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RESEARCH ARTICLE

The role of serum amyloid A as an inflammatory biomarker in patients with chronic inflammatory conditions

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ABSTRACT

Aim: This study aimed to evaluate the diagnostic value of serum amyloid A (SAA) by comparing it with conventional acute phase markers (APMs), such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fibrinogen, in patients experiencing pain related to chronic inflammatory and gallbladder diseases.

Materials and Methods: We retrospectively examined data retrieved from the medical records of 601 patients diagnosed with chronic inflammatory disease, gallbladder stones who underwent cholecystectomy between January 2020 and June 2023. We compared serum levels of ESR, SAA, CRP, and fibrinogen during episodes of pain.

Results: The study population consisted of 601 patients, of whom 401 (66.72%) were female and 200 (33.28%) were male. The mean age was 48.74±17.20 years for females and 46.62±17.52 years for males. Serum SAA, CRP, ESR, and fibrinogen levels showed a statistically significant positive correlation. The most significant correlation was between SAA and CRP. However, there was no rise in CRP or other acute phase markers (APMs), even though SAA rose in about one-fourth of the patients (24.7%).

Conclusion: Monitoring chronic inflammatory diseases with SAA is thought to be useful for detecting subclinical inflammation and underlying chronic inflammatory diseases. It may also prevent the development of amyloidosis and therefore morbidity and mortality.

Keywords: Chronic inflammatory diseases, serum amyloid A, C-reactive protein, erythrocyte sedimentation rate, fibrinogen

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INTRODUCTION

Acute phase markers (APMs) are biomarkers that show significant changes in serum concentration when inflammation is present. The most common APMs used in clinical practice are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A (SAA), and fibrinogen (1,2).

Persistent inflammation, resulting from prolonged exposure to stimulation or an inappropriate immune reaction against self-molecules, can progress to the chronic phase, in which tissue damage and fibrosis take place. Chronic inflammation may contribute to numerous diseases, including arthritis, atherosclerosis, autoimmune diseases, and age-related conditions (3).

The acute phase protein SAA plays an important role in acute and chronic inflammation (4). SAA amyloidosis, also known as secondary amyloidosis, is a known consequence of chronic inflammation (5). Patients with Familial Mediterranean fever (FMF) have been the focus of the most comprehensive studies on SAA. In patients with FMF, SAA levels are increased not only during attacks but also during attack-free periods. These attack-free periods have been shown to result in persistent subclinical inflammation and, eventually, amyloidosis (6,7).

Gallstone disease affects approximately one-fifth of the world's population (between 15% and 25%) (8). One cause of stone and sludge formation in the gallbladder is amyloid deposition due to increased level of SAA protein. There are few case reports about amyloid deposition in the gallbladder or biliary tract (9,10). However, these reports do not refer to SAA levels.

The aim of this study was to compare serum levels of SAA with those of CRP, ESR, and fibrinogen in patients with gallbladder stone disease without acute cholecystitis, patients suffering from persistent abdominal and back pain after cholecystectomy, and patients with chronic inflammatory diseases.

MATERIALS AND METHODS

Subjects

This single-center study was conducted by retrospectively scanning the files of admitted patients from the hospital database of Lokman Hekim University Ankara Hospital, covering the period between January 2020 and June 2023. The study was approved by the scientific research ethics committee of Lokman Hekim University (Date: 03/06/2023 Number: 2023/88). Due to the retrospective nature of the study, obtaining informed consent from patients was waived. This study was conducted in accordance with the ethical principles defined in the Declaration of Helsinki. No artificial intelligence was used in preparing this article for publication.

The patients included in the study were those whose symptoms persisted despite treatment with nonsteroidal anti-inflammatory drugs, glucocorticoids, or other medications for their diagnosed conditions. Those who met the study's requirements were at least 18 years old, and had a confirmed diagnosis of one of the following: FMF, rheumatoid arthritis (RA), seronegative arthritis (SnA), psoriatic arthritis (PA), inflammatory bowel disease (IBD) (ulcerative colitis or Crohn's disease), gallstones without acute cholecystitis; or had undergone a cholecystectomy due to gallstones, and had abdominal, back, or joint pain that had lasted for at least six months despite ongoing treatment. ESR, SAA, CRP, and fibrinogen levels were measured during episodes of pain. The study excluded individuals under the age of 18, those without a definitive diagnosis, and whose SAA, ESR, CRP, and fibrinogen levels were not measured during the pain episodes.

Laboratory analysis

SAA levels were measured using the nephelometric method with the Snibe Maglumi 2000 device (Shenzhen New Industries Biomedical Engineering Co., Ltd., China), with a normal value of <0.3 mg/dL (11). Fibrinogen levels were measured by the photooptic

method using a Sigma Diagnostics Amelung AMAX 200 analyzer (Sigma-Aldrich Co., Inc., Germany), with a reference range of <400 mg/dL (12). CRP was measured by the turbidimetric method with a Cobas C501 Chemistry Analyzer (Roche Diagnostics GmbH, Mannheim, Germany), with a normal value of <5 mg/L (13). ESR was measured by the Westergren method (mm/h).

Statistical analysis

All data were evaluated using SPSS statistical software for Windows (version 26, SPSS, Armonk, NY, USA). Descriptive statistics were presented as n (%), minimum-maximum values, mean, and % standard deviation. Normality of distribution was assessed using the Kolmogorov–Smirnov test for all variables. Since the data did not fit into the normal distribution, correlation analysis was performed using the Spearman correlation test to evaluate the relationships between SAA, CRP, ESR, and fibrinogen. A P value of <0.05 was considered statistically significant.

RESULTS

The study population consisted of 601 patients, including 401 females (66.72%) and 200 males (33.28%). Age was between 18-90, mean ± SD: 48.74±17.20 years in females, and between 18-88, mean ± SD: 46.62±17.52 years in males. Out of the 601 patients, 143 (23.79%) had seronegative arthritis, 109 (18.14%) had RA, 23 (3.83%) had psoriatic arthritis, 123 (20.46%) had FMF, 120 (19.97%) had inflammatory bowel disease, 54 (8.98%) had undergone cholecystectomy, and 29 (4.83%) had gallstones (Table 1).

Serum concentrations of fibrinogen, CRP, ESR, and SAA assessed during pain episodes were compared. Fibrinogen levels ranged from 28 to 853 mg/dL (mean ± SD: 328.81± 90.90), CRP levels ranged from 0.18 to 280 mg/L (mean ± SD: 25.86±49.85), ESR levels ranged from 2-140 mm/h (mean ± SD: 25.34 ± 23.7), and SAA levels ranged from 0 to 135 mg/dL (mean ±

Table 1. Demographic, clinical, and laboratory characteristics of patients

Age (Year)	48.64 ± 17.47 (16-90)
Gender	
Female	401 (66.72)
Male	200 (33.27)
Diagnosis	
Rheumatoid arthritis	109 (18.13)
Psoriatic arthritis	23 (3.82)
Familial Mediterranean Fever	123 (20.46)
Seronegative arthritis	143 (23.67)
Inflammatory bowel disease	120 (19.96)
Gallstones	29 (4.82)
Cholecystectomy	54 (8.98)
Laboratory	
SAA (n=601)	6.29 ± 11.86 (0.00 - 135.00)
CRP (n=401)	25.86 ± 49.85 (0.18 - 280.00)
ESR (n=172)	25.34 ± 23.97 (2.00 - 140.00)
Fibrinogen (n=419)	328.81 ± 90.90 (28.00 - 853.00)

SAA: Serum Amyloid A (mg/dL), CRP: C-Reactive Protein (mg/L), ESR: Erythrocyte Sedimentation Rate (mm/hour), Fibrinogen (mg/dL).

Category data is presented in the form of n (%).

Metric data is presented in the form of mean ± standard deviation (min-max).

Table 2. Laboratory Values of Patients

	n	%	Minimum	Maximum	Mean	% SD
SAA (Total)	601	100	0.00	135.00	6.29	11.86
Female	401	66.7	0.00	135	5.36	11.90
Male	200	33.3	0.01	51.80	8.15	11.59
CRP (Total)	401	66.7	0.18	280.00	25.86	49.85
Female	270	67.4	0.19	235	22.19	43.84
Male	131	32.6	0.18	280	33.44	59.85
ESR (Total)	172	28.6	2.00	140	25.34	23.97
Female	122	70.6	4	140	27.81	24.46
Male	50	29.4	2	122	19.49	21.91
Fibrinogen (Total)	419	69.4	28.00	853.00	328.81	90.90
Female	293	69.9	28.00	853.00	326.60	92.94
Male	126	30.1	171.00	746.00	333.95	86.11

SD: Standard Deviation, SAA: Serum Amyloid A (mg/dL), CRP: C-Reactive Protein (mg/L), ESR: Erythrocyte Sedimentation Rate (mm/hour), Fibrinogen (mg/dL).

Table 3. Correlation between SAA and other APMs

	r	p
CRP	0.774	<0.001
ESR	0.533	<0.001
Fibrinogen	0.518	<0.001

SAA: Serum Amyloid A (mg/dL), APM: Acute Phase Marker, CRP: C-Reactive Protein (mg/L), ESR: Erythrocyte Sedimentation Rate (mm/hour), Fibrinogen (mg/dL).

SD: 6.29±11.86). Even though SAA increased, there was no rise in CRP or other APMs in about a quarter of the patients (24.7%) (Table 2).

The levels of serum fibrinogen, CRP, ESR, and SAA exhibited a statistically significant positive correlation ($p<0.001$). SAA and CRP showed the strongest correlation (Spearman's rho: 0.77) (Table 3).

DISCUSSION

CRP is the most commonly used APM. However, CRP does not always increase during acute inflammation, whereas SAA often does. In fact, it is common to find elevated SAA levels while CRP or other APMs remain within normal limits, but it is rare for CRP or other APMs to increase without a rise in SAA. Additionally, in cases of mild chronic inflammation, SAA can remain elevated even when CRP is within the normal range (14-16).

While some studies suggest that CRP could substitute for SAA, especially in the follow-up of FMF, it is clear that CRP alone is not sufficient. A study by Duzova et al. confirmed that SAA is the most reliable marker for monitoring inflammation in FMF patients during attack-free periods (17). Similarly, in a study, Sözel et al. reported that SAA is the best marker during attack-free periods in FMF, but CRP can be used as an alternative in cases where SAA levels cannot be measured (18). SAA levels, which are considered to be related to amyloidosis, were reported to be high in nearly 30% of cases during inter-episode periods (19).

In the present study, 24.7% of patients exhibited increased SAA levels, while CRP and other APMs remained within normal limits. This suggests that although CRP is generally considered a reliable indicator of inflammation, approximately one-quarter of patients still experience inflammation without a corresponding rise in CRP. Therefore, SAA appears to be a superior marker for detecting persistent inflammation compared to traditional APMs.

This study is also unique in that it includes patients with gallbladder diseases to assess chronic inflammation. These patients were compared with those suffering from other chronic inflammatory diseases. This comparison is important because amyloid deposits have been detected in the gallbladder and bile ducts in some cases (9,10). The patients in these cases also face a long-term risk of developing amyloidosis.

Amyloidosis is a serious cause of morbidity and mortality, affecting organs such as the kidneys, heart, gallbladder, and biliary tract. Monitoring ongoing inflammation in patients with chronic conditions is crucial to prevent complications such as renal failure and cardiovascular disease caused by amyloidosis. This benefits both the patients and the healthcare system.

The reason for including symptomatic gallbladder diseases in this study is that, similar to other chronic inflammatory diseases where complaints continue despite treatment, symptoms may persist due to chronic inflammation in gallbladder diseases. Another reason is the possibility of undiagnosed FMF in patients with symptomatic gallbladder disease and other chronic inflammatory conditions.

In patients experiencing abdominal and back pain attacks, if such attacks recur post-cholecystectomy and acute phase reactants remain elevated, FMF could be considered as the underlying cause. In instances where referred back pain due to gallstones is under consideration, postoperative back pain may be attributable to FMF-related sacroiliitis.

Although it has not been conclusively proven that the persistent abdominal and back pain seen in patients with gallstones or post-cholecystectomy is linked to elevated SAA levels and amyloid deposits in the gallbladder or biliary tract, this study provides a foundation for future research on this topic.

Measuring SAA levels during pain episodes in chronic inflammatory diseases is considered to be a reliable chronic phase marker, in addition to being a better APM than CRP, since it also shows ongoing mild chronic inflammation. Although SAA testing is more expensive than CRP when considered individually, it has been shown to be more economically beneficial in the long term. This is due to its ability to detect chronic inflammation, facilitate the early diagnosis of undiagnosed FMF cases, and help prevent the development of amyloidosis, thereby reducing the associated morbidity and mortality. Furthermore, providing symptomatic pain relief with colchicine for patients who experience persistent pain after cholecystectomy will increase patient comfort and reduce pain-related visits to health institutions.

This study has a retrospective design, which limits the ability to control for confounding factors and ensure consistency in treatment protocols, medication adherence, and symptom documentation over time. Pain assessment was based on clinical records without standardized scales or structured follow-up intervals, which may have introduced subjectivity or inconsistencies in symptom classification. Although increased SAA levels may suggest ongoing inflammation or potential amyloid deposition, no histopathological confirmation of amyloidosis was obtained in patients with persistent symptoms after cholecystectomy. SAA levels were measured only once during a painful episode, so they may not fully reflect the dynamic inflammatory profile or its progression over time.

Future prospective studies incorporating serial SAA measurements, standardized pain assessment tools, and histopathological examination of tissues may help confirm the clinical value of SAA in the diagnosis and management of chronic inflammation and assessing the risk of amyloidosis.

CONCLUSION

The findings of this study suggest that monitoring SAA levels may be more useful than monitoring other conventional APMs, particularly during painful periods, for patients with chronic inflammatory and gallbladder diseases. Monitoring chronic inflammatory diseases with SAA has proven to be a useful tool for detecting subclinical inflammation, identifying underlying chronic inflammatory diseases, and preventing the development of amyloidosis and its associated morbidity and mortality.

Ethical approval

This study has been approved by the Lokman Hekim University Scientific Research Ethics Committee (approval date 03/06/2023, number 2023/88).

Author contribution

Concept: AOA; Design: AOA; Data Collection or Processing: AOA; Analysis or Interpretation: AOA; Literature Search: AOA; Writing: AOA. The author reviewed the results and approved the final version of the article.

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Conflict of interest

The author declare that there is no conflict of interest.

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