A Study of Lipid Profile Abnormalities in Rheumatoid Arthritis and its Relation with Disease Activity

Dr. P. K. Sinha[1], Dr. Amit Kumar Tony[2], Dr. U. C. Jha[3]

[1]Associate Prof. Department of Medicine, DMCH, Laheriasarai, Darbhanga, Bihar, India

[2]Junior Resident, Department of Medicine, DMCH, Laheriasarai, Darbhanga, Bihar, India

[3]Professor And Head, Department of Medicine, DMCH, Laheriasarai, Darbhanga, Bihar, India

Corresponding Author: Dr. Amit Kumar Tony

Abstract

Background: Rheumatoid arthritis (RA) is a chronic systemic disease affecting primarily the synovium, leading to joint damage and bone destruction[1] RA causes significant morbidity as a result of synovial inflammation, joint destruction and associated disability [2]. Epidemiological studies have shown an increased premature mortality in patients with RA compared with the general population. Several investigators reported an excess of cardiovascular morbidity and mortality among RA patients.

Material and methods: This is cross sectional study, total 50 Patients attending Rheumatology outpatient department of General medicine, at Darbhanga medical college and Hospital, Laheriasarai, Darbhanga. Duration period of two years.

Conclusion: Patients with Rheumatoid arthritis had significantly reduced levels of serum total cholesterol, LDL-cholesterol, triglyceride, as compared to controls. HDL-cholesterol level was not significantly altered in Rheumatoid arthritis as compared to controls.

Keywords: Rheumatoid arthritis (RA), LDL cholesterol, triglyceride, HDL cholesterol.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease affecting primarily the synovium, leading to joint damage and bone destruction[1] RA causes significant morbidity as a result of synovial inflammation, joint destruction and associated disability [2]. Epidemiological studies have shown an increased premature mortality in patients with RA compared with the general population[3-7]. Several investigators reported an excess of cardiovascular morbidity and mortality among RA patients. Though rheumatoid vasculitis in severe RA cases with high rheumatoid factor titres occasionally causes acute myocardial infarction theoverwhelming majority of cardiovascular deaths in RA result from accelerated atherosclerosis. , the lipid profile of patients with active or untreated RA is primarily characterized by a decrease in serum levels of HDL-C whereas contrasting results have been published on the serum levels of TC and LDL-C. Importantly, the reductionin HDL-C has as a consequence the increase in the TC/HDL-C ratio. This ratio represents an atherogenic index, which is an important prognostic marker for cardiovascular disease[15]the risk of myocardial infarction increases, considerably when this ratio is higher than five, and it should ideally be four or less Risk factors for atherosclerotic events and cardiovascular disease include male sex, increased age,

elevated plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), high blood pressure, smoking and diabetes mellitus. Approximately 50% of atherosclerotic coronary artery disease (CAD) in the community occurs in the absence of traditional risk factors. Rheumatoid arthritis and inflammatory activity altering lipid profile in RA patients.

Objectives
To assess the correlation between Lipid abnormalities and severity of thedisease. To assess the role of Lipid abnormalities in the development ofcardiovascular disease in Rheumatoid arthritis.

Review of Literature
Rheumatoid Arthritis is defined as a chronic systemic inflammatory disorder characterized by deforming symmetrical polyarthritis of varying extent and severity, associated with synovitis of joints and tendon sheath, articular cartilage loss, erosion of juxta articular bone and in most patient the presence ofIgM rheumatoid factor in the blood. Genetic studies of the distribution of RA in families and in mono &dizygotic twins show that there is a small but definite contribution of genetic factors to the disease. In twins studies, there is around 30% concordance of disease in identical twins and around 5% in non-identical twins. 10% of patients with RA will have an affected first degree relatives. Recent studies have shown an association between HLA-DR, (HLA- DW4 and HLA-DW14) and seropositive disease. In Indians RA ismost commonly associated with HLA-DR1.

More specially , the disease susceptibility is associated with sharped epitope of specific amino acid sequence on the beta-1 chain of a number of class II –alleles located in the third allelic hypervariable region of HLA-DR B1, between amino acid residue 67 and 74 which flank the T-cell recognition site.

Rheumatoid disease process in the joints is characterized by
Synovitis, Inflammatory effusion, Cellular exudates into the joint space Extra articular features associated with RA consist of two typesof lesion. First is fibrointimal hyperplasia without inflammatory changes leading to vascular occlusion. Second lead to extravascular lymphocyte macrophage granuloma lesion of RA

The inflammatory synovial membrane produces large amountof immunoglobulins mainly as RF. Lymphokines: The inflammatory synovium contains activated T- lymphocyte, which produce lymphokines into the synovial fluid. activate additional T-Lymphocytes, act as helper factors for B-cell proliferation, stimulate fibroblast to produce collagen and stimulate macrophage.

The most common symptoms are pain and stiffness. The latter frequently exhibit diurnal rhythms, worse on early morning. The affected joints worse asthe disease advances, muscle atrophy , tendon sheath and joint destruction results in limitation of joint movement, joint instability , subluxation and deformity. There are six families of lipoproteins , which are graded in size and lipidcontent. The density of these lipoproteins (and consequently the speed at which they sediment in the ultracentrifuge) is inversely proportionate to their lipidcontent. In general, the lipoproteins consist of a hydrophobic core of triglycerides and cholesteryl esters surrounded by phospholipids and protein The way these lipoproteins are organized into an exogenous pathway, which transports lipids from the intestine to the liver, and an endogenous pathway, which transports lipids to and from the tissue, 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. Department of medicine, University of Illinois, Chicago, Concentration of serum lipids and serum LDL were measured, and agarose gel electrophoresis of serum lipoprotein were performed in 69 persons of RA and65 healthy blood donors. RA patients had significantly decreased concentration of total serum lipids & serum cholesterol, LDL & HDL. By Lorber M, Aviram M, Linn S, Scharf Y, Brook JG. Plasma lipids & lipoprotein patterns were determined in 54 female RA patients. There was 26% reduction in total cholesterol, 36% reduction in both LDL & HDL were observed. Serum total, HDL, LDL, cholesterol and triglycerides levels in patients with rheumatoid arthritis· -By Lakatos J, Harsagyi A, United sanitary institution, pecs, Hungary. In this study, patients with rheumatoid arthritis (26 men, 103 women) theserum total cholesterol, HDL cholesterol & triglycerides were lowered when compared to controls. (625 men & 749 women). By Kim SH, Lee CK, Lee EY, park SY, Choys, Yoo B. Division of allergy & rheumatology, Department of medicine, University ofUlsan college of medicine, Orsan medical centre, Seoul, Korea. Compared with healthy women, those with active RA, had increased serumoxidized LDL level, which may contribute to the increased risk of cardiovascular diseases in these group of patients.

Material and methods:
This is cross sectional study, total 50 Patients of diagnosed rheumatoid arthritis and fifty age and sex matched healthy control will be selected for the study from indoor and outpatient department of General medicine, at Darbhanga medical college and Hospital, Laheriasarai, Darbhanga, Bihar. After taking through history taking and clinical examination and by exclusion criteria, study Duration period of two years.

Inclusion criteria
Arthritis of hand joints:
Soft tissue swelling of 3 or more than 3 joints
Morning stiffness for at least one hour.

Exclusion criteria
Patients with rheumatoid arthritis with the following conditions wereexcluded from the study.
*Malabsorption syndrome
*Nephrotic syndrome
*Diabetes mellitus
*Thyroid disorders
*Liver disorders

All the RA patients were selected on the basis of 1987 revised criteria ofAmerican rheumatism Association for the classification of rheumatoid arthritis. Fifty patients with the age group ranging from 20 to 70 years were studied, theywere at different stages of rheumatoid arthritis. Age & sex matched healthy persons, between the age of 20 to 70 years weretaken for the control study. Concentration of total cholesterol, HDL-cholesterol, and triglycerides were assessed enzymatically with commercially available reagents. Concentration of LDL-cholesterol was calculated by use of the Friedewald equation for participants who had triglycerides (< 400 mg/dl) Statistical analysis was carried out for 100 participants [50 RA patients, 50 controls] after categorizing each variable. Base line data was collected from patients Age, sex, duration of early morning stiffness, Lipid profile, ESR were analyzed.

Results

In our study, 50 RA patients matched with 50 healthy controls were studiedfor lipid abnormalities and the following observation were made. Patients with age group ranging from 20 to 70 years were studied.

Table 1: AGE DISTRIBUTION IN THIS STUDY

AGE IN YEARS	NUMBER OFPATIENTS	PERCENTAGE %
20 - 30	15	30%
31 - 40	14	28%
41 - 50	9	18%
51 - 60	9	18%
61 - 70	3	6%

In this study, Rheumatoid arthritis diseased patients lies more in the age groupof 20 to 40 years.

Table 2: SEX DISTRIBUTION IN THIS STUDY

SEX	NUMBER OFPATIENTS	PERCENTAGE
FEMALE	43	86%
MALE	7	14%

This study shows females are affected more than males.

Table 3: CORRELATION BETWEEN AGE AND TOTALCHOLESTEROL LEVEL

AGE (YEARS)	<100 mgs%		101 – 150 mgs%		151 – 200 mgs%		>200 mgs%
	controls	cases	controls	cases	controls	cases	controls
20 - 40	0	0	4	8	26	21	2
41 - 60	0	0	2	2	13	16	0
>60	0	0	0	0	3	3	0

In the study group, TC levels in 40 patients were in the range of 151- 200mgs% , out of which 21 patients lie in the age group of 20 to 40 years.

Table 4: CORRELATION BETWEEN SEX AND HDL CHOLESTEROLLEVEL TC/HDL RATIO

SEX	HDL<30 mgs%		HDL 31 - 35 mgs%		HDL 36 – 40 mgs%		HDL >40 mgs%		TC /HDL >6
	controls	cases	controls	cases	controls	cases	controls	cases	controls
FEMALE	20	15	9	16	10	11	4	1	16
MALE	1	4	5	2	1	1	-	-	1

Table 4: 23 CORRELATION BETWEEN LIPID ABNORMALITY AND ESR

ESR(mm/hr)	TOTAL NO. OF PATIENT	TC (mgs%)	LDL (mgs%)	TGL (mgs%)	HDL (mgs%)	TC/HDL
20 - 40	4	171±3.82	105± 3.7	158 ±16.8	34± 1.4	5± 0.21
41 - 60	10	168.3±5.9	102 ±5.2	156.5± 12.4	34.3± 2.2	4.9±0.37
61 - 80	15	156.4±8.6	92.5± 9.7	155± 15.8	32.5± 5.2	4.9±0.74
>80	21	153.3±7	93.8± 8.6	138.7± 17.9	30.9± 3.6	5 ±0.62

This study shows negative correlation between ESR and lipids .

Table 5:

EARLY MORNING STIFFNESS	TOTAL NO. OF PATIENT	TC(mgs%)	LDL (mgs%)	TGL (mgs%)	HDL (mgs%)	TC/HDL
≤30 min	5	164.4 ±14.6	100± 10.9	166.4± 10	33.2± 5.2	5.1± 0.91
31 – 60 min	30	152.3± 17.3	95.7± 8.5	158.5± 9.1	32.8± 4	4.9 ±0.54
>60 min	15	136.3± 13.1	96.8± 9.9	156.3± 9.9	31.1 ±3.6	5.1± 0.59

This study, shows that TC and TGL cholesterols negatively correlate significantly with duration of early morning stiffness in RA patients. Whereas LDL-C, HDL-C are negatively correlating insignificantly with duration of early morning stiffness.

Discussion

They were studied on the basis of clinical features, biochemical features, radiological features with special reference to lipid profile. Some characteristic features noted in the study are given below. In this study out of 50 cases, 43 were females, 7 were males. The female to male ratio was 6.14:1. The age of the patient ranged from 20 to 70 years with mean age 40.38±12.64 in study group and 40.04±11.7 in control group. All the 50 patients (100%) fulfilled the revised criteria of American Rheumatism Association for Rheumatoid arthritis. Total cholesterol was significantly reduced in rheumatoid arthritis patients, when compared to controls. The total cholesterol levels in our patients was158.64± 9.59. LDL cholesterol was significantly reduced in RA patients, when compared to controls. In our patients, LDL-C level was 96± 9.14. In control, the level was 106.5 ± 18.20 (p value < 0.0004), Triglyceride level was also significantly reduced in RA patients, when compared to controls. In our patients, the triglyceride level was 148.68± 17.7. In controls, it was 166.32± 12.43. (p value < 0.0001), In our study, HDL-C cholesterol was not significantly reduced, when compared to controls. In our study, it was 32.32± 3.96. In controls, it was 32.46± 5.24.(p value is 0.8806). Total cholesterol in eight patients were in the range of 101 to 150 mg%and in 21 patients were in the range 151 to 200 mg% . LDL –C in four patients were in the range of 61 to 80mg% , 20 patients were in the range of 81 to 100mg% and in 5 patients were above 100mg% TGL in nine patients were in the range 101 to 140mg% and 20 patients were in the range of 140 to 180mg% . No patients had above 180 mg%of TGL. HDL-C in ten patients were below 30mg% , 10 patients were in the range of 31 to 35mg% and in 9 patients were in the range of 36 to 40 mg%. No patient had above 40mg%. LDL-C in five female patients were in the range of 61 to 80mg%. 29 female patients & 4 male were in the range of 81 to 100mg% . 10 female patients and in 3 male were above 100mg% . TGL in fifteen female patients and in one male patient were in the range of 101 to 140mg%. 28 female and in 6 male patients were in the rangeof 141 to 180mg% . HDL-C in fifteen female and in 4 male patients were below 30mg%. 16 female and in 2 male patients were in the range of 31 to 35 mg% . 11 Females and in 1 male

patient were in the range of 36 to 40mg% . HDL-C in one female patient was more than 40mg%. Thirty patients had early morning stiffness of between 31 to 60 min., with total cholesterol was 152.3 ±17.3, LDL-C was 95.7± 8.5, TGL was 158.5± 9.1, HDL-C was 32.8± 4 & TC/HDL ratio was 4.9± 0.54. Early morning stiffness of more than 60 min in   fifteen patients., with total cholesterol was 136.3 ±13.1, LDL-C was 96.8± 9.9, TGL was 156.3± 9.1, HDL-C was 31.1± 3.6 & TC/HDL ratio was 5.1± 0.59

In our study, TC,LDL, TGL ,TC/HDL are significantly reduced with insignificant reduction in HDL levels in RA compare to controls. A significant negative correlation is present between all lipid parameters and ESR. The lipid profile of patients with RA has been evaluated in several of theabove studies . Most of the studies, Lazarevic et al, Rantapää-Dahlqvist et al, Svenson et al, Kakati et al, Park YB,et al, Munro et al, Nurmohamed Mt et al, had reported an overall reduction in all lipid sub-fractions in cases of active disease. Our study results are in line with above mention studies.

Vottery et al had reported significant reduced TC, TGL levels. Lakatos et al had reported significantly raised TC, LDL, reduced TGL, HDL. Lorber et al[18]had reported significant reduced LDL, HDL. Park YB,et al, Asanuma et al, Veil cobankara et al had reported significantly raised Lipoprotein(a).These contrasting results in various previous studies could be attributed to the size of the samples, the type of study (prospective or cross-sectional), differences in the disease type (established or early), or to differences in the disease activity. presence of circulating autoantibodies to VLDL and LDL in active RA . byforming immune complexes. may also have pre-atherogenic effects on the vascular wall. cardiovascular disease in RA may result from accelerated atherosclerosiscaused by clinical or subclinical vasculitis. Reduced cardiovascular fitness caused by immobility. medication, increased homocysteine level, and increased thrombotic factors (fibrinogen, von Willebrand factor, plasminogen activator antigen, and fibrin D- dimer). many similarities have emerged between the inflammation paradigm in the pathogenesis of atherosclerosis and the well established inflammation mechanism in the pathogenesis of RA. These similarities raise the possibility that inflammatory mechanisms responsible for synovial lesions in patients with RA may directly participate in producing atherosclerotic lesions resulting in excess cardiovascular disease in RA patients. The limitation of this study is that there was no consideration and analysis ofthe effects of patients' average daily physical activity, The sample size was likely to be insufficient , thus we cannot rule out type IIerror in these results.

Conclusion

Patients with Rheumatoid arthritis had significantly reduced levels of serum total cholesterol, LDL-cholesterol, triglyceride, as compared to controls. HDL-cholesterol level was not significantly altered in Rheumatoid arthritis as compared to controls. It is observed that there is significant negative correlation between the lipid parameters -TC, LDL-C, TGL, HDL-C in active Rheumatoid arthritis patientsand erythrocyte sedimentation rate

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