

Plasma Fibrinogen Levels in Rheumatoid Arthritis

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ABSTRACT

Introduction: Rheumatoid arthritis [RA] is a chronic systemic disease that primarily targets synovium, leading to synovial inflammation and proliferation. Inflammatory joint disorder has increased cardiovascular disease [CVD] risk. In fact, the increase risk of cardiovascular events in RA patients is not fully explained by other classical cardiovascular risk factor. The precise inflammatory, thrombotic mechanism linking RA to excess CV risk remains incompletely understood. Fibrinogen represents a link between inflammation, thrombosis and CV risk. The aim of present study was to compare the levels of plasma fibrinogen in patients of RA with healthy controls. We also tried to investigate any correlation between plasma fibrinogen levels and disease activity score DAS28.

Material and methods: The present study was a cross sectional study conducted in ASCOMS hospital Jammu from October 2017 to February 2018. A total of 80 subjects were enrolled in this study. All patients satisfied the 1987 ACR classification criteria of RA. The quantitative determination of plasma fibrinogen levels was done using clot detection method. We also measured ESR using westergren method and CRP levels. The assessment of disease activity was recorded by using 100mm visual analogue scale [VAS]. Statistical analyses were performed using SPSS software. All data presented as frequency and mean \pm SD, unpaired t-test was used to compare between means of all parametric continuous variable. Chi square test statistic was used to test association between categorical variables.

Results: The following observations were deduced for the 80 subjects enrolled in the study. The mean levels of plasma fibrinogen was 488.7 mg/dl in patients of rheumatoid arthritis [RA] versus 361.5 mg/dl in healthy controls. This difference was statistically significant $p < 0.000$. The levels of plasma fibrinogen were 26% higher than in control. On evaluation of fibrinogen levels and disease activity in RA patients, it was noted that the patients with higher DAS28 score [3.9] had significantly higher median plasma fibrinogen [600mg/dl] [$r = 0.33$ $P < 0.001$]. We also report a statistically significant elevation of 2 acute phase reactants in cases of rheumatoid arthritis, ESR [mm 1st/hr] [21.8 \pm 7.87 SD] [$P < .000$] and CRP levels [24.5 mg/dl \pm 3.76 SD] [$P < .000$].

Conclusion: The study concluded that in patients of rheumatoid arthritis [RA] the levels of plasma fibrinogen are significantly elevated. Fibrinogen predicts and is a risk factor for coronary artery disease. The treating clinician should be aware of this fact and recognize the importance of elevated plasma levels of fibrinogen in rheumatoid arthritis.

Key words: Rheumatoid Arthritis (RA), Fibrinogen, Acute Phase Reactants (APR).

and proliferation. The natural history of the disease is one of progressive joint damage.² A sizable group of patients of RA develop extra articular manifestation. Patients of rheumatoid arthritis and other inflammatory joint disorder have increased cardiovascular disease [CVD]³ risk compared with general population. For patients of [RA], the magnitude of this excess risk appear comparable to that reported for patients with diabetes mellitus.⁴ Multiple mechanistic links between systemic inflammation⁵ and accelerated atherosclerosis have been described in the setting of RA. In last decade a large amount of evidence linked rheumatoid arthritis to atherosclerosis.⁶ In fact, increased risk of cardiovascular events in RA patients is not fully explained by other classic cardiovascular risk factors. Inflammation⁷ has been implicated in the pathogenesis of atherosclerosis and subsequent cardiovascular disease. Increased concentration of mediators or markers of inflammation predicts subsequent atherosclerotic cardiovascular disease. The precise inflammatory, thrombotic or other mechanism linking RA to excess CV risk, however remain incompletely understood. ESR⁸ and C-reactive protein [CRP] are the most widely used assay to measure the laboratory aspect of the acute phase response. Fibrinogen⁹ is a glycoprotein with a molecular weight of 340 K Da. Fibrinogen, while of primary importance as a coagulation protein, is also an acute phase reactant¹⁰ and its plasma concentration is increased in disease involving tissue damage or inflammation. Fibrinogen represents a link between inflammations, thrombosis¹¹ and CV risk. The aim of present study was to compare levels of plasma fibrinogen in patients of rheumatoid arthritis [RA] with healthy controls. We also tried to investigate any correlation between plasma fibrinogen levels and DAS28 score, and the various acute phase reactants [APR] level.

MATERIAL AND METHODS

The present study was a cross sectional study conducted in ASCOMS hospital Jammu from October 2017 to February 2018. A total of 80 subjects were enrolled into the study. They were recruited from the out patients department and indoor wards of medicine department. They were divided into 2 groups. The first group was of 40 patients of rheumatoid

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INTRODUCTION

Rheumatoid arthritis [RA] is a chronic, systemic disease¹ that primarily targets synovium, leading to synovial inflammation

arthritis and other group consisted of 40 healthy controls. All patients satisfied the 1987 ACR classification criteria for RA. The platelet poor plasma was prepared by centrifugation at 2000 rpm for 15 min at 4c for measuring fibrinogen level; while serum was used to measure Anti CCP, CRP. The ESR was done by westergren method. CRP was measured by turbidometric method using automated chemistry analyzer. Plasma fibrinogen was measured by clot detection using commercial kit [Fibrinosticon organon Teknika, boxtel] reference interval 2-4 g/l. The assessment of disease activity was recorded using standard 100mm horizontal visual analogue scale [VAS] in which 0 = no activity, 100 = maximal activity. The DAS 28 was calculated using swollen and tender joint counts. Ethical approval for this study was obtained from the Ethics committee of this institute.

STATISTICAL ANALYSIS

All statistical analysis was performed using SPSS software. All data presented as frequency (percentage) and mean \pm SD and median (interquartile range) were appropriate. Unpaired T test was used to compare between two means of all parametric continuous variable. The Chi-square test was used to test association between categorical variables. Linear regression analysis was performed to test association between biochemical parameters. A P-value < 0.05 was considered statistically significant.

RESULTS

The demographic characteristic of study participants including mean value \pm SD are shown in table 1. The series included 40 RA patients and 40 healthy controls. The mean age of RA patients was [42.6 years] and was not significantly different from control group mean age [45.1 years].

Fibrinogen levels in RA versus control. The mean levels of fibrinogen in RA group was 488.7 mgm/dl \pm 76.25 SD, while the fibrinogen levels in control group was 361.5 mgm/dl \pm 38SD. This difference was highly significant. The levels of plasma fibrinogen was 26% higher than in control (95% CI 101.76, $p < .000$). The study showed that acute phase reactant [APR]: ESR, CRP levels were statistically significantly higher in rheumatoid arthritis group compared to healthy controls. Mean ESR (mm^{1st} hr) in case 21.8 \pm 7.87 SD versus ESR control 3.2 \pm 1.22 SD. [P $< .000$]. CRP case [mean \pm SD] 18.52 \pm 2.5 mg/l, CRP control [mean \pm SD] 2.95 \pm 1.54 P = .000. The analysis of this study noted a strong positive correlation between Anti CCP and ESR (P-value.0002). We tried to evaluate the association of disease activity with plasma fibrinogen levels in RA patients. It was noted that

patients with higher DAS-28 score (3.9) significantly higher median plasma fibrinogen levels (600 mg/dl). [$r = 0.33$ $p < 0.01$]

DISCUSSION

Rheumatoid arthritis (RA) is a chronic systemic disease usually manifesting as inflammation of multiple joints. It is characterized by a number of extra-articular manifestation.¹² Rheumatoid arthritis is associated with increased cardiovascular (CV) morbidity and mortality, which cannot be fully explained by traditional CV risk factors; cumulative inflammatory burden¹³ seem to be an important contributor.

Inflammation underlies the accelerated atherosclerosis in RA.

Inflammation contributes to all stages of atherosclerosis¹⁴, from plaque formation to instability and eventual plaque rupture. Elevated acute phase reactant (APR)¹⁵ has been recently shown to be an important factor in subclinical atherosclerosis. ESR Erythrocyte sedimentation rate and C-reactive protein (CRP)¹⁶ are the most widely used assay to measure laboratory aspect of the acute phase response. Fibrinogen has been identified as an independent risk factor for cardiovascular disease. The role of elevated fibrinogen¹⁷ suggest that it may be on the casual pathway of certain risk factor to exert their effect. These association remain incompletely characterized. In our study we compared the plasma levels of fibrinogen, in patients with rheumatoid arthritis with those of healthy controls. The mean levels of plasma fibrinogen (488.7 mgm/dl \pm 76.25 SD) in RA patients was significantly elevated (P $< .000$) then control group (361.5 mgm/dl \pm 38SD). We also compared two more acute phase reactants, ESR and CRP in rheumatoid arthritis patients versus healthy control. The two observation also confirmed a significant (P $< .000$) of [ESR mm/ 1st hr 21.8 \pm 7.8 SD, CRP 24.5 mg/dl \pm 1.2 SD] in patients of RA. The results are in agreement with study done by Terence Rooney et al¹⁷ [2011] in which they reported elevated levels of fibrinogen in 105 RA patients compared to healthy controls. Other study done by N.G. Arvidson et al¹⁸ [2002] had also evaluated the correlation between ESR, CRP and fibrinogen and reported a strong mutual correlation between studied acute phase reactant. We study also noted a positive correlation between Anti-CCP and raised ESR, similar finding was reported by M.B.O Babikir et al.¹⁹ In our study evaluation of any association of elevated plasma fibrinogen in RA patients with disease activity score [DAS 28]. There was marked elevation of fibrinogen levels [600 mg/dl] in patients with higher score DAS 28 and significant positive correlation

| | Group I (cases) Rheumatoid Arthritis Mean \pm SD | Group II Healthy control Mean \pm SD | t-Value P-Value |
|-----------------------------|--|---|--------------------|
| Age (years) | 42.6 \pm 7.5 | 45.1 \pm 8.9 | 2.8 > 0.05 |
| Fibrinogen Levels (mg/dl) | 488.77 \pm 76.25 | 361.5 \pm 38 | 0.000 |
| ESR (mm 1 st hr) | 21.8 \pm 7.87 | 3.2 \pm 1.22 | 0.000 |
| CRP (mg/dl) | 18.52 \pm 2.5 | 2.95 \pm 1.54 | 0.000 |

Table-1: Provide table header g???

[r0.332 P< 0.01]. Similar finding have also been observed by Yildirim K²⁰ [2004] in his study.

CONCLUSION

This study concluded that the levels of plasma fibrinogen was significantly elevated in patients of rheumatoid arthritis [RA]. It was also seen that fibrinogen levels were higher in patients with higher disease activity score. It is known that fibrinogen predicts and is a risk factor for coronary heart disease. Therefore clinicians should be aware of this and recognize the importance of elevated fibrinogen levels in RA patients.

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