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Lipid Peroxidation Levels in Untreated Rheumatoid Arthritis and the Effect of Acute Phase Reactant

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Abstract

Aim: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease associated with potentially debilitating joint inflammation as well as altered skeletal bone metabolism and co-morbid conditions. Formation of reactive oxygen species and lipid peroxides as a result of disease activity may play an important role in rheumatoid arthritis.

Methods: The biochemical parameters and methods to be used for their estimations were as follows. These parameters are compared with concentration of malondialdehyde as reference parameter. Using the colorimetric method, we examined samples of 60 participants (30 patients with knee joint effusion were assigned to the RA synovial fluid group.

Results: It is found that an antioxidant ceruloplasmin is increased significantly ($p<0.001$) in rheumatoid arthritis 7 for scavenging the free radicals formed. Increased activity of ceruloplasmin ($p<0.001$) correlates with increase in concentration of malondialdehyde and in turn with severity of rheumatoid arthritis.

Conclusion: Serum ceruloplasmin can be used as novel marker to detect extent of lipid peroxidation seen in rheumatoid arthritis and also helps to know 10 severity of rheumatoid arthritis.

Keywords: Rheumathoid arthritis; C-reactive protein; Ceruloplasmin

Abbreviations: RA: Rheumatoid arthritis; ARA: American Association for Rheumatism; ESR: Erythrocyte Sedimentation Rate; VAS: Visual Analogue Scale; H_2O_2: Hydrogen Peroxide

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease associated with potentially debilitating joint inflammation as well as altered skeletal bone metabolism and co-morbid conditions [1]. Ceruloplasmin is α2 globulin - a glycoprotein carrying six copper atoms per molecule. It is one group of serum protein which rises after any form of tissue injury. Ceruloplasmin synthesis and/or secretion is altered by inflammation, hormones, and copper. Physiological factors like cancer, exercise, chronic inflammation, pregnancy increase its level. It also acts as a host defense mechanism by its radical scavenging and copper donor activity. Ceruloplasmin functions as ferroxidase by catalyzing the Oxidation of Fe^{2+} to Fe^{3+}, and correlates well with its level and antioxidant activity. Ceruloplasmin is an important intravascular antioxidant and it protects tunica intima against free radical injury [2,3].

In this research we were concentrated on serum ceruloplasmin as it is related with scavenging of free radicals in the body. This study was an attempt to look for the diagnostic and prognostic importance of serum ceruloplasmin in patients of rheumatoid arthritis.

Materials and Methods

The diagnosis of the patients included in the study is based on the revised diagnostic criteria for classification of Rheumatoid arthritis proposed in 1987 by the American Association for Rheumatism (AAR) [4]. In order to include the patient in the group with RA, he should fulfill at least 4 of the 7 criteria. Criteria 1-4 should persist at least 6 months. Other patients negated use of other drugs such as golden salts, antibiotics or diuretics. Specimens are collected in the period of 2 years. Using the colorimetric method, Ceruloplasmin was determined using its copper oxidase activity by method of Ravin. In this method, action of ceruloplasmin on p-phenylenediamine is used to measure the amount of ceruloplasmin present in the serum. Dark lavender color was read at 530nm using control tube as

blank. Concentration of ceruloplasmin in mg/dl is absorbance X 87.5. The 5ml of venous blood were collected in a plain bulb from 60 patients of rheumatoid arthritis for the study from various hospitals in the solapur city The sample were collected after the diagnosis of patient for rheumatoid arthritis in hospital. The blood samples for the controls (n=60) were collected from the healthy volunteers. The obtained blood was centrifuged at 3000rpm for 15 minutes. The serum were collected and used for assay. The biochemical parameters and methods to be used for their estimations were as follows. These parameters are compared with concentration of malondialdehyde as reference parameter.

Inclusion criteria

In the study are included patients with RA, aged 18-65 years, not previously treated with NSAIDs or DMARDs.

Exclusion criteria

From the study are excluded patients with diseases or conditions that could influence results directly or indirectly:

- Patient younger than 18 years.
- Patients with previous history of disease of the spleen, thyroid gland, liver, kidneys, hematological, cardiovascular, neurological, autoimmune and lung diseases.
- Patients with diabetes mellitus, febrile conditions, acute infections, neoplasms.
- Patients with uric arthritis, SLE, mixed connective tissue disese, vasculitis.
- Patients with history of blood transfusion and patients with body overweight.
- All the patients took part in this study voluntarily, so the ethic criteria for this study are fulfuled.

Clinical estimation of disease activity

Clinical estimation is made by subspecialist in the field. Disease activity is estimated using DAS 28 index (Disease Activity Score - DAS 28). The index uses mathematical formula to obtain unique composite quantitative score, which consists of: palpabile painful joints (maximal niumber 28), swallen joints (maximal niumber 28), Erythrocyte sedimentation rate (ESR) and patient's estimation for disease activity (0-100mm). Visual Analogue Scale - VAS) and morning stiffness (minutes).

DAS 28 index ranges from 0 to 10 and score <3.2 qualifies the disease as low active.

Statistical Analysis

To test the significance of the differences between two arithmetical means i.e., proportions is used the Student t-test. To compare the mean values of certain numerical parameters between two groups was used Wilcoxon-matched test for independent species. Sensitivity and predictivity for positive and negative test of the examined markers is determined with the sensitivity and specificity test. P-value between 0.05 and 0.1 is considered statistically significant. Data analysis is performed with statistical package Statistica 7.0.

Results

Present study indicates increased oxidative stress, which is reflected by increased lipid peroxidation in peripheral blood of patients with rheumatoid arthritis. These results are also in accordance with the earlier studies [5]. Malondialdehyde is the product of lipid peroxidation reacts with lysine residues in protein to produce immunogenic molecules, which can exacerbate inflammation. The longer chain polyunsaturated fatty acids are especially potent at increasing lipid peroxidation and causing cell damage by oxidative stress [6,7]. Depolymerization of hyaluronic acid in synovial fluid results into loss of lubricating property of the fluid. It has been reported that, it is very important consequence of exposure of synovial fluid to super oxide (O_2) and hydrogen peroxide (H_2O_2) [8,9]. Increased plasma ceruloplasmin levels are associated with the generation of oxidation products, i.e., $\bullet O_2$- and H_2O_2. Oxidation of ferrous ion leads to superoxide ion and leads to peroxidative damage. Ceruloplasmin - due to its ferroxidase activity can catalyze the oxidation of Fe^{2+} with concomitant production of H_2O from H_2O_2 and acts as an acute phase reactant. Antioxidants play an important role in preventing free radical damage. Ceruloplasmin is an important extracellular antioxidant. Ceruloplasmin being an acute phase reactant protein, its level rises immediately after cellular damage in rheumatoid arthritis. Ceruloplasmin acts as an antioxidant through ferroxidase activity, and it also scavenges superoxide anion radical ($\bullet O_2$-) [10,11].

Malondialdehyde in rheumatoid arthritis patients

As compared to healthy controls, the concentration of malondiadehyde were continuously and significantly increased ($p<0.001$) from group I to group V in rheumatoid arthritis patients. As compared to healthy controls there was a increase in malondialdehyde concentration as, 1.33 times for group I, 2.13 times for group II, 2.6 times for group III, 3.0 times for group IV and 3.63 times for group V.

Discussion

RA is characterized by polyarticular inflammation associated with synovitis, osteitis, and peri-articular osteopenia, often associated with erosion of subchondral bone and progressive joint space narrowing. These features commonly lead to progressive joint damage, impaired function, and progressive disability [12,13]. Exact reason behind bone erosion and joint deformities is not fully understood. Formation of reactive oxygen species and lipid peroxides as a result of disease activity may play an important role in rheumatoid arthritis. While, lowered concentrations of antioxidants in the blood considerably increase the probability of the occurrence of rheumatoid arthritis [14]. Many investigators have focused on oxidative stress since last few

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years and suggest that rheumatoid arthritis patients are more prone to lipid peroxidation [15]. Growing evidences implicate nitric oxide (NO•) in immune regulations, inflammation, autoimmunity and arthritis. It is possible that, generation of reactive oxygen species may be particularly important factor for bone resumption in inflammatory process [16]. Over production of reactive oxygen species results in oxidative stress, a deleterious process that can be an important mediator of damage to cell structures, including lipids and membranes, proteins and DNA. Prime targets of reactive oxygen species attack are the polyunsaturated fatty acids in the membrane lipids causing lipid peroxidation which may lead to disorganization of cell structure and function. Further decomposition of peroxidized lipids yields a wide variety of end-products, including malondialdehyde [17]. Measurement of malondialdehyde is widely used as an indicator of lipid peroxidation. Elevated levels of malondialdehyde have been reported in the serum and synovial fluid of rheumatoid arthritis patients [18]. Treatment is commonly determined by the extent or severity of disease activity, assessed by counting the number of swollen and tender joints, measuring patient-reported outcomes (for example, patient global quality of life assessment), and assaying acute phase responses, such as the erythrocyte sedimentation rate and C-reactive protein levels. Ceruloplasmin is another parameters which alter in rheumatoid arthritis [19].

Oxidation of ferrous ion leads to superoxide ion and leads to peroxidative damage. Ceruloplasmin - due to its ferroxidase activity can catalyze the oxidation of Fe_{2+} with concomitant production of H_2O from H_2O_2 and acts as an acute phase reactant. Antioxidants play an important role in preventing free radical damage [20]. Ceruloplasmin is an important extracellular antioxidant. Ceruloplasmin being an acute phase reactant protein, its level rises immediately after cellular damage in rheumatoid arthritis. Ceruloplasmin acts as an antioxidant through ferroxidase activity, and it also scavenges superoxide anion radical ($•O_2$-).

Present study indicates increased oxidative stress, which is reflected by increased lipid peroxidation in peripheral blood of patients with rheumatoid arthritis. These results are also in accordance with the earlier studies.

Conclusion

It is found that an antioxidant ceruloplasmin is increased significantly in rheumatoid arthritis for scavenging the free radicals formed. Increased activity of ceruloplasmin significantly correlates with increase in concentration of malondialdehyde and in turn with severity of rheumatoid arthritis. Thus ceruloplasmin can be used as novel marker to detect extent of lipid peroxidation seen in rheumatoid arthritis and also helps to know severity of rheumatoid arthritis.

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