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A Hospital Based Case Control study on Serum Lipid Profile in Patients with Active Rheumatoid Arthritis attending a tertiary care center in Chennai, Tamil Nadu, India.

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ABSTRACT

Epidemiological studies have observed increased premature cardiovascular morbidity and mortality in Rheumatoid Arthritis patients. Lipid profile has not been evaluated as a primary risk factor for Cardiovascular morbidity and mortality in these patients. The present study was carried out to assess the Lipid Profile in RA patients. A Case control study was carried out on 55 RA patients with active disease and 27 age, sex matched healthy controls. Rheumatoid arthritis patients were chosen based on ACR criteria 2010. Serum Total Cholesterol, Triglyceride, HDL and LDL were measured. Statistical analysis was done using Epi info version 7.2.5.0. Unpaired student's t-test at 5 % significance was done to compare the parameters between cases and controls. There was a significant difference between cases and controls with regards to mean Total Cholesterol (170±36.2mg/dL in cases vs 149±39.2 mg/dL in controls, p=0.017), mean Triglyceride (123±41.1mg/dL Vs 98±34.1 mg/dL, p=0.006), mean HDL (47±11.4mg/dL Vs 43±9.6mg/dL, p= 0.049) and mean LDL (98±25.1mg/dLVs 87±27.8mg/dL, p =0.075). The Lipid Profile and the derived atherogenic indices from this lipid profile are elevated in Cases compared to controls, which indicates a higher Cardiovascular risk in RA. Hence early diagnosis, health education, awareness and management of cardiovascular diseases is of paramount importance in subjects with RA.

Keywords: Rheumatoid Arthritis, Lipid profile, HDL, LDL, Triglycerides, Cholesterol

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INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic inflammatory disease-causing bone destruction and disability [1]. Epidemiological studies stand as evidence for increased premature cardiovascular morbidity and mortality in these patients [2,3]. In most of the studies, Lipid levels were analyzed only as a variable in assessing the Cardiovascular risk. It was not considered as a primary risk factor. Altered lipid profile has been associated increased cardiovascular risk [4-6]. Rheumatoid arthritis affects 0.5 to 1 % of general population in age group of 4th and 5th decade of life, with female to male ratio 2:1 to 3:1 [7]. Increase in LDL cholesterol, decrease in HDL cholesterol, Increased Triglyceride in plasma associated with Diabetes Mellitus, smoking, male sex and elderly age group were established risk factors for Atherosclerosis and thereby cardiovascular disease [8]. Altered Lipoprotein levels in RA could be added risk for cardiovascular morbidity [9]. The chronic inflammation in RA causes Subclinical atherosclerosis. In severe Rheumatoid Arthritis, vasculitis occurs in patients with high rheumatoid factor titres and cause Acute Myocardial infarction in some patients. But accelerated Atherosclerosis is the major cause of Myocardial Infarction in RA patients. Some studies are available that determine the Lipid profile in RA patients. The purpose of this study is to determine the lipid concentration in RA patients and compare it with controls and thereby to help in determination of Cardiovascular risk of these patients. The inflammatory markers were correlated with lipid profile for better understanding of cardiovascular risk in RA patients.

MATERIALS AND METHODS

A hospital based case control study was conducted in Madras Medical College- Institute of Biochemistry and Rheumatology for a period of 9 months after obtaining Ethical committee approval.

Study subjects, inclusion and exclusion criteria

Rheumatoid arthritis patients were chosen based on ACR criteria 2010. 55 patients above 20 years of age with symmetrical joint involvement – swelling of soft tissue, pain, tenderness in joints and early morning stiffness for more than one hour were included as cases. Patients with associated disorders like Thyroid disorders, Diabetes Mellitus, Hypertension, Obesity, Alcoholic, Nephrotic syndrome, Malabsorption syndromes, patients already on treatment with steroids, oral contraceptives, Thiazide diuretics, liver diseases, lipid storage disorders, chronic kidney disease were excluded from the study. 27 sex and age matched apparently healthy controls were included. Informed consent was obtained from all the study participants.

Consecutive sampling was done during the study period till the sample size was achieved. Controls were the relatives of the patients.

Investigations done

Body height, weight , Blood pressure were measured for all the study participants. 5 mL venous blood was collected from all the study participants after 12 hours of fasting. Hemoglobin, ESR, CRP, RF, Urea, Creatinine, Uric Acid, Total Cholesterol, Triglyceride, HDL, LDL were measured. CRP and RF were assessed by Qualitative methods. CRP and RF by Latex Agglutination method . Hemoglobin was measured in a three-part Sysmex -cell counter. ESR was measured using Westergrens method. All the Biochemical analytes were measured in Fully automated clinical Chemistry analyser-ERBA XL 640.Total Cholesterol was estimated by CHOD-PAP method, Triglyceride by GPO method, D-HDL by PVS&PEGME coupled with precipitation method, D-LDL by PVS&PEGME coupled with precipitation method. Ratio between LDL& HDL, Total Cholesterol & HDL and Non-HDL were calculated. Non HDL includes lipoproteins other than HDL. Non HDL is calculated using the formula Non HDL= Total Cholesterol- HDL.

Statistical Analysis

Statistical analysis was done using Epi info version 7.2.5.0. Quantitative data was expressed as Mean with standard deviation while qualitative data was expressed as proportion with confidence intervals. Unpaired student's t-test at 5 % significance was done to compare the serum Total Cholesterol, Triglyceride, HDL and LDL and atherogenic indices between cases and controls.

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RESULTS

Base line characteristics of study subjects

The mean age of subjects with RA was 41.5 ±11.6 years while in the controls, the mean age was 40±12.7 years. There was no significant difference across the cases and controls with respect to age groups. 89% were females in cases while 85.2% were females in controls. The mean BMI of cases were 23.74±21 while in the controls, the mean BMI was 24.7±2.7 . There was no significant differnce in baseline characteristics such as age, gender, BMI, Blood pressure between the groups.

Table 1 Comparison of Baseline characteristics among cases and controls

S.No	Characteristic	Case (n=55)	Control (n=27)	P-Value
1.	Age in years(Mean±S.D.)	41.5±11.6	40±12.7	0.595
2.	Age groups (N,%) 1. 21 to 30 years 2. 31 to 40 yrs 3. 41 to 50 yrs 4. 51 to 60 yrs 5. >60 yrs	 10 (18.2%) 18 (32.7%) 14 (25.4%) 10 (18.2%) 3 (5.5%)	 8 (29.6%) 8 (29.6%) 3 (11.2%) 6 (22.2%) 2 (7.4%)	0.525
3.	Gender (Female in N,%)	49,89%	23, 85.2%	0.624
4.	BMIin kg/m^2(Mean±S.D.)	23.74±2.1	24.7±2.7	0.082
5.	BMI categories (N) 1. Normal 2. Overweight 3. Obese 4. Underweight	 39 16 0 0	 14 13 0 0	P value could not be derived
6.	Blood pressure in mm of Hg 1. Systolic (Mean±S.D.) 2. Diastolic(Mean±S.D.)	 123.6±6.3 76.9±4.7	 120.8±7.3 74.4±5.1	 0.077 0.031

There was a significant difference between cases and controls with regards to mean Total Cholesterol (170±36.2mg/dL in cases vs 149±39.2 mg/dL in controls, p=0.017), mean Triglyceride (123±41.1mg/dL Vs 98±34.1 mg/dL, p=0.006), mean HDL (47±11.4mg/dL Vs 43±9.6mg/dL, p= 0.049) andmean LDL (98±25.1mg/dLVs 87±27.8mg/dL, p =0.075).

Table 2: Comparison of Lipid Profile among cases and controls.

S.No	Analyte	Case	Control	P- Value
1	Total Cholesterol	170.3±36	149±39.2	0.017
2	Triglyceride	123±41.1	97.5±34.1	0.006
3	HDL Cholesterol(Direct)	47.8±11.3	42.7±9.6	0.049
4	LDL Cholesterol(Direct)	97.8±25.1	86.8±27.8	0.075
5	Non- HDL Cholesterol	112.5±27.6	106±31.3	0.02
6	Total Cholesterol/HDL	3.6±0.9	3.5±0.4	0.34
7	LDL/HDL	2.1±0.8	2.01±0.4	0.5

DISCUSSION

Rheumatoid Arthritis a systemic inflammatory disease, is associated with increased mortality and reduced life expectancy. Patients with RA face an increased risk of developing premature cardiovascular disease and limited ability to modify risk factors [10]. Though rheumatoid vasculitis in severe RA cases with high rheumatoid factor titres occasionally causes acute myocardial infarction the overwhelming majority of cardiovascular deaths in RA result from accelerated atherosclerosis [11, 12]. The high levels of Acute Phase Reactants may impair cholesterol trafficking in liver. C-reactive protein enhances uptake of LDL and Oxidised LDL in Liver Cells. Pro inflammatory cytokines increases the expression of SRB1 and LDL receptors that increases LDL uptake in liver. The Composition of HDL

isolated from RA patients were altered. Cholesterol catabolism is increased in RA patients. HDL associated anti-oxidant -Paroxanase enzyme level is altered in RA patients.

In the present study, there was a significant difference between Total Cholesterol, Triglycerides, HDL, Non-HDL levels between the groups. All the lipid profile parameters were significantly elevated in cases compared to controls. Although HDL levels were higher in cases, compared to controls, the level of significance of difference in HDL (p=0.49) was very low compared to other parameters. The baseline characteristics were comparable between the groups. 89% were females in cases while 85.2% were females in controls.

Patient with active rheumatoid arthritis exhibit various lipid abnormalities, when compared with controls. RA is associated with an abnormal lipoprotein pattern, principally low levels of high density lipoprotein (HDL) cholesterol [13]. Vottery R et al in their Lipid profiles of 25 rheumatoid arthritis cases were compared with age and sex matched controls. Serum triglyceride & total cholesterol were found to be significantly lowered in RA patients, while serum LDL & HDL cholesterol were not altered significantly [14]. A higher index implies an increased cardiovascular risk, and lowering this ratio has shown decrease in risk. Total cholesterol, Triglycerides VLDL & LDL increased, HDL cholesterol decreased among RA study group compared to the control group [15].

AbouAssi, H et al in their study observed that subjects with RA had fewer total and small LDL-P as well as larger LDL and HDL size ($P < 0.05$). The RA-associated lipoprotein profile is associated with a lack of physical activity [16].

Total Cholesterol, Triglyceride levels, HDL Cholesterol, LDL Cholesterol, Non-HDL cholesterol, Total Cholesterol / HDL, LDL/HDL values were high in cases in the present study. But in the present study, we did not assess the drugs affecting the dislipidemic status.

The ratio between Total Cholesterol and HDL is known as castelli index I and the cutoff is ratio of 4. Less than 4 is considered as no risk and more than or equal to 4 is at risk for cardiovascular diseases. Only 3 among the cases had risk when castelli index 1 is calculated. The ratio between LDL Cholesterol and HDL is known as castelli index II and the cutoff is ratio of 3. Less than 3 is considered as no risk and more than or equal to 3 is at risk for Cardiovascular diseases.none of the cases had risk based on castelli index II. Total Cholesterol less than 200 mg/dL, Triglyceride less than 150 mg/dL, HDL more than 60 mg/dL , LDL less than 100mg/dL are considered as desirable levels of lipids according to NCEP guidelines. Levels more than desired levels have increased risk of cardiovascular disease.10 individuals among cases had undesirable Lipid levels.

The mean age of subjects with RA was 41.5 ±11.6 years while in the controls, the mean age was 40 ±12.7 years . There was no significant difference across the cases and controls with respect to age groups.

The BMI of cases in our study was low (23.74±21)compared to controls (24.7±2.7). Patients with RA are more likely to have lower muscle mass and low body mass index, which may result from uncontrolled inflammation, limitations of physical activity, or both [17].

Södergren, A et al found no signs of atherosclerosis in patients with newly diagnosed RA compared with controls [18]. However, in patients with early RA, IMT and ED-FMD were, to a greater extent than in controls, related to biomarkers known to be associated with endothelial dysfunction and atherosclerosis. After 18 months, IMT had increased significantly in RA patients but not in controls.

CONCLUSION

The present study showed that RA was predominantly found among the subjects aged 31 to 40 years. Patients with RA had significantly higher values of total cholesterol, triglycerides compared to controls. significantly higher values of other parameters of lipid profile found among RA patients. Higher atherogenic indices indicate higher cardiovascular risk among RA patients.

Lipid levels should be monitored and managed in patients with RA to minimize the long-term risk of cardiovascular disease. More research is needed to quantify the relationship between systemic

inflammation and lipoprotein levels and to determine the impact of specific lipoprotein particles, eg, small dense low-density lipoprotein and subfractions of HDL on long-term risk. Control of inflammation may have an effect on modifying cardiovascular risk.

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