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# Adiponectin: A novel prognostic marker for rheumatoid arthritis: A case control study in a tertiary care hospital in central India

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A B S T R A C T

**Introduction:** Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by symmetrical synovitis, progressive damage to the articular cartilage and the subchondral bone, pain, fatigue, and disability**.** Recognition of RA as early as possible is important, because a significant proportion of the patients develop irreversible joint damage shortly after disease onset & risks associated with its treatment. The adiponectin is an active participant in the regulation of physiological and pathological processes, inflammatory process as mediator. This study was done to compare the progression of rheumatoid arthritis in conjunction with changes in levels of adiponectin and to evaluate its role as a prognostic marker.
**Aim:** Analyse serum adiponectin level to evaluate its potential role to assess disease severity in patients of rheumatoid arthritis & compare its level in normal healthy control subjects.
**Materials and Methods:** This study was conducted in MY Hospital, Indore. We enrolled 50 cases of confirmed rheumatoid arthritis patients of 20-70 years age group and 50 age and sex matched apparently healthy controls. Both cases (n=50) and controls (n=50) were assessed for haematological tests and biochemical tests, lipid profile, uric acid, CRP & adiponectin. The data were expressed as mean ± SD and analysed by using SPSS version 20. P-value of $< 0.05$ was accepted as statistically significant.
**Result:** The mean age of the cases was 44.74 ± 13.10 and that of controls was 42.26 ± 8.09. Maximum number of study patients were in the age group of 31-40 years & women. The rheumatoid arthritis group was divided into subgroup according to DAS28 Score. Out of 50 cases, 2 patients (4.0%) had remission, 2 patients (4.0%) had low disease activity, 30 patients (60.0%) had moderate disease activity and 16 patients(32.0%) had high disease activity. The mean CRP in the rheumatoid arthritis group was 21.56 ± 25.46 mg/dL while in the control group was 11.09 ± 7.95 mg/L. The difference was found to be statistically significant ($p<0.05$).The mean ESR in the rheumatoid arthritis group was 21.26 ± 8.88 mm/hour while in the control group was 15.70 ± 5.40 mm/hour. The difference was found to be statistically significant ($p<0.05$).The mean adiponectin level in the rheumatoid arthritis group was 30.13 ± 13.04 $\mu$g/ml while in the control group was 17.08 ± 8.69 $\mu$g/ml. The difference was found to be statistically significant ($p<0.05$).The mean adiponectin level was highest in the high disease activity subgroup and lowest in the low disease activity subgroup.
**Conclusion:** In our study we concluded that patients of rheumatoid arthritis have raised level of adiponectin & CRP as compared to normal healthy control group. Adiponectin might be better marker for RA compare to CRP & ESR. Also higher levels of adiponectin were observed in patients with severe disease. Therefore, adiponectin might be used for screening which will help in predicting disease progression.



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## 1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by symmetrical synovitis, progressive damage to the articular cartilage and the subchondral bone.[1]

RA is chronic inflammatory disease characterised by raised level of inflammatory markers such as CRP, ESR and many other. Recognition of RA as early as possible is important, because a significant proportion of the patients develop irreversible joint damage shortly after disease onset.[2] In rheumatoid arthritis (RA), early diagnosis and early therapeutic intervention can improve clinical outcomes and reduce the occurrence of joint damage and major irreversible long-term disabilities.[3] Finding serum biomarkers that can be used to identify patients at high risk of structural disease progression early in the disease is important because joint lesions occur mainly during this period and which may be reduced by early intervention.

Levels of inflammatory biomarkers {i.e. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)} and presence of autoantibodies {i.e. rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies} are associated with subsequent RA structural severity.[4] However, the predictive value of these markers for early radiographic disease progression remains weak, especially in early disease. WAT is also considered a highly active endocrine organ that produces a number of biologically active molecules, called adipokines[5] that are involved in various important physiological processes. Adipokines are adipose tissue-specific soluble proteins, also produced by synovium and cartilage, as well as mononuclear blood cells, measurable in biologic fluids.[6] Adipokines, including resistin, leptin, and adiponectin. Inflammatory cytokines TNF-$\alpha$, IL-6, and IL-1b, and interferon-g (IFN-g), can regulate the expression and the secretion of adiponectin.[7] RA is characterised by chronic inflammation associated with increased production of inflammatory factors, as well as disturbances of the endocrine system. In RA there is also synovial hyperplasia and progressive joint destruction.[8,9]

Adiponectin stimulates the production of IL-8 and prostaglandin E2 by rheumatoid synovial fibroblasts & attenuates the inflammatory response mediated by tumour necrosis factor-$\alpha$ (TNF-$\alpha$), inhibits macrophage phagocytic activity and TNF-$\alpha$ production and also inhibits myelomonocytic cell proliferation by inducing apoptosis.[6] Adiponectin is able to induce the expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinase-1 (MMPs-1) in the fibroblast like synoviocytes (FLSs) leading to joint inflammation and destruction.[10] The important role of adipokines in inflammation provides novel links between adipose tissues and inflammatory disorders including RA, thus attracting the interest of both basic researchers and clinical physicians.[9,10]

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## 2. Materials and Methods

A case control study was carried out in MGMMC & MYH, Indore with 50 newly diagnosed rheumatoid arthritis patients and 50 apparently healthy controls between the age group of 20 to 70yrs. Cases are further divided into subgroups on the basis of DAS 28 Score, group B1-remission, group B-2 included mild cases of rheumatoid arthritis, group B-3 of moderate & group B-4 of severe cases of rheumatoid arthritis**.**

### *2.1. Exclusion criteria*

1. Past history of other autoimmune disease.
2. Spondyloarthropathy
3. Diabetes mellitus
4. Oncological disease
5. Chronic kidney disease
6. Chronic liver disease
7. Pregnancy
8. Alcoholism
9. Smoking

After overnight fasting of 8-10 hours, 5 ml of venous blood sample was drawn by venepuncture from a peripheral vein under all aseptic precautions in a disposable syringe. The blood was collected in clot activator tube & EDTA tube. Clot activator tube was allowed to stand for 30 minutes at room temperature for the retraction of clot. Then it was centrifuged at 3000 r.p.m. for 10 minutes to separate the serum. Care was taken to avoid haemolysis of the sample. Routine haematological (ESR) (from EDTA tube) and biochemical tests (lipid profile, uric acid & CRP) (from serum) were performed on the fresh samples on the same day. Then remaining serum sample was stored at -20°C for further analysis. Sample were only exposed to a single freeze/thaw cycle to minimise the risk of contamination of the samples. The stored serum samples were analysed for Adiponectin.

All the data was analysed by using SPSS version 20. Results on continuous measurements were presented as Mean ± SD. P value < 0.05(95% confidence interval) was considered significant and p value < 0.001 considered as highly significant. Unpaired student t test was applied to find the significance of study parameters on continuous scale between two ANOVA and POST HOC TUKEY tests were applied for comparisons within multiple groups (control with mild cases, control with moderate/severe cases and between mild and severe cases).

The above table shows the distribution of patients according to sex in both the groups. In the control group, there were 40 females (80.0%) and 10 males (20.0%). In the rheumatoid arthritis group, there were 43 female (86.0%)

**Table 1:** Distribution of patients according to sex in both the groups

| Sex | Control Group | | Rheumatoid Arthritis Group | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Female | 40 | 80.0 | 43 | 86.0 |
| Male | 10 | 20.0 | 7 | 14.0 |
| Total | 50 | 100.0 | 50 | 100.0 |

**Table 2:** Distribution of patients according to DAS-28 grading in Rheumatoid Arthritis group

| | Control Group | | Rheumatoid Arthritis Group | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Remission (<2.6) | 0 | 0.0 | 2 | 4.0 |
| Low disease activity (>2.6-<3.2) | 0 | 0.0 | 2 | 4.0 |
| Moderate disease activity(>3.2-<5.1) | 0 | 0.0 | 30 | 60.0 |
| High disease activity (>5.1) | 0 | 0.0 | 16 | 32.0 |
| Total | 0 | 0.0 | 50 | 100.0 |

**Table 3:** Comparison of various biochemical parameters between the two groups

| Parameter | Control group (Mean±SD) | Rheumatoid Arthritis Group (Mean±SD) | 't' value | P value |
|---|---|---|---|---|
| Cholesterol | 167.02 ± 25.87 | 169.14 ± 32.93 | -0.358, df=98 | 0.721, NS |
| HDL | 50.15 ± 6.95 | 47.35 ± 9.49 | 1.682, df=98 | 0.096, NS |
| LDL | 93.13 ± 27.38 | 90.52 ± 28.67 | 0.466, df=98 | 0.643, NS |
| Triglycerides | 121.28 ± 21.96 | 156.32 ± 63.58 | -3.683, df=98 | 0.000* |
| VLDL | 24.26 ± 4.39 | 31.26 ± 12.72 | -3.683, df=98 | 0.000* |
| Uric acid | 3.98 ± 1.39 | 4.04 ± 1.57 | -0.206, df=98 | 0.838, NS |

**Table 4:** Comparison of hematologial parameters between the two groups

| Parameter | Control group (Mean±SD) | Rheumatoid Arthritis Group (Mean±SD) | 't' value | P value |
|---|---|---|---|---|
| ESR | 15.70 ± 5.40 | 21.26 ± 8.88 | -3.784, df=98 | 0.000* |
| CRP | 11.09 ± 7.95 | 21.56 ± 25.46 | -2.776, df=98 | 0.007* |

**Table 5:** Comparison of mean adiponectin level between the two groups

| Parameter | Control group (Mean±SD) | Rheumatoid Arthritis Group (Mean±SD) | 't' value | P value |
|---|---|---|---|---|
| Adiponectin Level ($\mu$g/ml) | 17.08 ± 8.69 | 30.13 ± 13.04 | -5.892, df=98 | 0.000* |

**Table 6:** Comparison of mean adiponectin level in the rheumatoid arthritis group in relation to DAS-28 grading

| DAS-28 Grading | No. | Mean ± SD | F value | P value |
|---|---|---|---|---|
| Remission | 2 | 35.2 ± 14.4 | 5.75 | 0.002* |
| Low disease activity | 2 | 13.51 ± 1.20 | | |
| Moderate disease activity | 30 | 26.25 ± 11.44 | | |
| High disease activity | 16 | 38.86 ± 11.72 | | |
| Total | 50 | | | |

and 7 males (14.0%). In both the groups, there was a female preponderance.Table 1

The above table shows the distribution of patients according to DAS-28 grading in both the groups. In the rheumatoid arthritis group, there were 2 patients (4.0%) had remission, 2 patients (4.0%) had low disease activity, 30 patients (60.0%) had moderate disease activity and 16 patients (32.0%) had high disease activity. In majority of the patients in the rheumatoid arthritis group were having moderate to high disease activity.Table 2

One-way ANOVA test applied. P value =0.002, Significant. The above table shows the comparison of mean adiponectin level in the rheumatoid arthritis group in relation to DAS-28 grading. The mean adiponectin level in the remission subgroup was 35.2 ± 14.4 $\mu$g/ml, in the low disease activity subgroup was 13.51 ± 1.20 $\mu$g/ml, in

the moderate disease activity subgroup was 26.25 ± 11.44 $\mu$g/ml and in the high disease activity subgroup was 38.86 ± 11.72 $\mu$g/ml. The mean adiponectin level was highest in the high disease activity subgroup and lowest in the low disease activity subgroup.

The comparison of mean adiponectin level between the DAS-28 grades was found to be statistically significant ($p<0.05$), showing that there is a statistically significant difference in the mean adiponectin level between the DAS-28 grades.

## 3. Discussion

Adiponectin seems to be the most interesting and promising biologically active molecule released from fat cells. In this study majority of the patients were in the age group 31-40 years with female preponderance i.e. 43:7 (F:M) which is in concordance with study by Kang, Lee, Kim et al (2014) in which female to male ratio was32:8.[11]

The main finding of our study is increase in plasma adiponectin levels in all patients with RA compared with the control group (P=0.000). This result is in concordance with the results of Ozygen et al.[12] They found that serum adiponectin levels were significantly higher in RA group than control group (P<0.05). We found that serum adiponectin level was increased with increase in the severity of the disease. In mild disease activity subgroup adiponectin concentration was low as compared to high disease activity subgroup. As adiponectin may be an important modulator of inflammatory response in patients with rheumatoid arthritis, it can be postulated that it may have a role in modulating the inflammatory response by inhibiting the expression of adhesion molecules on endothelial cells, suppressing macrophage function and inhibiting NFkB signalling, as reviewed by Fantuzzi et al.[13] Adiponectin has anti-inflammatory properties and can counteract the pro-inflammatory effects of TNF-$\alpha$, a pro-inflammatory cytokine, which may influence the production of IL-6 and CRP in rheumatoid arthritis.[14] Thus, the putative anti-inflammatory role of adiponectin in this scenario is worthy of further evaluation.

## 4. Conclusion

Significant changes in the level of inflammatory markers such as adiponectin, CRP, ESR in RA patients confirms role of inflammation in the pathogenesis of RA. This might be helpful to futher assessment of risk. Furher studies are also required for a general assumption on the aspect conducted to assess the effect of adiponectin on disease activity in Rheumatoid arthritis and its association with CRP.Also higher levels of adiponectin were observed in patients with severe disease. Therefore, adiponectin might be used for screening which will help in predicting disease progression.

## 5. Source of Funding

None.

## 6. Interest of Conflicts

None.

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