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Study of Lipid Profile and High Sensitivity C - reactive protein as Prognostic Indicators of Cardiovascular Risk in Rheumatoid Arthritis: A Prospective Study

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ABSTRACT

Dyslipidaemia in Rheumatoid arthritis (RA) is associated with accelerated atherosclerosis. A prospective clinical evaluation study was undertaken from January 2010 to June 2011 to find out the proportion of rheumatoid arthritis patients suffering from dyslipidaemia and change in lipid levels and disease activity after an intervention with antirheumatic therapy. To study the disease activity in Rheumatoid arthritis patients by measuring serum levels high sensitivity C-reactive protein, correlating disease activity with lipid profile and assessing cardiovascular risk in RA patients. The study was done on 30 RA patients (fulfilling the American College of Rheumatology criteria). Lipid profile estimation was done by enzymatic, colorimetric method and high sensitivity C-reactive protein was estimated by chemiluminescence method. Dyslipidaemia was defined by taking the cut-off values of NCEP-ATPIII guidelines. Patients with other comorbid illness and on statins were excluded. Patients were followed up after 12 weeks of starting anti rheumatic therapy. 36.7% of patients had high total cholesterol, 53.3% of patients had high triacylglycerol levels, 73.3% of patients had decreased HDL-cholesterol and 33.3% of patients had high LDL-cholesterol. 86.7% of patients had hsCRP levels above the reference range. After treatment the number of patients with dyslipidaemia came down, with 23.3% of patients having high total cholesterol, 43.3% of patients having elevated triacylglycerols, 46.7% of patients having low HDL-cholesterol and 20% of patients having elevated LDL-cholesterol. Only 23% of patients had hsCRP above the reference range. The proportion of dyslipidaemic patients had decreased in the follow up visit along with decrease in disease activity as indicated by decreased levels of hsCRP. Management of dyslipidaemia in RA should be a part of a general cardiovascular risk management. Therefore good control of disease activity should be given priority so that both quality of life and long-term outcomes can be improved.

Keywords: Rheumatoid arthritis, Dyslipidaemia, high sensitivity C-reactive protein, cardiovascular risk.

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INTRODUCTION

Rheumatoid arthritis (RA) is one of the common inflammatory diseases of the joints of unknown etiology characterized by symmetric erosive synovitis and extra articular involvement like Rheumatoid nodules, Rheumatoid vasculitis, Pleuropulmonary manifestations, Felty's syndrome, etc [1].

The prevalence of Rheumatoid arthritis is between 0.7% to 1.5%. Malviaya et al found the prevalence in Indian rural population to be 0.75% [2].

Three important inflammatory cytokines are implicated in the pathophysiology of Rheumatoid arthritis, i.e., Interleukin (IL)-1β, Interleukin (IL) -6 and Tumor necrosis factor (TNF) - α. Among these IL-1 is the most potent inflammatory mediator causing damage to the joints and as well causing systemic effects by stimulating synthesis of IL-6 and C-reactive protein [3].

High sensitivity CRP testing reveals systemic inflammation that is generally not detectable with routine CRP assays and that is associated with disease activity in RA [4].

Atherosclerotic cardiovascular disease is the major cause of mortality in Rheumatoid arthritis. Dyslipidemia is an important risk factor for cardiovascular disease and is influenced by disease activity of Rheumatoid arthritis, which is the combined effect of these inflammatory mediators [5].

The pattern of lipid profile described in Rheumatoid arthritis comprises low total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C), low high density lipoprotein cholesterol (HDL-C) and elevated triacylglycerol (TG) [6].

Data on inflammatory mediators and lipid profile in Rheumatoid arthritis patients will help in reducing the morbidity and mortality.

Objectives

To study the disease activity in Rheumatoid arthritis patients by measuring serum levels of high sensitivity C-reactive protein, correlating disease activity with lipid profile and assessing cardiovascular risk in RA patients.

MATERIALS AND METHODS

The study was conducted over a period of one and half year from January 2010 to June 2011. The study was approved by the ethical committee of the institute and an informed consent was obtained from all subjects who took part in the study.

Study comprised of Rheumatoid arthritis patients attending the outpatient and inpatient departments of Medicine of Victoria hospital and Bowring & Lady Curzon hospitals attached to Bangalore Medical College and Research Institute, Bangalore.

Patients fulfilling the modified American College of Rheumatology criteria for Rheumatoid arthritis [7] were included in the study.

Patients with history of other chronic inflammatory disorders and neoplastic conditions which are known to influence serum levels of inflammatory mediators, history of co-morbid conditions known to influence lipid profile like Diabetes Mellitus, Cardiac disease, Chronic renal failure and hypothyroidism and patients on Statins and other lipid lowering drugs were excluded from the study.

The study consisted of thirty cases of RA, whose serum samples were taken and analyzed twice, i.e., before starting treatment and after 12 weeks of starting treatment with Disease Modifying Anti Rheumatoid Drugs (DMARDs).

Following selection of subjects and after obtaining informed consent about the proposed study, about 5ml of fasting venous blood sample was collected from median cubital vein by venepuncture. Serum was separated by centrifugation. Lipid profile parameters, hsCRP and rheumatoid factor were estimated immediately.

Total cholesterol, Triacylglycerols and High Density Lipoprotein cholesterol were estimated by enzymatic, colorimetric method [8, 9, 10] using COBAS integra 400 plus analyzer. Low Density Lipoprotein cholesterol and Very Low Density Lipoprotein cholesterol were calculated using Friedewald's equation [11].

High sensitivity C-reactive protein was estimated by chemiluminescence method using IMMULITE 1000 analyzer12.

Statistical Methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean $\pm$ SD (Min to Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (inter group analysis on metric parameters).

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Statistical software

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 , Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS AND OBSERVATIONS

The mean age of the patients was 45.6 years with an SD of 9.02 years.

The gender distribution of the patients is, males= 16.7%, females= 83.3%. Incidence of the disease is more in females compared to males.

Table 1 Evaluation of Lipid parameters before and after treatment

Lipid parameters	Before treatment (n=30)	After treatment (n=30)	P value	Effect size
Total cholesterol (mg/dl)	185.53±43.70 (99-292)	174.13±34.86 (106-259)	0.029*	0.29(S)
Triacylglycerol (mg/dl)	173.13±92.94 (55-574)	147.93±57.47 (41-285)	0.060+	0.34(S)
HDL-Cholesterol (mg/dl)	36.33±7.04 (26-54)	40.20±8.89 (24-58)	0.021*	0.50(M)
LDL-Cholesterol (mg/dl)	114.12±35.94 (53.6-211.30)	107.03±31.16 (54.5-178.0)	0.254	0.21(S)
VLDL-cholesterol (mg/dl)	34.78±18.56 (11.10-115.0)	29.59±11.49 (8.30-57.00)	0.053+	0.35(S)

S: Small; M: Moderate.
+ Suggestive significance (P value: 0.05 to < 0.10)
* Moderately significant (P value: 0.01 to $\leq$ 0.05)
** Strongly significant (P value: $\leq$ 0.01)
Results are presented as Mean ± SD (Min-Max), P value obtained by student't' test (Paired)

From table-1and graph-1, the mean total cholesterol level before treatment is 185.53mg/dl with an SD of 43.70 mg/dl and after treatment the mean is 174.13 mg/dl with an SD of 34.86 mg/dl.

Mean of triacylglycerol before treatment is 173.13 mg/dl with an SD of 92.94 mg/dl and after treatment the mean is 147.93 mg/dl with an SD of 57.47 mg/dl. There was a statistically significant decrease in the triacylglycerol levels after treatment.

Mean of HDL-cholesterol before treatment is 36.33 mg/dl with an SD of 7.04 mg/dl and after treatment the mean is 40.20 mg/dl with an SD of 8.89 mg/dl. There was a statistically significant increase in the HDL-cholesterol levels after treatment.

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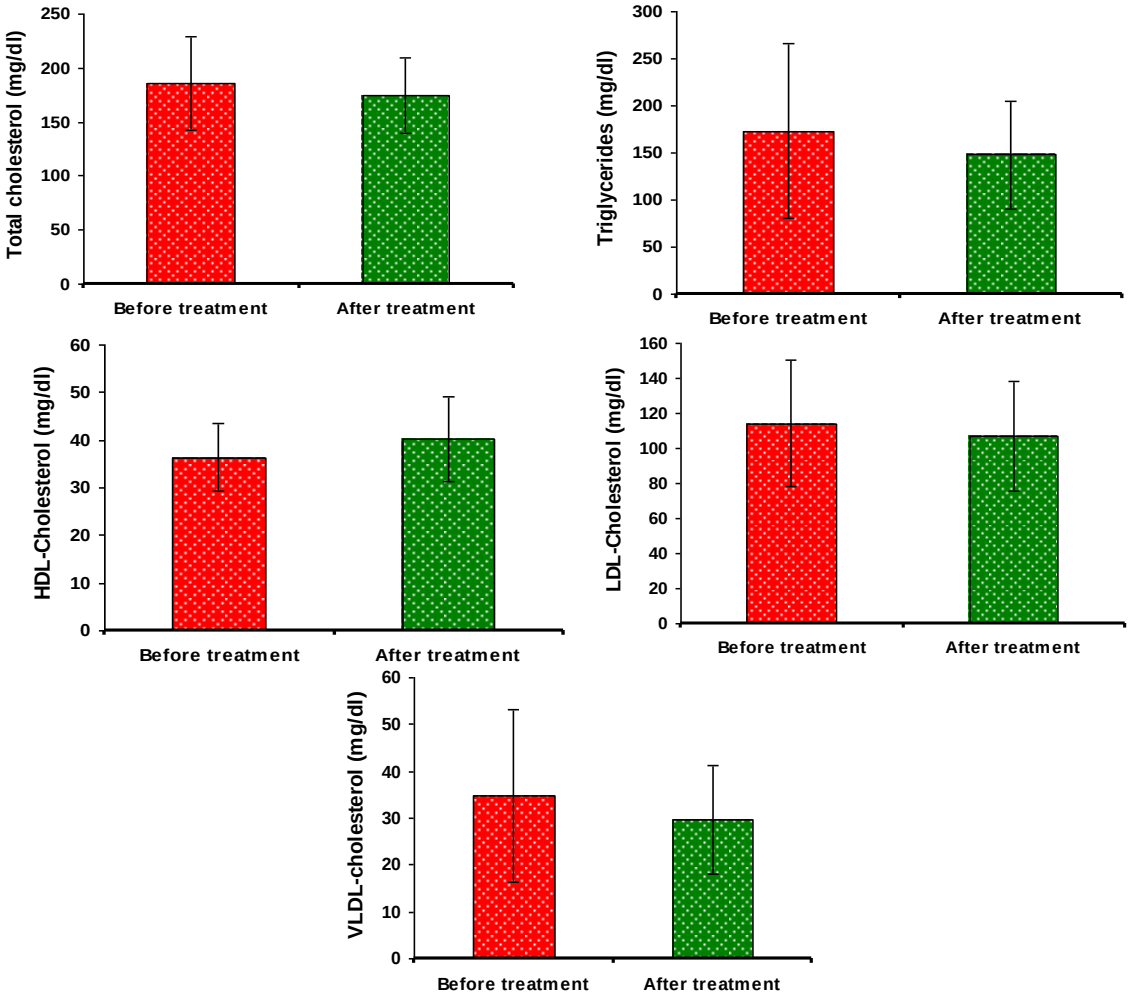

Table 2: Levels of Lipid parameters of patients studied

Lipid parameters	Before treatment (n=30)		After treatment (n=30)	
	No	%	N0	%
Total cholesterol (mg/dl)				
<200	19	63.3	23	76.7
>200	11	36.7	7	23.3
Triglycerides (mg/dl)				
<150	14	46.7	17	56.7
>150	16	53.3	13	43.3
HDL-Cholesterol (mg/dl)				
<40	22	73.3	14	46.7
>40	8	26.7	16	53.3
LDL-Cholesterol (mg/dl)				
<130	20	66.7	24	80.0
>130	10	33.3	6	20.0
VLDL-cholesterol (mg/dl)				
<30	12	40.0	17	56.7
>30	18	60.0	13	43.3

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Mean of LDL-cholesterol before treatment is 114.12 mg/dl with an SD of 35.94 mg/dl and after treatment the mean is 107.03 mg/dl with an SD of 31.16 mg/dl.

From table-2, before treatment, 19 (63.3%) patients had total cholesterol of <200 mg/dl and 11(36.7%) patients had >200 mg/dl. After treatment, 23(76.7%) patients had total cholesterol level of <200 mg/dl and 7(23.3%) patients had >200 mg/dl.

Before treatment, 14(46.7%) patients had triacylglycerol of <150 mg/dl and 16(53.3%) patients had >150 mg/dl. After treatment, 17(56.7%) patients had triacylglycerol of <150 mg/dl and 13(43.3%) patients had >150 mg/dl.

Before treatment, 22(73.3%) patients had HDL-cholesterol of <40 mg/dl and 8(26.7%) patients had >40 mg/dl. After treatment, 14(46.7%) patients had HDL-cholesterol of <40 mg/dl and 17(53.3%) patients had >40 mg/dl.

Before treatment, 20(66.7%) patients had LDL-cholesterol of <130 mg/dl and 10(33.3%) patients had >130 mg/dl. After treatment, 24(80.0%) patients had LDL-cholesterol of <130 mg/dl and 6(20.0%) patients had >130 mg/dl.

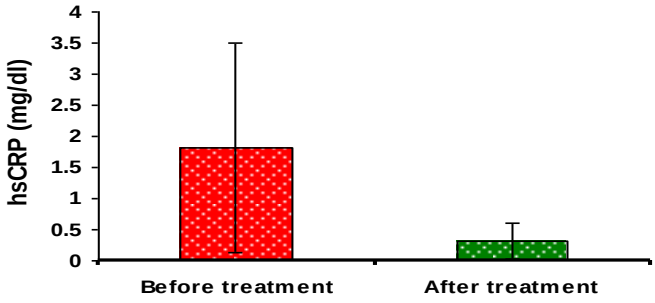
Before treatment, 12(40.0%) patients had VLDL-cholesterol of <30 mg/dl and 18(60.0%) patients had >30 mg/dl. After treatment, 17(56.7%) patients had VLDL-cholesterol of <30 mg/dl and 13(43.3%) patients had >30 mg/dl.

Table 3: Evaluation of hsCRP before and after treatment

hsCRP	Before treatment (n=30)	After treatment (n=30)	P value	Effect size
hsCRP (mg/dl)	1.82±1.68 (0.24-7.63)	0.32±0.29 (0.03-1.24)	<0.001**	1.52(VL)

VL: Very large, **strongly significant (P value: < 0.01).

Graph 2: Evaluation of hsCRP before and after treatment



From table-3 & graph-2 the mean level of hsCRP before treatment is 1.82 mg/dl with an SD of 1.68 mg/dl and after treatment mean is 0.32 mg/dl with an SD of 0.29 mg/dl. There was a statistically significant decrease in hsCRP levels after treatment.

Table 4: Pearson correlation between hsCRP with Lipid parameters

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Pair	Before treatment (n=30)		After treatment (n=30)	
	r value	P value	r value	p value
hsCRP (mg/dl) vs Total cholesterol (mg/dl)	0.080	0.673	-0.260	0.165
hsCRP (mg/dl) vs Triglycerides (mg/dl)	0.021	0.910	0.039	0.838
hsCRP (mg/dl) vs HDL-Cholesterol (mg/dl)	0.345	0.062+	-0.233	0.216
hsCRP (mg/dl) vs LDL-Cholesterol (mg/dl)	0.004	0.985	-0.130	0.494
hsCRP (mg/dl) vs VLDL-cholesterol (mg/dl)	0.037	0.845	0.038	0.841

There was no significant correlation between hsCRP with lipid parameters as shown in table 4.

DISCUSSION

Rheumatoid arthritis, an immune-inflammatory condition aggravates the metabolic syndrome (including dyslipidaemia). In RA although the primary site of inflammation is the synovial tissue, cytokines like tumour necrosis factor (TNF)-α, IL-1β and IL-6 are also released into the systemic circulation and this leads to dyslipidaemia1. These circulating cytokines alter the function of distant tissues, including the adipose tissue, skeletal muscle, liver, etc, which in turn leads to dyslipidaemia. There is increased free fatty acid (FFA) release in the adipose tissue, increased FFA and TG synthesis in the liver and reduced lipoprotein lipase activity. Lipoprotein lipase is the principle catabolic enzyme for TG-rich lipids. High TG levels reduce HDL-C by virtue of neutral lipid exchange and this same process promotes synthesis of small dense LDL. High lipoprotein (a) also plays a role.

RA patients appear to have a high prevalence of abnormal blood lipid profile, as supported by three Indian studies conducted by Hadda V et al6, Grover S et al [13] and Vottery R et al [14] with 96, 56 and 25 patients respectively.

Vottery R et al study showed lower lipid levels and negative correlation with disease activity. Grover S et al study demonstrated only raised total cholesterol. Hadda V et al study showed 38.5% of patients were dyslipidaemic, commonest being low HDL-cholesterol in 34.3% of patients and observed a trend towards normalization of lipids and decrease in disease activity in the follow up visits. The present study showed that, before treatment, 36.7% of patients had high total cholesterol, 53.3% of patients had high triacylglycerol levels, 73.3% of patients had decreased HDL-cholesterol and 33.3% of patients had high LDL-cholesterol. 86.7% of patients had hsCRP levels above the reference range.

After treatment the number of patients with dyslipidaemia came down, with 23.3% of patients having high total cholesterol, 43.3% of patients having elevated triacylglycerols, 46.7%

of patients having low HDL-cholesterol and 20% of patients having elevated LDL-cholesterol. Only 23% of patients had hsCRP above reference range.

Thus the proportion of dyslipidaemic patients had decreased in the follow up visit along with decrease in disease activity as indicated by decreased levels of hsCRP.

In general, antirheumatic treatment has moderate effects on the lipid profile. Therefore, it is unlikely that the observed beneficial effects of antirheumatic drug treatment on cardiovascular morbidity and mortality in RA is mediated through effects on lipid metabolism. Whilst the routine use of statins as disease-modifying therapy for patients with RA is not yet routine practice, their use in selected patients with abnormal lipid profiles could also benefit their arthritis is also supported by White et al [15]. Management of dyslipidaemia in RA should be a part of a general cardiovascular risk management is also supported by Nurmohamed et al [16]. Therefore good control of disease activity should be the priority given that both quality of life and long-term outcomes can be improved.

Limitations of our study were, small sample size and only one follow-up visit were included. Because of only one follow-up we cannot comment on the long term effect of control of disease activity on lipids. While screening for dyslipidaemia seems warranted in all patients, interventional strategies need further study.

CONCLUSION

In conclusion our study reveals that lipid abnormalities are common in patients suffering from rheumatoid arthritis, with low HDL-cholesterol being the commonest dyslipidaemia encountered. Next common abnormality being elevated triacylglycerol levels. Disease activity was also high as indicated by significantly elevated levels of hsCRP.

The proportion of dyslipidaemic patients had decreased in the follow up visit along with decrease in disease activity as indicated by decreased levels of hsCRP. Management of dyslipidaemia in RA should be a part of a general cardiovascular risk management. Therefore good control of disease activity should be the priority given that both quality of life and long-term outcomes can be improved.

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