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To study lipid profile in patients of rheumatoid arthritis and it's correlation with inflammatory markers

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Abstract
Aim: To evaluate lipid profile in patients of rheumatoid arthritis and it's correlation with inflammatory markers.
Material and Method: The present study was conducted in the department of Medicine at Chattrapati Shivaji Subharti Hospital among 50 diagnosed cases of rheumatoid arthritis. Extra articular manifestations of Rheumatoid arthritis (eg. ILD, secondary Sjogren's, and the disease activity measured according to (DAS 28, no. of tender joints and no. of swollen joints scoring system) was also accounted for and was matched against other parameters. Serum uric acid levels, serum lipid levels and inflammatory markers levels (E.S.R, C.R.P R.A factor), was measured after overnight fasting by enzymatic methods using the chemical analyzer.
Results: The mean±SD of the age of study population was found to be 46.98±12.37 years. The RA was inactive in 28 (56%) of the study population. A strong positive correlation could be established with the total cholesterol and ESR as well as CRP levels. Reduced levels of HDLC are significantly correlated with the ESR as well as CRP levels. A significant positive correlation could be established with the increased LDL and ESR as well as CRP levels.
Conclusion: In summary, our study supports the observation that patients with rheumatoid arthritis have a more atherogenic lipid profile even in the preclinical phase of rheumatoid arthritis, which ultimately could explain the increased cardiovascular risk in patients with rheumatoid arthritis. Furthermore, we show that inflammation is associated with a (further) deterioration of the lipid profile.

Keywords: lipid profile, rheumatoid arthritis, inflammatory markers

Introduction

Rheumatoid arthritis (RA) is a chronic systemic disorder of unknown etiology that is dominated by a serious and debilitating sequelae associated with progressive destruction of articular joints [1]. Rheumatoid arthritis affects approximately 1-2% of the total world's population [2]. Annual incidence rate of rheumatoid arthritis between 0.5% and 1% of total population are reported every year in both developed and developing countries [3]. Lower incidences of rheumatoid arthritis are reported every year in East Asia. The true picture of annual incidence rate of rheumatoid arthritis in India has not been well documented[4]. The estimated prevalence of RA has been reported from Northern Pakistan as 0.55% [5]; while, the prevalence of RA in adult Indian population is reportedly 0.75% [6, 7].

Comorbid conditions especially cardiovascular disease (CVD), play a pivotal role in RA outcomes. These patients have reduced life expectancy owing to an increased mortality rate attributable mainly to CVD, primarily coronary heart disease, which results from a process of accelerated atherosclerosis, irrespective of the traditional cardiovascular risk factors[6], and is frequently silent and subclinical. The excess risk observed in RA and other autoimmune diseases appears to be driven by a complex interaction between traditional and non-traditional cardiovascular risk factors, where inflammation plays an important role through direct or indirect mechanisms such as damaging effects on the vasculature. Possible mechanisms involved include lipid metabolism disorders related to the inflammatory process itself [8, 9].

The present diagnostic protocol of RA is complicated and time-consuming. The diagnostic pipeline is based on the clinical presentation and serologic tests, while there is no singular test for it yet. Ultimately, rheumatoid arthritis is diagnosed based on a combination of the presentation of the joints involved, characteristic joint swelling and stiffness in the morning, the presence of blood rheumatoid factor (RF) and citrulline antibody, as well as the findings of rheumatoid nodules and radiographic changes (X-ray testing) [10].

Lipid abnormalities have been shown to contribute to accelerated atherosclerosis, leading to an increased risk for CVD[11]. For decades, increased low-density lipoprotein (LDL) levels have been recognized as strong predictors of CVD, and it is also known that high-density lipoproteins (HDL) usually protect from atherosclerosis. Data on dyslipidemia in RA are conflicting and it appears to be present in RA patients with both early and advanced disease [9].

But there are few studies in India about lipid profile abnormality in Rheumatoid arthritis and inflammatory, altering lipid profile in RA patients. There is lacuna of knowledge about this aspect of disease in Indian patient. Hence the present study was planned to evaluate lipid profile in patients of rheumatoid arthritis and it's correlation with inflammatory markers.

Material and Method

The present study was conducted in the department of Medicine at Chattrapati Shivaji Subharti Hospital from July 2019 to July 2021 among 50 diagnosed cases of rheumatoid arthritis. Patients were enrolled in the study after obtaining written informed consent and approval from Institutional Ethical Committee.

In this study the extra articular manifestations of Rheumatoid arthritis (eg. ILD, secondary Sjogren's, and the disease activity measured according to (DAS 28, no. of tender joints and no. of swollen joints scoring system) was also accounted for and was matched against other parameters. Serum uric acid levels, serum lipid levels and inflammatory markers levels (E.S.R, C.R.P R.A factor), was measured after overnight fasting by enzymatic methods using the chemical analyzer. From all patients 5 cc of blood was taken under strict aseptic techniques and sent to the hospital laboratory on the same day. Serum uric acid levels, serum lipid levels and other biochemical tests were done under supervision of a pathologist.

Sample size: 50. All the RA patients were selected on the basis of EULAR CRITERIA for rheumatoid arthritis[13].

Inclusion criteria

1. Patients of Rheumatoid arthritis diagnosed by 2010 ACR-EULAR criteria.
2. Age-group of above 20 years.
3. Disease duration of more than 6 months.
4. Receiving Disease Modifying Anti Rheumatic Drugs (DMARDS).

Exclusion criteria

Patients with rheumatoid arthritis with the following conditions were excluded from the study:

1. Pulmonary and extrapulmonary tuberculosis
2. Diabetes mellitus
3. Intake of drugs like:

a. Diuretics
b. Oral contraceptives
c. Lipid lowering drugs
d. Beta blockers
e. Thyroxine

4. Any form of carcinoma
5. COPD
6. Hypothyroidism
7. Extremes of ages
8. Moribund patients
9. Hypertension
10. Coronary artery disease
11. Other inflammatory disorders

LDL

The triglyceride level is used to calculate the LDL, however, to get a correct answer, the TG must be 400 mg/dL or less. A turbid serum specimen indicates a TG level of around 400 mg/dL. The method is by spectrophotometry.

Table 1

Value	Category
< 150 mg/dl	Normal
150 – 199 mg/dl	Borderline High
200 – 499 mg/dl	High
>500 mg/dl	Very High

HDL (High-Density Lipoprotein)

HDL is called the "good cholesterol". It tends to carry cholesterol away from tissues. All other risk factors considered, a high HDL is a good risk factor. The method is by spectrophotometry.

Table 2

Value	Category
<40 mg/dl	Low
>60 mg/dl	High

LDL (Low-Density Lipoprotein)

LDL cholesterol is called the "bad cholesterol". It is part of the lipid profile and is one of the more important "risk factors" for atherosclerotic (CHD) disease. LDL is the cholesterol component that binds to liver receptors and tends to control the formation of cholesterol. The method is by calculation using the Friedewald formula. The formula can only be used when the TG are less than 400 mg/dL. LDL core lipids contains about 10% TG and ``145% cholesterol.

Table 3

Value	Category
< 100 mg/dl	Optimal
100 – 129 mg/dl	Near Optimal
130 – 159 mg/dl	Borderline High
160 – 189 mg/dl	High
>190 mg/dl	Very High

Very Low Density Lipoprotein (VLDL)

VLDL is a type of lipoprotein and helps carry triglycerides to the liver and other parts of the body. Density refers to the amount of lipids per lipoprotein versus proteins. Core lipids in chylomicrons contain about 85% triglycerides and 5% cholesterol, VLDL contains about 60% TG and 15% cholesterol. Elevated VLDL levels are found in Type IV hyperlipidemias.

Cholesterol to HDL Ratio

The Cholesterol to HDL ratio is a calculation of your risk for heart disease. It is optimal to have a low ratio. A low ratio indicates that total cholesterol is comprised mostly of HDL particles. This ratio is considered the most important indicator for atherosclerosis. Average risk for male and female was 5.5-9.6 and 4.5-7.1 respectively.

LDL to HDL Ratio

The LDL to HDL ratio is also a heart disease risk indicator. It is best to have a low ratio as this indicates there is sufficient HDL in relation to LDL to aid in prevention of atherosclerosis. Excessively high or low levels can indicate a problem. It is best to maintain these in proper balance to HDL. Average risk for male and female was 3.7-6.3 and 3.3-5.0 respectively [14-16].

Lipid profile detection

Blood samples were obtained from patients before surgical treatment or endovascular management as well as other medicine intervention. Five milliliters of antecubital venous fasting blood was collected from each of the subjects, being allowed to clot and then centrifuged at 3,000 rpm for 15 min within 30 min of sample collection and analyzed within 6 h after the separation. The serum lipid profiles, including T-

CHOL, HDL-C, LDL-C, and TG, was measured with the FAITH-1000 automatic biochemistry analyzer, according to the manufacturer's. In addition, ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), APOA1 (apolipoprotein A-I), APOB (apolipoprotein B), APOE (apolipoprotein E), LPA (Lysophosphatidic acid), IgA, IgG and IgM antiglobulins of RF were measured in the RA patients to evaluate the correlation between these factors with lipid profile. Inverse normal transformation was applied to the data to improve the normality of variables in the process of correlation analysis.

DAS28 ESR score [16, 17]

Disease Activity in Rheumatoid Arthritis (Disease Activity Score in 28 joints)

DAS28=0.56×√ (TJC28) +0.28×√ (SJC28) +0.70×log (ESR) +0.014×GH.

TJC=Tender joint count,
SJC=Swollen joint count,
ESR=Erythrocyte sedimentation rate,
GH= assessment of global health, done by 100mm Visual analogue scale.
Patients with score less than 2.6 were considered to be in remission while those with score more than or equal to 2.6 were with active disease.

Statistical analysis

Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). The level of significance was set at $p < 0.05$.

Results

The present prospective study was conducted in the department of Medicine at Chattrapati Shivaji Subharti Hospital from July 2019 to July 2021 among 50 diagnosed cases of rheumatoid arthritis. The mean±SD of the age of study population was found to be 46.98±12.37 years. There were 4 males (8%) and 46 (92%) females in the study population. Hence there was female preponderance in our study (table 4).

Table 4: Age and gender distribution among the study subjects

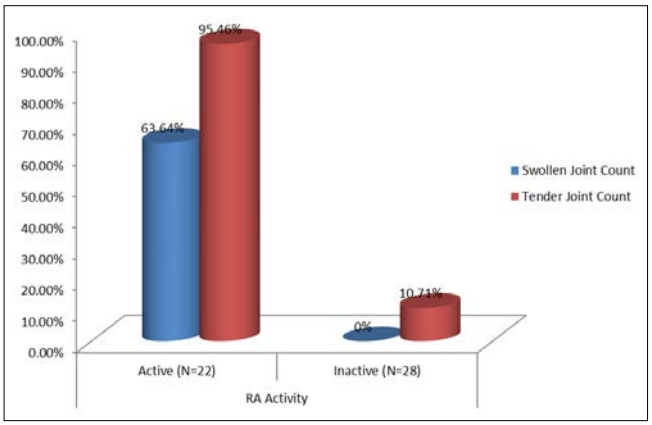
Variables	Value (N=50)
Male, N (%)	4 (8)
Female, N (%)	46 (92)
Age in years (Mean±SD)	46.98±12.37

Table 5: Clinical characteristics of RA patients

Variables	Value (N=50)
Disease Duration in years (Mean±SD)	10.82±5.79
Activity of RA	
Active, N (%)	22 (44)
Inactive, N (%)	28 (56)
RF (% Positive)	41 (82)
RF in IU/L (Mean±SD)	397.63±101.89

The duration of disease in the present study was found to be 10.82±5.79 years. RA was found to be active in 22 (44%) of patients. The RA was inactive in 28 (56%) of the study population (table 5).

The number of swollen joint count in active RA patients were 14 (63.64%). There were no swollen joint count present in patient with inactive RA activity. There are 21 (95.46%) tender joint counts in active RA patients. Only 3 tender joint counts were reported in inactive RA patient group (graph 1).



Graph 1: Swollen and tender joint count according to RA activity

Table 6: Inflammatory markers, Lipids and lipoproteins profile among the RA subjects

Inflammatory Markers	Mean	SD
CRP, mg/l	17.53	7.62
ESR, mm/h	34.26	22.17
VCAM, ng/ml	452.08	141.95
Lipid Profile		
TC, mmol/L	5.47	2.01
TG, mmol/L	1.42	0.73
HDLD, mmol/L	1.25	0.36
LDL, mmol/L	3.54	0.78
Lipoproteins		
Lp (a), mg/dl	31.91	11.88

The mean ±SD of the CRP (mg/L) in study population was found to be 17.53±7.62. The mean ±SD of the ESR (mm/h) in study population was found to be 34.26±22.17. The mean ±SD of the VCAM in study population was found to be 452.08±141.95. The mean±SD of total cholesterol was found to be 5.47±2.01 mmol/L. The mean±SD of triglycerides was found to be 1.42±0.73 mmol/L. The mean±SD of HDLD was found to be 1.25±0.36 mmol/L. The mean±SD of LDL was found to be 3.54±0.78 mmol/L. The mean±SD of Lp was found to be 31.91±11.88 mg/dL (table 6).

Table 7: Correlation between ESR (mm/h) and lipid fractions of RA patients

Inflammatory Markers	ESR (mm/h)		CRP (mg/l)	
	r value	p value	r value	p value
TC, mmol/L	0.62	<0.01*	0.59	<0.01*
TG, mmol/L	0.23	0.12	0.30	0.039*
HDLC, mmol/L	0.44	0.007*	0.68	<0.01*
LDL, mmol/L	0.57	<0.01*	0.34	0.036*

*: statistically significant

A strong positive correlation could be established with the total cholesterol and ESR levels (r value =0.62, p value <0.01). Reduced levels of HDLC are significantly correlated with the ESR levels (r value = 0.44, p value=0.007). A significant positive correlation could be established with the

increased LDL and ESR levels (r value=0.57, p value<0.01). A strong positive correlation could be established with the total cholesterol and CRP levels (r value =0.59, p value <0.01). A significant positive relation between CRP and raised triglyceride levels were found (r value=0.30, p value=0.039). Reduced levels of HDLC are significantly correlated with the CRP levels (r value = 0.68, p value<0.01) as shown in table 7.

Discussion

Dyslipidemia (DL) is frequently observed in patients with active RA. Systemic inflammation has a general effect in lowering circulating lipid levels. Moreover, patients with RA have an increased CVD risk at relatively low cholesterol levels, in contrast to that observed in the population without RA. These paradoxical changes in the lipid profiles of RA patients are still unclear, and the interactions between lipid fractions, inflammation and CVD risk in RA appears to be very complex [7]. When RA therapy is associated with significant improvement in clinical parameters, it is also often associated with an increase in circulating cholesterol levels [18]. However, the fundamental mechanisms driving the increase in circulating cholesterol levels in effectively treated RA patients remain largely unknown.

The present study was conducted in the department of Medicine at Chattrapati Shivaji Subharti Hospital from July 2019 to July 2021. The study group was consisted of 50 diagnosed cases of rheumatoid arthritis. In the present study we investigated the correlation between Lipid abnormalities and severity of the RA. We also evaluated the correlation between lipid profile and inflammatory markers in rheumatoid arthritis.

The mean±SD of the age of study population was found to be 46.98±12.37 years. in our study. In a study by Mahdi EA *et al*.[19], Refai TMK *et al*.[20], approximately similar mean age was found.

There were 4 males (8%) and 46 (92%) females in the study population. Hence there was female preponderance in our study. Similar female dominance was reported by Mahdi *et al*. [19], Yadav S *et al* [21]. and Refai TMK *et al* [20]. in their study.

The duration of disease in the present study was found to be 10.82±5.79 years. In a study by Refai TMK *et al* [20]., the duration of disease was found to be 10.6±6.6 years which is in accordance with the results presented by the present study. Erum U *et al* [7]. showed the mean duration of disease to be 3.82±3.03 years which was found to be lesser than the results presented by the present study.

RA was found to be active in 22 (44%) of patients. The RA was inactive in 28 (56%) of the study population. The status of RA was active in 14 (46.6%) of the study population and was inactive in 16 (53.4%) of the study population in a study by Refai TMK *et al* [20]. The results presented are in concordance with the results of the present study.

In our study, we found a significant increase in inflammatory markers (CRP & ESR) and vascular cell adhesion molecule VCAM (a marker of endothelial activation) in RA patients. Considerable existing indirect evidence that supports systemic endothelial activation in RA, reflected as increased levels of ICAM and VCAM that is correlated with the increase in inflammatory markers was found in other studies [22, 23]. The results were reported to be similar with a study conducted by Refai TMK *et al*.[20] ERA patients exhibited increased levels of inflammatory markers that involved C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) when compared with controls (p value<0.001) in a study conducted by Mahdi EA *et al* [19].

The mean±SD of total cholesterol was found to be 5.47±2.01 mmol/L. The mean±SD of triglycerides was found to be 1.42±0.73 mmol/L. The mean±SD of HDLD was found to be 1.25±0.36 mmol/L. The mean±SD of LDL was found to be 3.54±0.78 mmol/L. The mean±SD of Lp was found to be 31.91±11.88 mg/dL. ERA patients exhibited a mild dyslipidemia characterized by an increase in the serum levels of total cholesterol (TC), low density lipoprotein cholesterol(LDLC) and tri glycerides as well as by decrease in the serum levels of high density lipoprotein cholesterol (HDLC) in a study conducted by Mahdi EA *et al* [19]. In some studies, they reported a dyslipidemic pattern similar to our findings.[24,25] They attributed the atherogenic risk of this latter pattern to the increase in lipid peroxidation caused by the oxidative stress in RA patient.

A strong positive correlation could be established with the total cholesterol and ESR levels (r value =0.62, p value <0.01). Non-significant relation between ESR and raised triglyceride levels were found (r value=0.23, p value=0.12). Reduced levels of HDLC are significantly correlated with the ESR levels (r value = 0.44, p value=0.007). A significant positive correlation could be established with the increased LDL and ESR levels (r value=0.57, p value<0.01). Results of the current investigation were agreed with the findings of Mahdi EA *et al* [19]. Van Halm VP *et al* [26]. Douglas W. *et al* [27].

A strong positive correlation could be established with the total cholesterol and CRP levels (r value =0.59, p value <0.01). A significant positive relation between CRP and raised triglyceride levels were found (r value=0.30, p value=0.039). Reduced levels of HDLC are significantly correlated with the CRP levels (r value = 0.68, p value<0.01). A significant positive correlation could be established with the increased LDL and CRP levels (r value=0.34, p value<0.036). The results presented by the present study were found to be similar as revealed by Mahdi EA *et al* [19]. Van Halm VP *et al* [26]. Douglas W. *et al* [27].

Growing evidence indicates that inflammation has an important role in the pathogenesis of cardiovascular disease, particularly in atherosclerosis[28]. In addition to a postulated direct effect of inflammation on endothelial cells, there is mounting evidence that inflammation can also increase the cardiovascular risk by deterioration of the lipid profile. This is supported by the demonstration of a decrease in HDLc levels and an increase in triglycerides and during an acute phase response [21].

Further investigations into genetic markers that could single out the population at risk should be undertaken. The intention to treat those patients early and aggressively would not only improve disease outcome and decrease joint damage, but it will also improve long term survival by decreasing the risk of cardiovascular disease.

Conclusion

In summary, our study supports the observation that patients with rheumatoid arthritis have a more atherogenic lipid profile even in the preclinical phase of rheumatoid arthritis, which ultimately could explain the increased cardiovascular risk in patients with rheumatoid arthritis. Furthermore, we show that inflammation is associated with a (further) deterioration of the lipid profile. However, contrary to

expectations, inflammation can explain only a small part of the observed differences in lipids between people who later develop rheumatoid arthritis and controls. Whether lipids modulate the susceptibility to the development of inflammatory diseases such as rheumatoid arthritis remains to be elucidated.

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