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Correlation of adiponectin levels with disease activity score in rheumatoid arthritis patients

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***Abstract*---**Introduction: Rheumatoid arthritis is the most common chronic inflammatory joint disease of unknown etiology that primarily affects the joints and is marked by symmetric, peripheral poly arthritis. To estimation of adiponectin can be useful for early diagnosis and progression of rheumatoid arthritis. Materials and Methods: Total 90 subjects included in the present study were 60 patients were diagnosed with Rheumatoid arthritis and 30 age, gender and BMI matched healthy subjects were included as controls. biochemical, disease activity score and serum adiponectin levels were measured from all the subjects. Relevant statistical analysis was done by using SPSS and Microsoft Excel Spread Sheets. Results: Fasting blood sugars, post parandial blood sugars and triglycerides when compared to controls (P=0.0001**). Serum adiponectin concentration was found to be significantly increased in RA patients compared to healthy controls (p<0.0001). There was a significantly positive correlation between serum adiponectin and disease activity score. Conclusion: This study concludes significantly elevated levels of serum adiponectin might be used for early diagnosis and progression of rheumatoid arthritis.

***Keywords*---**adiponectin, disease activity score, rheumatoid arthritis.

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. Although considered to be known since ancient times, the exact etiology of RA remains still unknown. However, it is considered that the disease occurs as a result of immune dysregulation leading to loss of self-tolerance and auto immunity in genetically susceptible individuals under the influence of environmental triggers. The pathological hall mark of rheumatoid arthritis is synovial inflammation which further progresses to involve underlying bone causing joint destruction. The disease usually presents as symmetrical polyarthritis, involving preferably small joints, however, large joints such as hips and knee may also be involved. During its course, the disease does not confine itself to the joints it involves, but extends to become systemic as well. Earlier the diagnosis of RA was based on the 1987 revised ARA criteria. However, since these criteria could not identify RA patients in early stages, newer criteria were laid down by the joint collaboration of ACR/EULAR in 2010. In addition to suffering from joint symptoms, patients with RA experience physical disability. Hence, management of patients with RA primarily involves control of inflammation and achieving remission. Measurement of disease activity is used as a marker to evaluate the disease progression, treatment response and prognosis. Various criteria have been proposed based on clinical examination, laboratory findings and functional assessment to measure disease activity.

Adipose tissue is now considered as a metabolically dynamic organ that produces a number of substances, known as adipocytokines. Adiponectin is a 30 kDa adipocytokine consisting of 244 amino acids and is mainly produced by white adipocytes. Serum levels in humans are reported to be in the range of 5 to 30 µg/mL and are inversely related to BMI. Adiponectin was found to exert several beneficial effects through its insulin sensitizing, anti-inflammatory, vasoprotective and atheroprotective effects. In contrast to most of the adipokines that are pro-inflammatory, adiponectin exhibits anti-inflammatory properties by acting through its cellular receptors on different cell types including macrophages, natural killer cells, T and B lymphocytes and attenuating the inflammatory actions of cytokines such as TNF-α and IL-6. Through its anti-inflammatory effects, adiponectin is considered to play an important role in regulating the inflammatory responses in various clinical conditions.

Animal studies have demonstrated that the association of adiponectin with the key inflammatory mediator TNF-α is bi-directional and inverse. In vitro studies using human culture cells showed that TNF-α suppresses the expression and secretion of adiponectin from adipocytes. Conversely, adiponectin was shown to antagonize the inflammatory effects of TNF-α (27) and the adipocyte expression of C-reactive protein. Apart from these effects, adiponectin also inhibits matrix metalloproteinases (MMPs) and prevents the generation of oxidative stress. Thus, by all these effects, adiponectin is known to play anti-inflammatory role. However, Tsatsanis et al., (28) have shown that adiponectin induces pro-inflammatory cytokines and induces inflammation. Further, studies have shown that adiponectin also plays a role in the pathophysiology of rheumatoid arthritis.

Adiponectin was found to increase the gene expression and protein synthesis of several proinflammatory and pro destructive molecules that participate in the pathophysiology of RA (29). Thus, the exact role of adiponectin in inflammatory process appears to be understood completely since adiponectin was shown to exert anti-inflammatory as well as pro-inflammatory effects. The anti-inflammatory function of adiponectin might confer beneficial effects in human beings through inhibiting atherogenic phenomena via its actions on macrophages, adhesion molecules and other cells that are involved in the atherogenic process. Also adiponectin may play an important role in the regulation of inflammatory responses in and thus the disease process in various inflammatory conditions such as rheumatoid arthritis.

Material and Methods

Subjects

This cross sectional study conducted with 150 subjects, were classified into were 100 patients diagnosed with rheumatoid arthritis according to American College of Rheumatology/European League against Rheumatism classification criteria. Additionally fifty (50) age, gender and BMI matched healthy subjects were included as controls. All the subjects were recruited in the study after informed consent. The study was approved by the institutional ethics committee at Akash Institute of Medical Sciences and Research Centre.

Criteria

Inclusion criteria

All the subjects' age should be 30 to 70 years. Patients were diagnosed with rheumatoid arthritis as per the new 2010 American College of Rheumatology/European League against Rheumatism classification criteria for rheumatoid arthritis.

Exclusion criteria

Patients with other forms of arthritis, history of smoking and /or alcoholism, history of diabetes and hypertension, thyroid disorders, history of cardiovascular disease, liver and kidney diseases, active infection and whoever on lipid lowering drugs, thiazolidinediones and immunosuppressive drugs were excluded from this study.

Sample collection

Five (5) mL of fasting venous blood sample was collected from all the subjects into two tubes: 1 mL into a tube containing anticoagulant, 1 mL transferred into EDTA tubes and 2 mL will be taken into a plain tube. Plasma samples were separated immediately and plain samples were allowed to clot and separated by centrifugation at 3000 rpm for 15 minutes. The separated samples were transferred into appropriately labelled aliquots and stored at -80^0 C until biochemical analysis was done.

Methods

Fasting and post parandial blood sugars was measured by using glucose oxidase peroxidase (GOD-POD) Method, Total cholesterol (mg/dL) and Triglycerides (TGL) (mg/dL) were analysed by enzymatic end point colorimetric method, High density lipoprotein (HDL) cholesterol (mg/dL) by analysed selective inhibition method, Disease Activity Score was calculated and serum adiponectin was measured by Enzyme linked immunosorbent assay (ELISA).

Statistical Analysis

Normality of data was checked using Kolmogorov Smirnov test. The data was expressed as mean ± standard deviation or median (inter quartile range), for normally and non-normally distributed data, respectively. The difference in the adiponectin levels between RA patients and controls was assessed using Student's t-test or Mann Whitney U test and ANOVA or Kruskal Wallis test as appropriate. The association between the variables was studied using Pearson or Spearman rank correlation analysis. Statistical analysis was performed using Microsoft excel spread sheets and SPSS for windows version 16.0. A p value <0.05 was considered statistically significant.

Results

Table-1: Shows the anthropometric, biochemical and experimental parameters studied in healthy controls and rheumatoid arthritis patients

Parameters	Controls	RA Patients	P Value
Age (years)	49.77 ± 5.42	52.30 ± 9.24	0.312
M/F	18/12	42/18	-
BMI (kg/m2)	21.06 ± 4.16	24.87 ± 2.53	0.731
Plasma FBS (mg/dL)	79.01 ± 7.31	96.61 ± 13.66	0.0001*
Plasma PPBS (mg/dL)	101.43 ± 16.11	131.61 ± 10.97	0.0001*
Serum TC (mg/dL)	141.10 ± 15.29	185.34 ± 21.39	0.636
Serum TGL (mg/dL)	160.49 ± 32.14	192.55 ± 43.13	0.0001*
Serum HDL-C (mg/dL)	48.16 ± 2.56	56.87 ± 6.97	0.243
Serum adiponectin (µg/dL)	4.13 ± 1.12	12.89 ± 6.34	0.0001*

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 shows the demographic characteristics and biochemical parameters studied in healthy controls and rheumatoid arthritis patients. Patients with rheumatoid arthritis had significantly higher fasting blood sugar, post parandial blood sugar and triglycerides when compared to controls (P=0.0001**). Serum adiponectin concentration was found to be significantly elevated in RA patients

compared to healthy controls (P=0.0001**). Furthermore there were no significance of age, BMI, TC, HDL-C in between RA and healthy controls (P>0.05).

Table-2: Shows the anthropometric, biochemical and experimental parameters studied among the groups

Parameters	Group-1	Group-2	Group-3	p-value
Age (years)	49.77 ± 5.42	45.62 ± 9.33	44.75 ± 8.14	0.524
M/F	18/12	22/8	20/10	-
BMI (kg/m2)	21.06 ± 4.16	24.23 ± 5.78	26.99 ± 2.19	0.764
Plasma FBS (mg/dL)	79.01 ± 7.31	84.13 ± 16.31	97.35 ± 15.80	0.0001**
Plasma PPBS (mg/dL)	101.43 ± 16.11	120.28 ± 13.08	132.35 ± 17.54	0.0001**
Serum TC (mg/dL)	141.10 ± 15.29	160.14 ± 28.35	196.47 ± 21.41	0.219
Serum TGL (mg/dL)	160.49 ± 32.14	136.24 ± 26.01	141.52 ± 32.16	0.542
Serum HDL-C (mg/dL)	48.16 ± 2.56	57.21 ± 4.63	37.89 ± 7.79	0.378
Serum adiponectin (µg/dL)	4.13 ± 1.12	13.26 ± 6.14	10.83 ± 3.49	0.0001**

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.

Table 2 shows the demographic characteristics, biochemical parameters studied in healthy controls and the two groups of rheumatoid arthritis patients. Analysis of variance showed significantly increased fasting blood sugar, post parandial blood sugar, serum adiponectin concentration across the three study groups (P = 0.0001**). There is no significance of age, BMI, TC, TGL and HDL-C in between the groups (P > 0.05).

Table-3: Shows Disease activity score (DAS28) in rheumatoid arthritis patients

Group	DAS28
Rheumatoid arthritis patients in remission	1.56 ± 0.25
Newly diagnosed RA patients	7.22 ± 2.49

Table 3 shows the demographic characteristics, biochemical parameters studied in two groups of rheumatoid arthritis patients. There was a significantly increased DAS 28 in newly diagnosed RA patients and also observed decreased DAS 28 in patients with RA remission.

Table-4: Correlation of adiponectin with DAS28 in RA patients

Adiponectin		
Parameter	RA patients in remission (n=20)	newly diagnosed RA patients (n=20)
DAS28	r = 0.261 p = 0.001*	r = 0.713 p = 0.001*

Table 4 shows the correlation of serum adiponectin with DAS 28 in patients with RA. There was a significantly positive correlation between serum adiponectin and DAS 28.

Discussion

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 1). Patients with rheumatoid arthritis had significantly increased serum adiponectin levels when compared to controls (P=0.0001**). Similar findings were reported by El Hini et al., (14) who studied adiponectin levels in newly diagnosed untreated rheumatoid arthritis patients and compared them with age and gender matched healthy controls. Li et al., (15) measured total adiponectin as well as its isoforms, the low molecular weight, middle molecular weight and high molecular weight forms of adiponectin in RA patients. They observed the concentration of total adiponectin and all its multi mers were significantly lower in rheumatoid arthritis patients than in age and gender matched healthy controls. However, majority of studies on adiponectin in rheumatoid arthritis patients have reported an increase in adiponectin levels in RA patients. A meta-analysis by Lee et al., (16) reported that circulating adiponectin levels are significantly higher in RA patient than in controls. Some of the studies which reported increased adiponectin levels in RA patients have included patients undergoing treatment. It has been reported recently that anti-TNF, methotrexate, or glucocorticoid treatments were associated with an increase in adiponectin levels (17). However, other factors including difference in disease duration, sample size, and ethnicity of the study population might also contribute to the differences in findings observed between studies (18). Physiologically, adiponectin is known to inhibit the release of pro-inflammatory cytokines and increase the production of anti-inflammatory cytokines from activated inflammatory cells. The general consensus is that pro inflammatory mediators suppress adiponectin production and the decreased adiponectin levels, in turn, further promote inflammation thus resulting in a self-sustaining inflammatory loop. Experimental studies have demonstrated that the association of adiponectin with the key inflammatory mediator TNF-α is bi-directional and inverse. In vitro studies using human culture cells showed that TNF-α suppresses the expression and secretion of adiponectin from adipocytes. This effect has also been demonstrated using therapeutic interventions in human beings. Nagashima et al., (19) reported that adiponectin was increased upon treatment with anti-TNF-α treatment. In contrast, Gonzalez Gay et al., (20) have not observed any change in

adiponectin levels with TNF- α antagonist infliximab. Moreover, the low molecular weight form of adiponectin is considered to have anti-inflammatory effects, whereas its globular form with high molecular weight was shown to exhibit pro-inflammatory effects. The results of Li et al., (21) indicate that the LMW adiponectin is more strongly associated with the DAS28 than total, HMW, and MMW adiponectin forms. The various multi meric forms of adiponectin appear to be differentially generated depending on in vivo physiological conditions (22). Thus, measurement of the different multi meric forms and their ratios might help in understanding their individual roles in inflammatory processes.

In order to find if any difference existed in adiponectin concentrations between newly diagnosed RA patients and patients in disease remission, RA patients in the present study were further sub grouped into two groups based on the disease activity score calculated using 28 joint count. Results of ANOVA showed that both newly diagnosed RA patients and patients in disease remission had significantly increased serum adiponectin levels than in healthy controls (P= 0.0001**). The levels were not significantly different between RA patients who were newly diagnosed and had a higher disease activity and patients in remission and with lower disease activity. Kim et al., (23) who evaluated the effect of treatment on adiponectin levels in RA patients have reported that the baseline adiponectin and the other adipokines studied were not significantly different in patients with moderate and high disease activity who were classified based on DAS28. They also suggested that disease activity in rheumatoid arthritis does not significantly affect adiponectin levels.

In the present study, patients with rheumatoid arthritis had significantly higher fasting blood sugar, post parandial blood sugars and triglyceride levels when compared to controls (P= 0.0001**). However, the mean FBS and triglyceride levels in RA patients were found to be within the normal limits. Total cholesterol and HDL cholesterol levels were found to be similar between RA patients and controls. Several studies have evaluated serum lipid levels in RA patients and compared them with controls. Varying patterns of dyslipidemia were reported, however a more consistent finding was decreased HDL cholesterol in active or untreated RA subjects. Dessein et al., (24) have reported similar findings as observed in the present study with respect to total cholesterol, triglycerides and HDL cholesterol levels. The increase in the triglyceride levels in RA patients is attributed to the cytokines which can cause alterations in the lipoprotein metabolism. The cytokines released from the inflamed synovium enter the systemic circulation and cause an increase in the free fatty acid release from the adipose tissue, an increased synthesis of free fatty acids and triglycerides in the liver and also a decrease in the activity of vascular endothelial enzyme, lipoprotein lipase which catalyzes triglyceride-rich lipids (25).

Thus, the results of the present study indicate that circulating adiponectin levels are significantly increased in RA patients when compared to healthy controls. Although findings of earlier studies indicate that adiponectin participates in the pathophysiology of rheumatoid arthritis through its pro-inflammatory effects and thus correlates with the degree of inflammation, it appears in the present study that the increased adiponectin levels appear to reflect the underlying inflammatory process in the synovium.

Conclusion

Thus, findings of the present study concludes serum adiponectin can be used for early diagnosis and prognosis of rheumatoid arthritis

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