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# Association of adiponectin levels with disease activity score, RA factor and ESR in rheumatoid arthritis patients

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***Abstract***---Introduction: Rheumatoid arthritis is a chronic inflammatory polyarthritis of relatively common occurrence affecting about 1-2% of adult population world-wide and 0.75% of Indian adults. The disease occurs at all ages and affects all ethnic groups. For early diagnosis and progression of rheumatoid arthritis might be useful for to better treatment of the patients. Present study aimed to assessment of adiponectin in newly diagnosed and remission rheumatoid arthritis patients. Materials and Methods: 100 Rheumatoid arthritis patients and 50 healthy volunteers with matching age, gender, and BMI were included in the study. All the subjects' biochemical, disease activity score, RA factor,ESR Rheumatoid Arthritis Patients and serum adiponectin levels were assessed. SPSS and Microsoft Excel Spreadsheets were used to conduct the necessary statistical analysis. Results: The patients with rheumatoid arthritis shown significantly higher levels of fasting blood sugar, postprandial blood sugars ,triglycerides , RA factor, ESR when compared to healthy controls (P=0.001**). Additionally we also discovered to be considerably significantly elevated levels of serum adiponectin (P= 0.001**). Furthermore there was very high significant positive correlation between serum adiponectin and disease activity score, RA factor, ESR. Conclusion: According to the study's findings, dramatically high serum levels of adiponectin could be utilized to diagnose and track the development of rheumatoid arthritis.


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***Keywords***---adiponectin, disease activity score ESR, RA factor, rheumatoid arthritis.

## Introduction

The most prevalent chronic inflammatory joint disease of uncertain an etiology, rheumatoid arthritis is characterized by symmetric, peripheral polyarthritis and mostly affects the joints. Even though it's precise a etiology is unknown, RA is regarded as an autoimmune condition. RA primarily affects the synovium and frequently causes severe joint damage and physical impairment (1-2). Loss of self-tolerance and the emergence of auto immunity are the first steps in the pathophysiology, which then advances to local joint inflammation and, finally, joint destruction (3). Immune dysregulation and autoimmunity, which are characterized by the presence of autoantibodies like rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) in the blood, may be caused by a complex interplay of various phenomena including genetic, environmental, and immunological factors (5).

The development of self-reactive T cells later on propels the chronic inflammatory response forward. As a result, it appears that the first sign of rheumatoid arthritis is a non-specific inflammatory reaction brought on by an unknown stimulus, followed by an amplification stage brought on by T cell activation, and lastly a stage of chronic inflammation with tissue damage (6). A variety of chemicals, including cytokines, chemokines, and antibodies are released during the process, setting off a chain of events that ultimately trigger and intensify the inflammatory response. Numerous cell types, including osteoclasts, macrophages, fibroblasts, T lymphocytes, and B lymphocytes, actively contribute to the pathogenesis of rheumatoid arthritis (7). Along with the clinical examination, test data, and radiographic findings, the diagnosis of rheumatoid arthritis is mostly based on the signs and symptoms of chronic inflammatory arthritis. Previously, the diagnosis was made using the standards established in 1987 by the American College of Rheumatology (ACR) and American Rheumatism Association (ARA) (8). However, these criteria could not identify people who would benefit from treatment with anti-rheumatic medications that treat the disease in its early stages. Because of this, the European League against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have collaborated to produce guidelines that aid in the identification of patients with early rheumatoid arthritis (9).

The main site of synthesis and secretion for the protein hormone adiponectin is adipose tissue. Through its effects on insulin sensitivity, anti-inflammatory activity, vasoprotection, and atheroprotection, adiponectin has been discovered to have a number of positive impacts (10). Adiponectin may also play a role in inflammatory diseases such inflammatory bowel disease, cystic fibrosis, rheumatoid arthritis, and systemic lupus erythematosus, according to a number of studies. Adiponectin operates through all three of its cellular receptors, known as adipo R1, adipo R2, and cadherin, to exert an anti-inflammatory effect through multiple routes (11). These receptors were expressed on a variety of immunological inflammatory cells, including monocytes, NK cells, T and B

lymphocytes, and natural killer cells. According to experimental research, adiponectin inhibits the transformation of macrophages into foam cells, stimulates their production of the inhibitory cytokine IL-10, prevents the expression of the adhesion molecules VCAM-1 and ICAM-1 on endothelial cells, and also inhibits toll-like receptor-mediated NF-B activation in macrophages (12). Inflammatory illnesses like rheumatoid arthritis, the anti-inflammatory characteristics of adiponectin may be crucial in controlling the inflammatory processes and disease activity. Variations in blood adiponectin levels in RA patients are helpful for determining the diagnosis and prognosis of the disease (13). The current study focused on to association of serum adiponectin with disease activity score, RA factor and ESR in rheumatoid arthritis.

## Material and Methods

### Subjects

This cross sectional study, conducted with 100 rheumatoid arthritis diagnosed according to 2010 American College of Rheumatology/European League against Rheumatism classification criteria and further classified into newly diagnosed rheumatoid arthritis ( Group 2: n = 50) and rheumatoid arthritis with remission ( Group 3: n = 50). As controls, fifty (50) healthy people with matched BMI, age, and gender were included. After receiving informed consent from each subject, the study recruited them all. The institutional ethics committee gave its approval to the project.

### Criteria

### Inclusion criteria

Ages of all subjects should range from 30 to 70. According to the updated 2010 American College of Rheumatology/European League against Rheumatism classification criteria for rheumatoid arthritis, patients were diagnosed with the condition.

### Exclusion criteria

Patients with other types of arthritis, a history of smoking or drinking, diabetes or hypertension, thyroid disorders, cardiovascular disease, liver or kidney disease, active infection, or those taking lipid-lowering medications, thiazolidinediones, or immunosuppressive medications were excluded from this study.

### Sample collection

All individuals gave a fasting venous blood sample of five (5) mL, which was transferred; one (1) mL went into an anticoagulant-containing tube, and one more (1) mL transferred into EDTA, while the remaining three (3) mL went into a plain tube. While plain samples were allowed to coagulate before being separated by centrifugation at 3000 rpm for 15 minutes, plasma samples were separated right away. They were the separated samples aliquots that were properly labeled were transported and kept at -80$^0$C until a biochemical analysis was conducted.

**Methods**

Blood sugar levels during fasting and after meals were measured using the glucose oxidase peroxidase (GOD-POD) method, total cholesterol (mg/dL), triglycerides (mg/dL), high density lipoprotein (HDL) cholesterol (mg/dL). The Erythrocyte Sedimentation Rate (ESR) were determined by wintrobe method and Rheumatoid Factor (RF) was estimated by latex agglutination method. Serum adiponectin were all examined using Enzyme Linked Immuno Sorbent Assay (ELISA).

**Statistical Analysis**

The Kolmogorov-Smirnov test was used to determine whether the data were normal. For normally and non-normally distributed data, the data were reported as mean standard deviation or median (inter quartile range), respectively. Analysis of variance (ANOVA) used for comparison of parameters among the groups. The Pearson or Spearman rank correlation was used to investigate the Association between the variables. With the help of SPSS for Windows version 16.0 and Microsoft Excel spreadsheets, statistical analysis was carried out. Statistical significance was defined as a p value 0.05.

**Results**

Table 1
Demonstrates the anthropometric, biochemical, and experimental parameters examined in rheumatoid arthritis patients and healthy controls

| Parameters | Controls (50) | RA Patients (150) | P Value |
|---|---|---|---|
| Age (years) | 45.75 ± 3.40 | 50.28 ± 7.22 | 0.287 |
| M/F | 28/22 | 73/27 | - |
| BMI (kg/m2) | 22.07 ± 5.17 | 25.88 ± 8.54 | 0.001** |
| Plasma FBS (mg/dL) | 83.05 ± 11.35 | 100.65 ± 17.70 | 0.001** |
| Plasma PPBS (mg/dL) | 106.49 ± 21.16 | 136.66 ± 15.102 | 0.001** |
| Serum TC (mg/dL) | 146.15 ± 20.34 | 190.39 ± 26.44 | 0.02* |
| Serum TGL (mg/dL) | 158.47 ± 30.12 | 190.53 ± 40.11 | 0.001** |
| Serum HDL-C (mg/dL) | 45.13 ± 2.56 | 53.84 ± 3.94 | 0.03* |
| ESR | 18.36 ± 6.23 | 79.57±13.09 | 0.001** |
| RA Factor | 8.04 ± 1.52 | 36.94 ± 5.61 | 0.001** |
| Serum adiponectin (µg/dL) | 9.18 ± 6.17 | 17.94 ± 11.36 | 0.001** |

Data expressed as mean±SD, p value obtained using student t test, *statistically significant, RA: Rheumatoid arthritis; M/F: Male/Female; BMI: body mass index; FBS: fasting blood sugar; PPBS: post parandial blood sugar; TC: total cholesterol; TGL: triglycerides; HDL-C: high density lipoprotein cholesterol.

Table 1 lists the demographic details and biochemical measurements examined in rheumatoid arthritis patients and healthy controls. There was a significantly higher BMI, fasting blood sugars, post parandial blood sugar, triglycerides (P=0.001**). The lipid profile such as TC, TGL, HDL – C, ESR and RA Factor

significantly very high in patients with rheumatoid arthritis when compared to healthy controls.The patients with RA serum adiponectin concentrations were found to be considerably higher (P=0.001**). Furthermore, there was no difference between RA and healthy controls in terms of age(P>0.05).

Table 2
Displays the anthropometric, biochemical, and experimental variables that were examined for each group

| Parameters | Group-1 (50) | Group-2 (50) | Group-3 (50) | P-value |
|---|---|---|---|---|
| Age (years) | 45.75 ± 3.40 | 47.77 ± 5.40 | 51.82 ± 9.45 | 0.03 |
| M/F | 28/22 | 34/16 | 42/8 | - |
| BMI (kg/m2) | 22.07 ± 5.17 | 24.09 ± 7.19 | 27.12 ± 10.22 | 0.001 |
| Plasma FBS (mg/dL) | 83.05 ± 11.35 | 86.05 ± 14.38 | 89.05 ± 17.41 | 0.001 |
| Plasma PPBS (mg/dL) | 106.49 ± 21.16 | 109.52 ± 24.20 | 112.55 ± 27.23 | 0.001 |
| Serum TC (mg/dL) | 146.15 ± 20.34 | 149.50 ± 23.37 | 152.53 ± 26.40 | 0.746 |
| Serum TGL (mg/dL) | 158.47 ± 30.12 | 161.50 ± 33.15 | 164.53 ± 36.18 | 0.001 |
| Serum HDL-C (mg/dL) | 45.13 ± 2.56 | 48.16 ± 5.59 | 51.19 ± 8.62 | 0.046 |
| ESR | 18.36 ± 6.23 | 21.39 ± 9.26 | 24.42 ± 12.29 | 0.001 |
| RA Factor | 8.04 ± 1.52 | 11.07 ± 4.55 | 14.10 ± 7.58 | 0.001 |
| Serum adiponectin (µg/dL) | 9.18 ± 6.17 | 12.21 ± 9.20 | 15.24 ± 12.23 | 0.001 |

Data expressed as mean±SD, p value obtained using analysis of variance (ANOVA), followed by post hoc tests, *statistically significant, Group-1= healthy controls; Group-2=newly diagnosed RA patients; Group-3= RA patients in disease remission, M/F: Male/Female; BMI: body mass index; FBS: fasting blood sugar; PPBS: post parandial blood sugar; TC: total cholesterol; TGL: triglycerides; HDL-C: high density lipoprotein cholesterol.

The two groups of patients with rheumatoid arthritis and the biochemical parameters that were examined in healthy controls are shown in Table 2 along with some demographic information. The anthropometric parameters like age and BMI shown significance across the study groups. In the three study groups, the analysis of variance revealed significantly higher serum adiponectin concentrations, fasting blood sugar, and post-parandial blood sugar levels (P = 0.001**). Additionally there was a significantly elevated levels TGL, HDL-C, ESR and RA factor in group 3 subjects when compare to group 2 and group 1, respectively (p value = 0.001 and 0.046 ). Furthermore, the serum adiponectin levels were proportionally elevated in both the group 2 and group 3 when compare to group 1, the P Value is 0.001. Moreover, no significance of TC Observed in among the subjects significantly different across the groups (P> 0.05).

Table 3
Displays the DAS-28 in patients with rheumatoid arthritis

| RA Patients | DAS28 |
|---|---|
| Rheumatoid arthritis patients in remission | 3.59 ± 0.28 |
| Newly diagnosed RA patients | 11.28 ± 6.53 |

The demographic information and biochemical markers examined in two groups of rheumatoid arthritis patients are shown in Table 3. The DAS - 28 was reported to be considerably higher in patients with newly diagnosed RA and to be significantly lower in those in RA with remission.

Table 4
The Pearson's correlation between serum adiponectin and DAS 28, ESR, RA factor among the study subjects

| Adiponectin | | | | |
|---|---|---|---|---|
| Parameter | RA patients in remission (n=50) | | newly diagnosed RA patients (n=50) | |
| | r | P | r | P |
| DAS28 | 0.443 | 0.001** | 0.645 | 0.001** |
| RA Factor | 0.851 | 0.001** | 0.964 | 0.001** |
| ESR | 0.654 | 0.001** | 0.746 | 0.001** |

Table 4 displays the relationship between serum adiponectin and DAS 28 in RA patients. Serum adiponectin showed a markedly positive link with DAS 28.

**Discussion**

Rheumatoid arthritis is the prototypical chronic inflammatory joint disease that primarily affects the joints and is marked by symmetric, peripheral poly arthritis. Rheumatoid arthritis is a widely prevalent condition, affecting 0.5% -1.0% of adult population in the world. In India, the prevalence of RA is reported to be 0.28% - 0.7%. Although the exact cause of RA is not known, the disease is considered to develop as a result of a complex interplay of genetic, environmental and immunological factors that stimulate an initial phase of nonspecific inflammation which is followed by an amplification phase that ultimately progresses to the stage of chronic inflammation with consequent tissue injury (14 – 16).

The present study was conducted to evaluate serum adiponectin concentration in rheumatoid arthritis patients along with measurement of fasting blood sugar and lipid profile and compare them with those in healthy controls. Rheumatoid arthritis patients and healthy controls matched with respect to age, BMI and

gender (Table 02). Patients with rheumatoid arthritis had significantly higher serum adiponectin levels when compared to controls ($p<0.001$). While majority of the adipocytes are pro-inflammatory, adiponectin is predominantly anti-inflammatory in nature. However, it was also reported that adiponectin exhibits proinflammatory effects. The report by Schaffler et al., (17) that adiponectin levels were increased in the synovial fluid of RA patients compared to those with osteoarthritis was probably the first report indicating the proinflammatory role of adiponectin. The increased adiponectin levels were observed even in the presence of increased CRP levels and showed a positive correlation with CRP levels. Further, Tang et al., (18) have shown that adiponectin resulted in a time and concentration dependent increase in IL-6 production in cultured synovial fibroblasts obtained from RA patients.

Subsequently, several authors have reported increased synovial as well as systemic adiponectin levels in RA patients. Rho et al., (19) found that adiponectin and other adipocytokines were significantly higher in RA patients compared to healthy controls. Similarly, Yoshino et al., (20) reported increased adiponectin levels in female RA patients when compared to female controls. Kondrat et al., (21) also found higher adiponectin levels in rheumatoid patients than in age matched healthy controls. Oranskii et al., (22) studied adiponectin and cytokine levels in RA patients and found that adiponectin levels were higher in RA patients with normal BMI and lower in obese RA patients when compared to controls. Thus majority of the studies have reported increased adiponectin levels in RA patients. A meta-analysis by Lee et al., (23) also showed 22 that RA patients had significantly higher plasma or serum adiponectin levels when compared to healthy controls. However, some of the other studies observed decreased levels of adiponectin in rheumatoid arthritis patients. El Hini et al., (24) reported decreased adiponectin levels in RA patients which correlated negatively with DAS. Similarly, Li et al., (25) also reported decreased adiponectin levels in rheumatoid arthritis patients when compared to controls. Thus, from the above studies, it is observed that both increased as well as decreased adiponectin levels were observed in RA compared to controls.

In the present study, patients with rheumatoid arthritis had significantly higher fasting blood sugar , post parandial blood sugar, total cholesterol, triglyceride and HDL C levels when compared to controls ($p<0.001$) However, the mean ESR and RA factor levels in RA patients were found to be highly when compare to healthy controls ($p <0.001$). Metabolic disturbances involving carbohydrate and lipid metabolism are commonly observed in rheumatoid arthritis patients (26). Sattar et al., (27) have mentioned that cytokines which are the classical mediators of the inflammatory responses in rheumatoid arthritis are also involved in mediating the metabolic effects such as alteration in the lipids and peripheral insulin resistance.

The inflammatory process which is the characteristic feature of the pathophysiological process of rheumatoid arthritis as well as treatment factors such as administration of glucocorticoids was linked to the insulin resistance that is observed in RA patients. Thus, it was reported that patients with rheumatoid arthritis experience a higher prevalence of insulin resistance and diabetes mellitus (28). Cytokines, notably TNF-α, is known to inhibit insulin mediated glucose uptake by skeletal muscle cells and also stimulate lipolysis in adipocytes

resulting in an increase in free fatty acid levels which can contribute to insulin resistance (29). However, insulin levels were not measured in RA patients and controls in the present study. Accordingly, the findings of the present investigation show that RA patients had significantly higher levels of circulating adiponectin than healthy controls. Despite the fact that results from earlier studies suggest that adiponectin contributes to the pathophysiology of rheumatoid arthritis through its pro-inflammatory effects and thus correlates with the severity of inflammation, it appears in the current study that the elevated adiponectin levels appear to reflect the underlying inflammatory process in the synovial.

## Conclusion

According to the study finding, dramatically high serum levels adiponectin could be utilize to diagnose and track the development of rheumatoid arthritis.

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