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Utilization of calprotectin in axial spondyloarthropathies - a review

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Abstract

Introduction and purpose

Axial spondyloarthropathies represent a group of chronic inflammatory conditions that primarily affect the joints. Calprotectin, an inflammatory biomarker, is predominantly utilized in the context of inflammatory bowel diseases. This paper aims to explore the potential relationship between calprotectin levels and axial spondyloarthropathies, as well as to discuss how this correlation could be applied in clinical settings.

Description

Axial spondyloarthritis (axSpA) is a chronic inflammatory disorder that primarily impacts the sacroiliac joints and the spine, leading to symptoms such as inflammatory back pain and stiffness. The etiopathogenesis of axSpA is complex and multifactorial, involving genetic factors like HLA-B27 and immune system dysregulation. Recently, calprotectin has emerged as a significant inflammatory biomarker, showing promise in relation to axSpA. Elevated calprotectin levels have been associated with increased disease activity, indicating its potential utility in monitoring inflammation and influencing treatment strategies. Nevertheless, the precise role of calprotectin in the pathogenesis and progression of axSpA remains unclear, necessitating further research to establish its clinical relevance.

Summary

Although axial spondyloarthritis (axSpA) is a condition that can be effectively managed, its chronic nature, along with symptoms like inflammatory back pain and stiffness, can significantly affect the quality of life for patients and induce anxiety in both patients and their families. The exploration of biomarkers such as calprotectin presents a promising opportunity for assessing disease activity and informing treatment strategies; however, its precise role remains unclear. Advancing research into calprotectin's involvement in axSpA is essential for developing innovative strategies for disease prevention, enhancing diagnostic accuracy, and deepening our understanding of the inflammatory mechanisms that underlie this condition.

Keywords: calprotectin; spondyloarthritis; axial spondyloarthritis; spondyloarthropathies; inflammatory bowel disease; calprotectin and spondyloarthropathies; arthritis.

Introduction and purpose

Spondyloarthritis (SpA) is a chronic inflammatory disease primarily affecting the spine and sacroiliac joints but can also involve peripheral joints and entheses (where tendons attach to bones). It typically develops in individuals under 45, most commonly between the ages of 20 and 30, and is more prevalent in men. Chronic inflammation in the sacroiliac joints and spine causes back pain and stiffness, which, over time, may lead to pathological new bone formation, structural damage, and, in some cases, fusion of these joints. Beyond joint involvement, the disease can also affect organs such as the intestines, uveal tract of the eye, and skin [1,2]. A distinction is made between the radiographic form of the disease, which is characterized by specific radiological findings, and the non-radiographic form, where clinical symptoms of SpA predominate but no changes are detected in imaging studies [3]. The HLA-B27 antigen plays an important role in the pathogenesis of the disease, though its exact mechanism remains incompletely understood [4]. The treatment of the disease includes both pharmacological and non-pharmacological approaches. The primary method for symptom relief involves nonsteroidal anti-inflammatory drugs (NSAIDs) and, more recently, biologic disease-modifying drugs. Additionally, rehabilitation, lifestyle changes, and patient education are recommended [5].

Calprotectin is a cytosolic protein produced mainly by neutrophils [6, 7]. It mainly has antibacterial functions and is part of the innate immune response. Calprotectin is found in virtually all body fluids; however, its concentration in stool is approximately six times higher

than in plasma. As a result, fecal calprotectin serves as a sensitive marker of inflammation, specifically associated with inflammation in the gastrointestinal tract [6].

Calprotectin is an important marker of ongoing inflammation in the body. It is important to note that spondyloarthropathies are chronic inflammatory diseases; therefore, calprotectin levels correlate with disease activity [8].

This article reviews the importance of fecal calprotectin in monitoring inflammatory activity in axial spondyloarthropathies.

Material and methods

The review was based on the analysis of materials collected in the „PubMed" and Google Scholar. The following keywords were entered during the search for scholarly articles: calprotectin; spondyloarthritis; axial spondyloarthritis; spondyloarthropathies; inflammatory bowel disease; calprotectin and spondyloarthropathies; arthritis. A total of 39 articles published between 2015 and 2024 were considered for the study and verified for their relevance to the topic of calprotectin in monitoring inflammatory activity in axial spondyloarthropathies.

Spondyloarthritis

Spondyloarthritis (SpA) is a group of inflammatory diseases with an immunological basis, strongly associated with the major histocompatibility complex (MHC) class I molecule, HLA-B27 [9].

Spondyloarthropathies can be divided into axial and peripheral types. In the peripheral form, there is involvement of the joints of the limbs and, for example, the sacroiliac joints. However, joint involvement of the spine is characteristic for both types. The term seronegative indicates that there is no rheumatoid factor IgM present in serum tests, while the HLA-B27 antigen is often present.

Disease entities classified as seronegative spondyloarthropathies include: ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease, and other spondyloarthropathies (SAPHO syndrome, juvenile, undifferentiated). Although these are different disease entities, they share many common features such as:

inflammation of the spine and sacroiliac joint, chronic back pain, extra-articular symptoms, early age of onset (<40 years), and elevated inflammatory parameters.

It is characteristic that the pain persists for more than three months, is most severe at night and in the morning, may be accompanied by morning stiffness, decreases after physical activity, does not improve with rest, and responds well to anti-inflammatory medications (NSAIDs).The most important and common extra-articular symptoms include: uveitis (about 20% of patients), psoriasis (about 10% of patients), inflammatory bowel disease (about 7% of patients), feelings of fatigue, weakness, and low-grade fever [10, 11, 12, 13].

Diagnosis

The diagnosis of axial spondyloarthritis (axSpA) can be challenging, and the average duration of symptoms before the diagnosis of axSpA is 13 years [10].

The main complaint that drives patients to undergo diagnostic procedures for axSpA is back pain. ASAS (The Assessment of SpondyloArthritis international Society) experts have developed criteria to identify patients with inflammatory back pain (IBP) (Table 1) [11].

Table 1. ASAS experts Inflammatory back pain (IBP) criteria.

BP if at least 4 out of 5 of the following parameters are present
1. age at onset <40 years
2. insidious onset
3. improvement with exercise
4. no improvement with rest
5. pain at night (with improvement upon getting up)

Diagnostic criteria for axSpA are based on the presence of sacroiliac joint inflammation in imaging or a positive HLA-B27 test result in the presence of other SpA features, such as: arthritis, colitis, Crohn disease, dactylitis, elevated CRP level, enthesis, family history of SpA or good response to NSAIDs [10].

Based on the radiological results of the sacroiliac joint, axial spondyloarthritis (axSpA) can be classified into radiographic axSpA (r-axSpA) with clear imaging damage and non-radiographic axSpA (nr-axSpA). In some patients with nr-axSpA, there is progression to r-axSpA [10, 14]. Research has shown that 5% to 25% of patients with nr-axSpA developed r-axSpA within 2 to 8 years after diagnosis [10].

Non-radiographic axSpA, which cannot be detected through conventional radiology, can be visualized using magnetic resonance imaging (MRI). MRI is currently the most accurate imaging method used in the diagnosis of axSpA. The advantage of using MRI in SpA is the ability to make an early diagnosis, both in cases of inflammatory symptoms and structural damage, which allows for the initiation of appropriate therapy [12].

Monitoring Disease Activity

Monitoring disease activity in patients with axSpA should include patient-reported outcomes (PROs), clinical findings, laboratory tests, and imaging studies. The frequency of monitoring should be determined individually based on symptoms, their severity, and the treatment being administered [15].

Commonly used instruments for assessing disease activity in patients with SpA are ASDAS (Ankylosing Spondylitis Disease Activity Score) and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index). BASDAI is a self-assessment tool that evaluates six symptoms measured on a visual analog scale (VAS) from 0 to 10. The measured symptoms include fatigue, spinal pain, pain and swelling in peripheral joints, pain at enthesis sites, and the severity and duration of morning stiffness. ASDAS incorporates components of BASDAI for spinal pain, pain and swelling in peripheral joints, and the duration of morning stiffness, as well as a global assessment of disease activity by the patient and the level of CRP [16]. The preferred scale remains ASDAS, which takes into account the patient's perspective and includes CRP as an objective measure of inflammation, while BASDAI reflects only the patient's perspective. Additionally, specific cut-off points have been established for ASDAS to define states of disease activity as well as criteria for improvement and worsening [15, 16].

MRI of the sacroiliac joints or spine can be used to assess inflammatory conditions. It is not routinely recommended for monitoring the activity of SpA. However, in cases of uncertainty regarding the origin of symptoms or the presence of inflammatory activity, MRI can help determine whether inflammation is present, thereby guiding therapeutic decisions [15].

X-rays of the spine can be used to assess structural damage to the joints. However, the progression of structural damage occurs slowly, so spinal X-rays should be performed at intervals of at least 2 years [15].

Musculoskeletal ultrasound (MSUS) is a widely available examination that allows for better assessment of disease activity in patients with SpA. However, a recent meta-analysis showed that MSUS of the sacroiliac joints demonstrates excellent effectiveness for diagnostic purposes but not for monitoring disease activity [12].

Treatment

In recent years, new medications have emerged for the treatment of SpA. With improved understanding of the pathogenic mechanisms underlying the disease, new targeted therapies and biological agents have been developed [12].

ZZSK – treatment

In the active form of the disease, treatment begins with non-steroidal anti-inflammatory drugs (NSAIDs). If after two weeks of taking the medication at the maximum or maximally tolerated dose the patient does not feel any improvement, the medication should be changed to another substance from the same group of drugs.
In cases of insufficient response to treatment, further management depends on the form of the disease. In cases where peripheral symptoms are dominant, local injections of corticosteroids or conventional disease-modifying drugs can be administered [17].

In axial spondyloarthritis, conventional disease-modifying drugs (e.g., sulfasalazine, methotrexate) should not be used, as they are not effective and do not alleviate the symptoms of the disease [18]. A TNF inhibitor, IL-17 inhibitor, or JAK inhibitor should be used. Currently used IL-17 inhibitor includes ixekizumab, for example. Promising results are also emerging from studies on a new JAK inhibitor drug – upadacitinib [17, 19, 20].

Psoriatic Arthritis – Treatment

According to the latest GRAPPA guidelines from 2021, the treatment of psoriatic arthritis should be tailored to the individual needs of the patient based on the clinical picture. First-line medications for both axial and peripheral forms are non-steroidal anti-inflammatory drugs (NSAIDs). In the peripheral form, classical disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, or sulfasalazine may also be considered, although they are not recommended for the axial form.

In cases where treatment for the peripheral form is ineffective, TNF-α inhibitors, IL-17, IL-12/23, IL-23, CTLA-4, PDE4 inhibitors, or JAK inhibitors should be administered. If therapeutic goals are not achieved in the axial form after four weeks of treatment, TNF-α and IL-17 inhibitors or JAK inhibitors may be introduced [21, 22].

In recent years, the role of pathobionts in the pathogenesis of HLA-B27-associated spondyloarthritis has been observed, making fecal microbiota transplantation (FMT) a promising therapeutic method for SpA. Research is ongoing regarding the use of FMT in patients with rheumatoid arthritis who are resistant to methotrexate treatment, as well as among patients with psoriatic arthritis and ankylosing spondylitis [9].

Calprotectin

Calprotectin (CLP) was first described in 1980, it belongs to the calcium-binding S100 group of leucocyte proteins, is a protein complex composed of S100A8 and S100A9 monomers, bound to a calcium ion. This protein is produced by neutrophils in the highest amount, and also by monocytes, dendritic cells, activated macrophages, oral keratinocytes, squamous mucosal epithelium and osteoclasts. Elevated levels of CLP are associated with the presence of the body's inflammatory response, infection or cancer [23, 24, 25]. It has antibacterial and antifungal activity due to its ability to bind with zinc and manganese ions and stimulate the secretion of pro-inflammatory cytokines [24, 26]. In addition to taking part in the inflammatory response, the protein is also responsible for maintaining cellular homeostasis and transmitting intercellular signals [27].

CLP levels are mainly tested in feces and serum. In serum, the normal range is about <1 ng/mL and <50 mg/gr in feces [27]. During an inflammatory reaction within the intestines, neutrophils migrate to intestinal cells and secrete CLP. It is a stable marker, resistant to intestinal proteases, and persists in feces at room temperature for up to 7 days, making it a very good indicator of the inflammatory response. In addition, this test is non-invasive and inexpensive. The main way to detect this protein in feces is by ELISA, but the point of care test (POCT) technique is also used [23, 27, 28]. It is worth noting that fecal CLP (fCLP) levels may be naturally elevated in children under 4 years of age compared to adults, and in newborns born by spontaneous delivery, compared to those born by cesarean section [23]. CLP in serum (sCLP) can be determined by ELISA and POCT, which is faster than ELISA. A

blood sample should be drawn into a tube of EDTA [27]. Elevated sCLP levels come from leukocytes circulating in the blood, which produce more of this protein in inflammatory disease [27].

In addition, CLP can also be determined in sputum in lung diseases, such as cystic fibrosis, and in joint fluid in inflammatory joint diseases like RA (rheumatoid arthritis) [24, 28].

CLP determination has a wide range of applications. The fCLP is used in the diagnosis of IBD (inflammatory bowel disease), assessing its progression and severity, which is possible due to the migration of inflammatory cells into the intestinal wall, which proportionately secrete calprotectin. The presence of blood in the stool, diarrhea, fever, unusual pain should prompt the doctor to evaluate fCLP. Low levels of it may indicate another diagnosis, such as IBS or viral infection [29].

Elevated sCLP levels can be seen in many situations involving inflammation in the body. Its level correlates with bacterial infection of the heart or kidneys, transplant rejection, the early stages of inflammation of lung tissue, bacterial sepsis and reflects ongoing arthritis. Some studies also indicate that determination of sCLP levels may be useful in cancer diagnosis - higher sCLP values have been observed in laryngeal cancer, compared to healthy patients and in those with benign laryngeal lesions [26]. Moreover, a study by Chen F. Et al. suggests that CLP monomer S100A9 may be a biomarker for cardiovascular disease, as it is observed to increase in atherosclerosis and myocardial hypoxia, which may help predict myocardial infarction [30]. In addition, sCLP is more specific for autoimmune diseases. It can be elevated in diseases such as systemic lupus, systemic scleroderma, rheumatoid arthritis, vasculitis, Sjogren's syndrome, myasthenia gravis and also can be used in the previously mentioned IBD [29]. In addition, studies indicate that sCLP has applications in the diagnosis of axial spondyloarthritis activity (axSpA), which will be described in more detail below [27].

Calprotectin in spondyloarthropathies

Calprotectin is regarded as one of the possible indicators of inflammatory activity in axial spondyloarthritis, as demonstrated by a number of studies . For example, one study attempted to determine values to differentiate ankylosing spondylitis (AS) from non-radiographic axial spondyloarthritis (nr-axSpA). Although no significant differences were found in calprotectin

levels to differentiate between these two diseases, the levels in both cases were higher than in the control group of healthy individuals [31].

Another study reports that elevated calprotectin levels in psoriatic arthritis(PsA) are present not only in fecal matter but also in blood serum, synovial fluid and psoriatic plaques [32].

Additional research indicates that calprotectin concentration is increased in ankylosing spondylitis (AS) compared to a healthy control group. Among 262 patients with AS and a control group of 260 healthy individuals, calprotectin levels were significantly higher in the AS group, showing a sensitivity of 80.2% and specificity of 92,7% [33].

In another article, the authors discussed the importance of serum inflammatory biomarkers in distinguishing early axial spondyloarthritis (axSpA) from other pathologies in patients referred for early back pain. The patients were divided into three groups: the first included 310 individuals, while the second 21. In addition, a control group consisting of 19 healthy individuals was formed. It was shown that C-reactive protein (CRP) levels and the erythrocyte sedimentation rate (ESR) were not increased in patients with early-stage axSpA compared to the control group of patients with back pain. However serum calprotectin levels were significantly increased in patients with early axSpA compared to control group (294 214–367ng/ml compared to 251 196–339 ng/ml) although individual identification of early-stage axSpA was not possible. The positive predictive value was only 38,7%, with a specificity of 90% and a sensitivity of 10% [34].

There are also reports that elevated calprotectin levels in patients with spondyloarthritis are associated with increased disease activity and a worse prognosis [35].

A good example of this is one of the reviews comparing biomarkers associated with both axial spondyloarthritis (axSpA) and idiopathic inflammatory bowel disease. A two-year study demonstrated that in patients with ankylosing spondylitis (AS), serum levels of calprotectin (sCLP) >0.5mg/ml were associated with disease progression in radiological assessments and worse outcomes on the modified Stoke Ankylosing Spondylitis Spine Score(mSASSS), as well as the formation or progression of syndesmophytes. sCLP levels were significantly higher in patients with axSpA exhibiting more progressive disease compared to healthy individuals. Furthermore, in this study, elevated sCLP levels correlated with levels of CRP, ESR, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) . scores and BASFI (Bath Ankylosing Spondylitis Functional Index)scores.

The importance of fecal calprotectin (fCLP) was investigated in a five-year cohort study of 164 patients with AS.High concentration of fCLP was shown to correlate with disease activity, as well as with CRP levels and scores on ASDAS and BASFI scales.

It is important to highlight that fecal CLP levels were significantly higher in patients with microscopic colitis, however only some of these patients exhibited concurrent symptoms of bowel inflammation [36].

The aim of the next reference study was to examine the levels of calprotectin in the serum and fecal matter of patients with ankylosing spondylitis (AS) and to demonstrate their possible association with the clinical symptoms of the disease. The study included 51 patients who met the New York criteria for AS and 43 age- and gender-matched healthy volunteers. Serum calprotectin (sCLP) concentrations were similar between AS patients and controls, so the results were not meaningful. However, a statistically significant association was found between serum calprotectin levels and scores on BASDAI and BASFI scales. In contrast, fecal calprotectin levels differed significantly between the groups. Elevated levels were found in 38(74,5%) patients with AS compared to 13 (30,2%) individuals in the control group, resulting in a significant finding for this biomarker compared to its serum counterpart. Furthermore, a significant correlation was found between fecal calprotectin (fCLP) levels and scores on the BASDAI, BASFI as well as with CRP and ESR levels.

In conclusion, this study demonstrated that fecal calprotein may serve as a significant biomarker indicating disease severity in AS, as it likely plays an important role in the pathogenesis of the disease. However, further research is needed in this area [37].

It should also be noted that lower levels of calprotectin may be associated with a good response to treatment and improvement in disease activity. One study examined changes in levels of various markers in response to pharmacological treatment of axial spondyloarthritis. Calprotectin was one of the markers studied, and a decrease in its levels correlated with a positive response to treatment. Therefore, we can conclude that calprotein can also serve as one of the markers indicating a good response to pharmacological therapy [38].

Another example is a study conducted in Prague in which 46 patients took part in an exercise program and 29 formed a control group. The goal of the study was to asses serum and fecal calprotectin levels and disease activity after a six-month period of intensive exercise in individuals with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Analysis of the results revealed a significant reduction in disease activity in training participants compared to the control group. Calprotectin was the only biomarker that showed a significant decrease after exercise therapy, with levels in patients with nr-axSpA from 2379,0 ± 243,20 to 1779,0 ± 138,3 μg/ml and from 2430,0 ± 269,7 to 1816,0 ± 148,2 μg/ml in patients with AS. To avoid errors, calprotectin levels were also checked in the control group,

with baseline values not significantly different from those seen in the intervention group and they did not change considerably over the six months nr-axSpA from 2514,0 ± 303,1 to 2324,0 ± 381,8 and AS from 3001,0 ± 334,8 to 2852,0 ± 375,2). In addition, changes in calprotectin levels have been shown to be associated with reduction in disease activity as well as its severity [39].

Different findings were reached by another study that was carried out on 1729 participants (451 with axSpA) in Switzerland between 2011 and 2013. The goal of this research was to investigate the relationship between serum calprotectin levels and the activity of rheumatological conditions like rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA). The median calprotectin levels were significantly higher in all three groups compared to the control group (axSpA 2.4μg/ml, control 1,2μg/ml). Higher serum calprotectin levels were also linked to higher scores on the Ankylosing Spondylitis Disease Activity Score (ASDAS) and the physician's global assessment of disease activity. However, according to the researchers, serum calprotectin levels were not considered a very good marker for assessing disease activity using BASDAI and BASFI scores. Disease activity was found to correlate more strongly with peripheral joint involvement, including hip joint involvement, than with axial involvement [25].

Summary

Calprotectin is an important biomarker that has garnered significant attention in the context of axial spondyloarthritis, a chronic inflammatory condition primarily affecting the spine and sacroiliac joints. This condition represents a substantial health burden worldwide, impacting patients' quality of life and imposing economic strain on healthcare systems.

Despite the growing understanding of axial spondyloarthritis, the precise role of calprotectin in its pathogenesis, risk stratification, and management remains an area of active investigation. Elevated calprotectin levels have been associated with disease activity, but further research is necessary to elucidate its potential as a diagnostic and prognostic tool, as well as its implications for treatment monitoring.

A deeper exploration of the pathophysiological mechanisms linking calprotectin to inflammation in axial spondyloarthritis could advance the development of targeted therapeutic strategies. Studies focusing on the interplay between calprotectin, immune responses, and other inflammatory markers are crucial for improving prevention, diagnosis, and management of this condition.

DISCLOSURES

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