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Original article

Markers of Inflammation in Rheumatoid Arthritis and Osteoarthritis

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ABSTRACT

Introduction: Rheumatoid arthritis is characterized by local and systemic effects of inflammation while osteoarthritis is an inflammatory degenerative disorder of joints. A wide range of inflammatory markers are implicated in pathogenesis of rheumatoid arthritis and osteoarthritis as a consequence of persistent imbalance between pro- and anti-inflammatory immune mechanisms, leading to chronic inflammation. Hence the present study is an attempt to estimate the levels of serum ceruloplasmin , C-reactive protein (CRP) and rheumatoid factor (RF) factor as inflammatory markers in serum of rheumatoid arthritis and osteoarthritis patients and compare them with normal healthy controls. **Materials and Methods:** Serum ceruloplasmin was estimated by spectrophotometric method while serum C-reactive protein and RA factor were detected using agglutination test in thirty patients of rheumatoid arthritis ,osteoarthritis and age and sex matched healthy controls each were included in the study. **Results:** Significant increase in ceruloplasmin was observed ($p<0.0001$) in rheumatoid arthritis and osteoarthritis as compared to healthy controls and in that especially ceruloplasmin was more elevated in rheumatoid arthritis than osteoarthritis. C-reactive protein was found to be positive in rheumatoid arthritis and osteoarthritis and none of the controls. RF factor was found positive in rheumatoid arthritis and none of the osteoarthritis and controls. **Conclusion:** There was increased level of serum ceruloplasmin in the patients with rheumatoid arthritis and osteoarthritis. C-reactive protein and RF factor was found to be positive in rheumatoid arthritis while C-reactive protein was found to be positive in rheumatoid arthritis and osteoarthritis. These findings suggest a possible role of these inflammatory markers in the pathogenesis of rheumatoid arthritis.

KEYWORDS: C-reactive protein (CRP), Ceruloplasmin, Osteoarthritis (OA), Rheumatoid arthritis (RA), Rheumatoid factor (RF).

INTRODUCTION

Rheumatoid arthritis is a chronic systemic inflammatory and autoimmune disorder of joints characterized by erosive synovitis , mainly peripheral joints which causes cartilage and bone destruction. Although the cause of rheumatoid arthritis remains unknown, genetic predisposition, environment and autoimmunity have important role in the pathogenesis of the disease. The prevalence of RA is 1% of the world wide population and women are more affected [1].
Osteoarthritis is a degenerative joint, is the most common type of joint disease characterized by the progressive erosion of articular cartilage1. This joint disorder is characterized by loss of balance between synthesis and degradation of articular cartilage leading to subsequent erosion of joints cartilage remodeling of the underlying bone osteophyte formation and variable degree of synovitis. Osteoarthritis is the most common form of arthritis affecting 3.8% of people as of 2010[2].

Different measures are used for evaluating disease activity of rheumatoid arthritis and osteoarthritis. Laboratory investigation such as serum CRP and RA factors have been integral part of diagnosis for many years for many years, used as markers of inflammation.
Serum concentration of ceruloplasmin (Cp), an α2 - globulin increases in the inflammation process or infection and this is mostly due to the Cp production in hepatocytes stimulated by proinflammatory interleukins, such as Il-1 and Il-6 [3]. Not only Cp levels increase in inflammation, but also its ferroxidase activity [4] by catalyzing Fe^{2+} to Fe^{3+} . Cp, this hepatic protein, seems to play a role in iron metabolism and protect the body from catalytically active Fe^{2+} [5].

C- reactive protein (CRP) is a biochemical marker widely used as an acute phase reactant and an indicator of inflammation in arthritis. Although an elevated CRP level is not specific for RA, it is nevertheless a useful indicator of tissue damage and its concentration in serum is related to disease activity [6].

Early biochemical tests for detection of established RA were based on measurement of Rheumatoid Factor (RF). The sensitivity of the RF test has been reported to be from 70% to 75% [7-9] and its specificity has been reported to be between 80% and 85% [7,8]. RA is typically associated with serological evidence of systemic autoimmunity as indicated by the presence of auto-antibodies in serum and synovial fluid. The first autoantibody in RA, rheumatoid factor (RF), was described by Waaler in 1940 and it was later found to be directed to the Fc region of IgG [10].
Hence, this study is designed to evaluate the association between inflammatory markers in rheumatoid arthritis and osteoarthritis patients.

METHODS AND MATERIALS

This study was conducted in the department of biochemistry, M.I.M.E.R. Medical College, Talegaon (D). The present study includes thirty clinically diagnosed patients of rheumatoid arthritis and osteoarthritis along with age and sex matched thirty healthy controls. Sample size was estimated by using power calculations in consultation with the statistician.

Subjects were selected from the departments of Medicine and Orthopaedics of Dr. Bhausaheb Sardesai Talegaon Rural Hospital, Talegaon (D). Rheumatoid arthritis patients fulfilled the American Rheumatism Association criteria [11] and osteoarthritis patients were diagnosed by carrying out X-ray analysis of joint destruction. Informed consent was obtained from all the study subjects. This study was also approved by the institutional ethical committee.

The study subjects were classified into following groups.

i) Group I subjects: Includes 40 cases of newly diagnosed rheumatoid arthritis.

ii) Group II subjects: Includes 40 cases of newly diagnosed osteoarthritis.

iii) Group III subjects: Includes 40 age and sex matched healthy controls.

Inclusion criteria:

Clinically newly diagnosed subjects with rheumatoid arthritis and osteoarthritis in the age group of 30-55 years.

Exclusion criteria:

Subjects with diabetes mellitus, hypertension, cardiovascular disease, other autoimmune and inflammatory diseases, infectious disease, any other drug medication, other types of arthritis and pregnancy were excluded from study.

Sample collection:

About 5 ml of fasting venous blood was collected with all aseptic precautions in plain bulb. Serum was separated by centrifuging the clotted blood at 2000 rpm for 5 minutes. Separated serum was used for the measurement of inflammatory markers such as ceruloplasmin, C- reactive protein and RF factor. Serum ceruloplasmin was estimated by kinetic method of Somani & Ambade [12] Serum C-reactive protein and RF factor was detected using Avitex CRP kit [13] and Avitex RF kit [14] which are rapid latex agglutination tests.

Statistical analysis:

Results were presented as mean ± standard deviation. Statistical analysis was done with the help of statistician using the student's t test. Correlations between parameters were calculated by Pearson Correlation test. p value < 0.001 was considered as significant.

RESULTS

The present study was conducted on 120 subjects aged between 35 to 55 years of both gender. The study group was further divided into three groups. The mean ± SD of age in group I (RA) was 46.73 ± 7.79 (yrs), group II (OA) was 47 ± 7.82 (yrs) and group III (control) was 46.35 ± 6.68 (yrs). [Table 1]**.**

Table 1: The age distribution of subjects in Group I, Group II and Group III.

Groups	Number	Age (Years)	
		Mean	Standard Deviation
Group I (RA)	40	46.73	7.79
Group II (OA)	40	47	7.82
Group III (control)	40	46.35	6.68

In present study , the serum ceruloplasmin levels were significantly increased in rheumatoid arthritis and osteoarthritis patients ($p < 0.0001$) as compared to controls and in that it is especially increased in rheumatoid arthritis ($p < 0.0001$) than osteoarthritis patients($p < 0.0001$) [Table 2]. C-reactive protein was positive in 76% cases of rheumatoid arthritis ($p < 0.0001$) and 70% cases of osteoarthritis patients ($p < 0.0001$). RF factor was positive in 93% cases of rheumatoid arthritis patients and negative for osteoarthritis in present study [Table 2].

Table 2 : Comparison of levels of inflammatory markers between study and control group.

Study group	Ceruloplasmin (IU/L)	C-reactive Protein (No. of cases positive)	RF factor (No. of cases positive)
Group I (RA)	1281±250.22*	34*	28*
Group II (OA)	1008.55±203.89*	29*	Nil
Group III (Control)	941±166.26	Nil	Nil

*p < 0.0001 – significant.

DISCUSSION

In an attempt to identify the etiological factors and possible risk in the pathogenesis of rheumatoid arthritis and osteoarthritis, acute phase proteins were studied in arthritis in present study. Inflammatory processes play a pivotal role in the pathogenesis of RA. Markers of inflammation such as C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor (TNF) and anti-inflammatory marker IL-10 are highly expressed in synovial fluid and serum of arthritic patients and play an important role in the pathophysiology of RA [15] Inflammation is the hallmark of arthritis (rheumatic disease). Analysis of inflammatory and autoimmune biomarkers is used in rheumatologic disease to monitor disease activity correlated with other clinical and laboratory data and to differentiate between active disease and the presence of infection [16]

The hepatic acute phase protein response is a prominent feature of many inflammatory diseases, including RA. It is recognized that inflammation is a contributing factor in OA pathology. Local productions of inflammatory mediators are well known to contribute to cartilage degradation and synovial activation in OA.

During inflammatory process the production of cytokines is increased. Both IL-1 and IL-6 are responsible for hepatocytes stimulation to increase the synthesis and secretion of an acute phase protein, ceruloplasmin in the blood [3]. This may explain the rise in serum ceruloplasmin levels indicating increased inflammation and pro-oxidant activity in both rheumatoid arthritis and osteoarthritis and being prominent in rheumatoid arthritis. The present study shows significantly higher ceruloplasmin levels ($p<0.001$) in both rheumatoid arthritis and osteoarthritis as compared to controls and in that it is higher in rheumatoid arthritis than osteoarthritis which correlates with other studies. Results are in agreement of Conforti et al (1983) [17] and Milanino et al (1993) [18]

C- reactive protein production in liver is triggered by release of pro-inflammatory cytokines from monocytes and macrophages. The pro-inflammatory response lead to increased secretion of interleukin 1 – β and tumor necrosis factor α which results in release of cytokine, interleukin-6 which in turn stimulates liver to secrete CRP [20]. In present study, positivity of CRP test was significant ($p<0.001$) in both rheumatoid arthritis (76%) and osteoarthritis (70%) as compared to controls which reflects the role of inflammation in the pathogenesis of rheumatoid arthritis and osteoarthritis that collaborates with other studies[21-22].

Our study demonstrated positive RF in (93%) of rheumatoid arthritis patients which may be associated with radiologic erosion and extra-articular manifestations rheumatoid arthritis which correlates with other studies. Rheumatoid factor specificity to rheumatoid arthritis is increased at high titers [20, 23]. Furthermore, RF has proven to be the most useful disease marker as included in the American College of Rheumatology classification criteria for rheumatoid arthritis [11].

Further research is needed in this area to identify other inflammatory markers which may help in differentiating rheumatoid arthritis from osteoarthritis for instituting appropriate treatment.

CONCLUSION

Elevated ceruloplasmin levels indicate inflammation in rheumatoid arthritis and osteoarthritis, denoting its crucial role in pathogenesis of both rheumatoid arthritis and osteoarthritis. Present study revealed the increase in serum ceruloplasmin level as an inflammatory marker in addition to CRP and RF (in Rheumatoid arthritis) for better therapeutic management of both rheumatoid arthritis and osteoarthritis. It was found that serum ceruloplasmin combined with RF could serve as a predictive combination to diagnose rheumatoid arthritis

LIMITATIONS

Larger sample size is required to affirm the above findings.

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