • Conference Abstracts

Table 1: Inclusion and Exclusion Criteria

In the past decade, calprotectin in the stool and serum has been explored as a possible marker of disease activity in patients with spondyloarthritis. Microscopic bowel inflammation in SpA patients occurs without gastrointestinal symptoms and may eventually develop into Crohn's disease. Minimizing the chances of disease progression in spondyloarthritis is reliant on an accurate and accessible marker of disease activity.

Objectives

1) To determine the efficacy of serum and faecal calprotectin in detecting subclinical bowel involvement in patients with Spondyloarthritis.

2) To determine if serum and/or faecal calprotectin are suitable markers of disease activity in spondyloarthritis.

Methods

Two databases were searched (Embase and PubMed). The inclusion and exclusion criteria are presented in Table 1. In total, 10 papers met the criteria, were included in the literature review, and are summarized in Table 2. To outline article quality, the EBL Validity questionnaire was applied to all articles and validity scores calculated (Table 4).

Primary Search

The initial search was conducted using Embase (Figure 1). The search made use of Boolean operators to structure results. The search strategy was: (spondylarthritis OR spondyloarthropathy OR spondyloarthritis OR SpA) AND (gastrointestinal OR digestive OR gut OR enteropathy OR intestine OR gi OR bowel) AND (calprotectin OR calprotectin test kit OR calprotectin elisa kit). This yielded 32 articles. Narrowing by human subjects only, adults and published 2010-2020, reduced the results to 16. Limiting to articles only, removed 12 con-

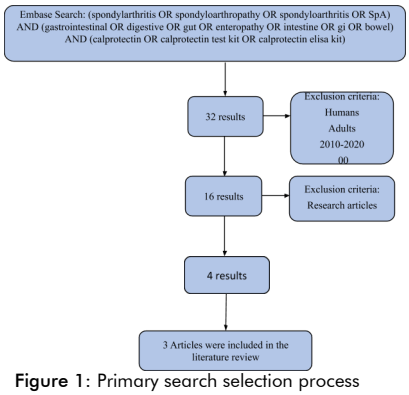

Figure 1: Primary search selection process

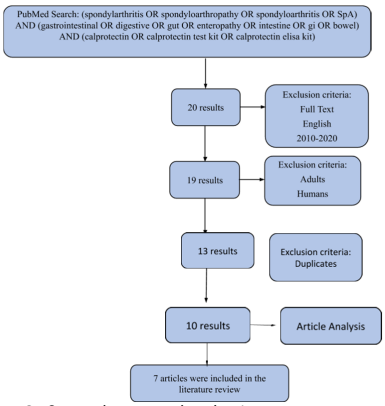

Figure 2: Secondary search selection process

ference abstracts. One did not meet inclusion criteria after article analysis. Three articles were included in the literature review. The selection strategy is visualised in Figure 1.

Secondary Search

The secondary search was conducted using PubMed (Figure 2). The same search strategy was repeated. This yielded 20 results. Narrowing the results to full text, English results published 2010-2020, left 19 articles. Further narrowing by adults and humans yielded 13 articles. Any duplicate articles that were selected through the Embase database were removed. After article analysis, only 7 articles met the inclusion criteria and were included. The selection strategy is visualized in Figure 2.

Results

Abbreviations used:

Anti-TNFα: anti- Tumour Necrosis Factor alpha

Anti-TTG: Anti-tissue Transglutaminase Antibody

AS: Ankylosing Spondylitis

ASDAS: Ankylosing Spondylitis Disease Activity Score

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASFI: Bath Ankylosing Spondylitis Functional Index

BAS-G: Bath Ankylosing Global Score

BASMI: Bath Ankylosing Metrology Index

BASRI: Bath Ankylosing Spondylitis Radiology Index

CBC: Complete blood count

CD: Crohn's Disease

CRP: C-reactive protein

DM: Diabetes Mellitus

ESR: Erythrocyte sedimentation rate

fCAL/FC: Faecal calprotectin

GI: Gastrointestinal

Hb: Haemoglobin count

HBI: Harvey- Bradshaw index

IBD: Inflammatory Bowel Disease

MRI: Magnetic Resonance Imaging

NSAID: Non-steroidal Anti-inflammatory Drugs

PLT: Platelet Count

QOL: Quality of Life

RA: Rheumatoid Arthritis

SI joints: Sacroiliac Joints

SpA: Spondyloarthritis

WBC: White blood cell count

Calprotectin and Disease Activity Questionnaires

All studies identified calprotectin to be significantly increased in patients with SpA. Only five articles reported a correlation with disease activity [9,10,12,14,17] as measured by validated disease activity questionnaires: BASDAI and ASDAS [18]. The studies had diverging results as some found a correlation between FC and ASDAS but not BASDAI [9] while another found a correlation with BASDAI/ BASFI [12]. One study found a correlation between FC and both ASDAS and BASFI [17] while another failed to correlate serum calprotectin with any of the disease activity questionnaires [11]. Higher fecal calprotectin levels and higher scores on BASDAI and BASFI were identified in patients who were subsequently diagnosed with co-morbid Crohn's Disease [15]. In a longitudinal study [14], a higher FC at baseline was correlated with increased disease activity on all questionnaires at a 5-year follow-up assessment.

Calprotectin and Radiology

Patients with higher FC levels have significantly more radiographic inflammatory lesions in the sacroiliac joints [16, 17].

Calprotectin and Bowel Inflammation

Those with higher FC are more likely to test positive for IBD related serology [10]. This is present in the absence of GI symptoms [9,12]. Higher serum and stool calprotectin are present in those with microscopic bowel inflammation, irrespective of CRP [6]. High FC and the presence of diarrhea with mucous are the best pre-

dictors of subsequent diagnosis with IBD [14].

FC was found to be correlated with histologically chronic inflammation of the bowels, while serum calprotectin was associated with acute inflammation [6]. A long-term study found development of bowel inflammation in 7.4% of patients tested with ileocolonoscopy at 5-year follow-up [14]. Capsule Endoscopy reveals higher FC levels to be better correlated with inflammation localized to the colon [15]. In patients with high FC, 80% had recognizable bowel lesions while only one patient with normal FC had bowel lesions [16].

Serum versus Faecal calprotectin

Two studies measured serum calprotectin [11,13], four measured faecal calprotectin [10,15,16,17] and four measured both [9,6,12,14]. Serum calprotectin was found to be higher in patients [11,13] when comparing to controls but failed to identify patients on an individual level [13]. When measured together, faecal calprotectin was superior in measuring disease activity. Two studies found faecal calprotectin to be increased in SpA patients while serum calprotectin was not [9,12]. One study found serum calprotectin to be positively correlated with faecal calprotectin but failed to identify it as a predictor of IBD diagnosis [14].

The effect of treatment

Frequent NSAID use was correlated with a higher FC, but occasional or rare use was not [9]. Patients with higher FC at baseline were found to have a better treatment response to anti-TNF alpha therapy [16].

Discussion

Disease Activity

This review aimed to discern the accuracy of serum and faecal calprotectin in reporting disease activity and/or bowel inflammation in spondyloarthritis (SpA). All studies identified calprotectin levels to be a significantly increased in patients with SpA. Faecal calprotectin was more effective than serum calprotectin at detecting disease activity. The bowel is close to the main sites of involvement in SpA, the sacroiliac joints and axial spine. Thus, the inflammation of the bowel may be due to an increase in circulating inflammatory mediators attacking vulnerable proximal tissue.

Serum calprotectin is a non-specific measure of inflammation. High levels are associated with various inflammatory processes: complications with organ transplants [19], early stages of pulmonary diseases [20] and rheumatoid arthritis [8], and may be deceptively negative in neutropenic patients [21]. Literature relating serum calprotectin levels to spondyloarthritis is limited. Articles included in this review did not conclusively agree that serum calprotectin used in isolation is a robust marker for disease activity.

Of the studies included, half studied patients with ankylosing spondylitis (AS) only. AS classically affects the sacroiliac joints and axial spine. In severe cases, the intervertebral discs calcify, the joint spaces narrow and this can lead to fusion of the facet joints, termed - "bamboo spine" [22]. Two studies in these patients [9,12] found a significantly higher faecal calprotectin when compared to controls but no difference in serum calprotectin. It is possible that axial symptoms in these patients contribute to inflammation of the bowel but not diffuse inflammation.

Since many different validated disease activity questionnaires exist to assess spondyloarthritis, there was some variation in correlations of calprotectin and disease activity. However, all but one study [11] using any disease activity questionnaire found a positive correlation between calprotectin and disease activity. It is important to note; the study in question had a small sample size (N=31) and only collected blood samples from AS patients. Another study [6] suggests serum calprotectin is better correlated with acute rather than chronic inflammation. It is possible, participants were long-term patients and thus well treated, minimizing serum calprotectin.

Bowel Inflammation

Studies using radiographic imaging or endoscopy found an association between faecal calpro-

tectin and disease activity. Patients with high faecal calprotectin were highly likely to have bowel lesions and increased risk of progression to inflammatory bowel disease. However, some studies [9,14,16] had target levels for faecal calprotectin in order to perform ileocolonoscopy. Since only patients with higher local inflammation provided histological samples it is possible that results were skewed. Nevertheless, studies that performed some sort of endoscopy on all patients [6,15,16], regardless of faecal calprotectin level, found similar significant results associating bowel inflammation severity to faecal calprotectin. Overall, faecal calprotectin was affective in detecting bowel inflammation, correlating to disease activity and providing a prognosis for the development of disease.

Effect of Treatment

NSAIDs utilized prior to sample collection can increase faecal calprotectin [23]. However, only five of studies [9,10,14,15,16] accounted for this via analysis of results or exclusion criteria. Though most studies found a positive relationship between faecal calprotectin and SpA patients, this may be in part, due to NSAID use. One study investigated the effect of TNF-alpha inhibitors. Participants with higher faecal calprotectin prior to the commencement of treatment, had a better treatment response. It is important to note that, Adalimumab, the TNF-alpha inhibitor used in the study, is also used to treat inflammatory bowel disease (IBD) [24]. Thus, the possibility cannot be excluded that these patients had some early changes consistent with IBD that the drug may have masked.

Quality of Studies

Most studies included were of reasonably high quality (64-95% validity). A recurring issue was the lack of inclusion of questionnaires in publication as well as appropriate description of physical assessments. Many participants were also patients receiving follow-up assessments of their illness, it was often unclear whether the individual performing the medical assessment was the same as the researcher. Sample sizes also varied due to the use of pre-existing cohorts in comparison to seeking participants for the current project only. Overall, studies were simple and well analyzed and thus, their results externally valid.

Study heterogeneity

The literature examined in this review were highly variable, limiting comparability. The study focus differed amongst the articles. The availability of participants is the likely reason why five articles studied AS only [9]. Though there was overlap in measures used to quantify disease, some studies did not include radiology and/or endoscopy. Thus, the reliability of measurement is reduced to that of surrogate markers. Furthermore, there was variation in the criteria used to diagnose disease. Some studies used the modified New York Criteria, others used ICD-10 and the rest relied on the European Spondyloarthropathy Study Group criteria. The exclusion criteria were not unanimous throughout all studies as some studies addressed many confounding variables and comorbidities while others did not.

Limitations

All articles were published in the last 8 years and one article was included that was published online ahead of print [16]. It is possible that new articles may have been published since the original database search or may appear in the near future. Only free full text English articles were included in this review. One study was not available through the University College Cork library and was accessed via another university's library. This review involved only one author and is susceptible to selection bias and human error.

Future studies

Future studies should seek to understand the practicality of faecal calprotectin in monitoring disease activity in response to treatment. Only one published study investigated the effect of one drug, a TNF-α inhibitor. Spondyloarthritis patients could be using many types of treatment including: NSAIDs, disease modifying anti-inflammatory agents, and corticosteroids [25]. Since bowel inflammation is prevalent in more than 50% of SpA patients [3], research must explore the effect of these treatments on bowel

inflammation to identify drugs that are superior in treating SpA, while preventing the progression of bowel disease.

Conclusion

Spondyloarthropathies are progressive diseases with adverse effects on quality of life, directly associated with disease activity [26]. Increased disease activity is also associated with risk of subsequent diagnosis of bowel disease. Many markers of disease activity exist but involve expensive and invasive procedures. This literature review suggests the use of faecal calprotectin as an effective surrogate marker for bowel inflammation and disease activity in spondyloarthritis patients. Additional studies are necessary to investigate the effect of treatment on faecal calprotectin and bowel inflammation.

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