ORIGINAL ARTICLE

Prevalence of Dyslipidemias in Autoimmune Rheumatic Diseases

Anila Nisar, Uzma Rasheed, Wajahat Aziz and Abid Zaheer Farooqi

ABSTRACT

Objective: To determine the frequency of dyslipidemias in various autoimmune rheumatic diseases and the difference in lipid profile according to the activity of these diseases.

Study Design: Cross-sectional study.

Place and Duration of Study: The Rheumatology Department of Pakistan Institute of Medical Sciences (PIMS), Islamabad, from May 2010 to April 2011.

Methodology: All patients who presented to Rheumatology Department with various autoimmune inflammatory rheumatic diseases were included. Fasting lipid profiles of patients were obtained after an overnight fast of 12 hours. Various diseases were classified as active or inactive on the basis of clinical features and relevant laboratory tests. Data were entered in SPSS 17 and analyzed. Association between disease activity and abnormal lipid profile was also determined.

Results: A total of 100 patients were included in the study. Out of these, 82% were females. Mean age was 34.15 ± 7.73 years. Rheumatoid arthritis (RA) was the most common disease present in 78 patients. Various types of dyslipidemias were found in 54% of patients. Low HDL and deranged cholesterol levels were significantly associated with active disease ($p = 0.044$ and $p = 0.048$ respectively). Patients with RA also had dyslipidemias in 45% of the cases. Disturbed cholesterol level was observed in active RA ($p = 0.044$).

Conclusion: Dyslipidemias are frequent among the patients with autoimmune rheumatic diseases (AIRD). Disturbance in total cholesterol is the most common abnormality with a significant association with disease activity.

Key words: *Autoimmune rheumatic disease. Dyslipidemia. Cardiovascular disease. Rheumatoid arthritis. Total cholesterol.*

INTRODUCTION

Dyslipidemias are being increasingly recognized as an important contributory factor towards the development of CVD. Framingham study showed that a 1% increase in total cholesterol cause 2% increase in the incidence of IHD.[1] CVD are also the leading cause of death in various autoimmune diseases mainly Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Ankylosing spondylitis and antiphospholipid antibody syndrome.[2,3] Dyslipidemias lead to atherosclerosis which is an important feature of CVD. Atherosclerosis is now considered as an inflammatory disease as it is a result of inflammation and inflammatory cytokines, are prevalent in atherosclerotic plaques.[2,3] RA is the most common inflammatory joint disease. Atherosclerosis in RA is as prevalent as in patients with DM.[4] Pre-mature CVD is very common in RA and SLE.[3,4] RA is associated with 50% increase in incidence of myocardial infarction (MI) and cardiovascular diseases as compared to general population.[6] SLE also causes increased risk of CVD in females even before the age of menopause. CVD is the most prominent cause of mortality and morbidity among SLE patients. Its prevalence ranges between 6 - 10%.[1] Patients with disease duration more than 5 years have been reported to have 52 times greater risk of MI than matched controls.[7]

Various studies have been done on patients with autoimmune rheumatic diseases to study the patterns of dyslipidemias. It has been observed that increased inflammation and active disease has an impact on lipid patterns in blood.[7] In RA, high grade disease activity results in decreased total cholesterol (TC), decreased low density lipoproteins (LDL) and a more consistent and marked decrease in high density lipoproteins (HDL).[8-10] It leads to increased atherogenic index i.e. total cholesterol ratio to HDL- cholesterol. Some studies have shown that there is increased TC and increased LDL whereas, HDL is low in patients with RA.[11]

In SLE, there is a decrease in HDL, increased TG and unchanged or slightly increased LDL and increased lipoprotein A. Blood lipids may be important disease markers in SLE.[2,6,7] Active ankylosing spondylitis also favours the development of atherogenesis as do the Antiphospholipid antibodies.[7] As local data is not available in this regard, the rationale of this study was to help gather local evidence. This would in turn help form a strategy to treat conventional risk factors for dyslipidemias in patients with rheumatic disorders to prevent CVD development.

Keeping these facts in mind, this study was conducted to determine the frequency of dyslipidemias in autoimmune rheumatic diseases and the effect of disease activity on lipid levels in blood.

Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad.

***Correspondence:** Dr. Anila Nisar, House No. NE-252, Milad Street, Near PAF, Rawalpindi (Dhok Farman Ali). E-mail: doctoranila01@yahoo.com*

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METHODOLOGY

This study was carried out in the Rheumatology Department of PIMS, Islamabad, from May 2010 to April 2011. Consecutive non-probability sampling technique was used to recruit the patients. All patients between ages of 18 and 45 years who had any autoimmune rheumatic disease were included. Patients with non-inflammatory conditions, postmenopausal females, patients on lipid-lowering drugs, obese patients with BMI more than 30 and patients with diabetes mellitus were excluded from the study. Informed consent was obtained from all subjects before enrollment in the study.

Complete medical history and physical examination including body mass index (BMI) and blood pressure measurement was done. Smoking status of patients was enquired. RA, SLE, ankylosing spondylitis, seronegative spondylarthritis and other autoimmune rheumatic diseases were diagnosed according to set ACR criteria.[12] Relevant tests including BSR, BSF, ESR, lipid profile and chest X-ray were done to look for evidence of cardiomegaly. Lipid profile including high density lipoproteins (HDL), low density lipoproteins (LDL), total cholesterol (TC) and triglycerides (TG) were checked after an overnight fasting of 12 hours. Normal values were considered according to reference values. Disease activity was classified according to clinical assessment and laboratory tests like ESR, CRP, complement levels and anti-ds DNA titres.

Data was entered in Statistical Package for Social Sciences (SPSS) version 17. Frequency and percentage of dyslipidemias in patients was calculated according to different disease groups and disease activity. Chi-square test was applied for comparing lipid profile in two groups of active and inactive diseases in all patients. P-value ≤ 0.05 was considered significant statistically.

RESULTS

A totoal of hundred patients were included in the study. Out of them, 18 were males and 82 were females. All patients had various types of autoimmune rheumatic diseases including RA, SLE, ankylosing spondylitis, seronegative spondyloarthropathies and scleroderma. Seventy-eight patients had RA, 10 patients had SLE, 4 patients had seronegative spondyloarthropathy, 2 patients had SSc and 3 patients had miscellaneous diseases. Mean age was 34.15 ± 7.73 years and most patients (n = 47, 47%) had long standing disease duration of more than 2 years. Disease duration in 40 patients was 6-24 months and only 13 patients had a disease of < 6 months duration. Disease was active in 65 patients while 35 patients had inactive disease.

Various types of dyslipidemias were found in 54 patients. Overall, there was not any association between dyslipidemias and status of disease activity (p = 0.101, Table I). The most common abnormality amongst various dyslipidemias was disturbed total cholesterol levels either high or low than normal. When various lipid fractions were analyzed individually, low HDL and deranged cholesterol was found to be significantly associated with active disease state (Table II, p = 0.044 and 0.048 respectively).

Table I: Association of dyslipidemias with disease activity.

Status of disease	Dyslipidemia		Total
	Present	Absent	
Active disease	39	26	65
Inactive disease	15	20	35
Total	54	46	100

p-value = 0.101 (chi-square test); p-value = 0.141 (Fisher's exact test)

Table II: Lipid status in AIRD.

Lipid level	Normal	Low	High	Relation with disease activity (p-value)*
HDL	77	23	-	0.044
LDL	99	-	1	0.461
TG	80	-	20	0.116
TC	63	20	17	0.048

**P≤0.05 is taken as level of significance; HDL: High Density Lipoproteins; LDL: Low Density Lipoproteins; TG: Triglycerides; TC: Total Cholesterol.*

Table III: Dyslipidemias in RA.

Lipid level	Normal	Low	High	Relation with disease activity (p-value)*
HDL	66	12	-	0.297
LDL	77	-	1	0.426
TG	66	-	12	0.297
TC	51	11	16	0.044

**p value ≤ 0.05 is considered statistically significant; HDL: High Density Lipoproteins; LDL: Low Density Lipoproteins; TG: Triglycerides; TC: Total Cholesterol.*

Seventy-eight patients in the study had RA; 11 were males and 67 were females. Out of them, 48 had active disease (61.5%) and 30 had inactive disease (38.5%). Overall derangement in lipid profile was seen in 44.87% (n = 35) of the patients. However, no statistically significant association was found between disease status (active or inactive) and presence of dyslipidemias (p = 0.249).

Classification Criteria

The revised criteria of 1987 (ARA/ACR) for diagnosis of rheumatoid arthritis.

Criteria	Comment
1. Morning stiffness	Duration >1 hour lasting > 6 weeks
2. Arthritis of at least three areas [a]	Soft tissue swelling or exudation lasting > 6 weeks
3. Arthritis of hand joints	Wrist, metacarpophalangeal joints or proximal interphalangeal joints lasting > 6 weeks
4. Symmetrical arthritis	At least one area, lasting > 6 weeks
5. Rheumatoid nodules	As observed by a physician
6. Serum rheumatoid factor	As assessed by a method positive in less than 5% of control subjects
7. Radiographic changes	As seen on anteroposterior films of wrists and hands

[a] Possible areas: proximal interphalangeal joints, metacarpophalangeal joints, wrist, elbow, knee, ankle, metatarsophalangeal joints. At least four criteria must be fulfilled for at least 6 weeks.

European Spondyloarthropathy Study Group (ESSG) criteria for diagnosis of spondyloarthropathy.

Inflammatory spinal pain or
Synovitis (asymmetrical [a] or predominantly in the lower limbs [a]) and
One or more of the following
Positive family history
Psoriasis
Inflammatory bowel disease
Enthesopathy
Alternate buttock pain
Sacroiliitis
Urethritis, cervicitis, or acute diarrhea within 1 month before arthritis

[a] Without sacroiliitis, sensitivity = 78.4%, specificity = 89.6%; with sacroiliitis, sensitivity = 87%, specificity = 86.7%.

New York criteria for the diagnosis of ankylosing spondylitis.

Clinical criteria
1. Limited movement of lumbar spine in frontal or saggital planes
2. Inflammatory low back pain for at least 3 months duration
3. Decreased chest expansion
Radiological criteria
4a. Bilateral sacroiliitis, grade 2-4
4b. Unilateral sacroiliitis, grade 3-4

Definite ankylosing spondylitis if 4a or 4b and any clinical criterion 1-3

Revised criteria of the American College of Rheumatology for the classification of SLE[a].

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
(a) pleuritis or
(b) pericarditis
7. Renal disorder:
(a) proteinuria > 0.5 g/24 hour or 3+, persistently, or
(b) cellular casts
8. Neurological disorder:
(a) seizures or
(b) psychosis (having excluded other causes, e.g. drugs)
9. Haematologic disorder:
(a) Haemolytic anaemia or
(b) Leucopaenia or < 4.0 x 10^9 /l on two or more occasions
(c) Lymphopaenia or < 1.5 x 10^9 /l on two or more occasions
(d) Thrombocytopaenia < 100 x 10^9 /l
10. Immunological disorders:
(a) anti-DNA antibody or
(b) AntiSm antibody or
(c) Positive finding of antiphospholipid antibodies based on
(1) an abnormal serum level of IgG/IgM anticardiolipin antibodies;
(2) a positive test result for lupus anticoagulant using a standard method, or
(d) A false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody in raised titre

[a]'. . . A person shall be said to have SLE if four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.'

ARA criteria for classification of systemic sclerosis.

A. Major criterion
Proximal scleroderma
Symmetrical thickening, tightening, induration of the skin of the fingers and the skin proximal to the metacorpophalengeal and metatarsophalengeal joints. Changes may affect the entire extremity, face, neck and trunk.
B. Minor criteria
1. Sclerodactyly, above indicated changes limited to the fingers.
2. Digital pitting scar or loss of substance from finger pad. Depressed area at tips of fingers or loss of digital pad tissue as a result of ischaemia.
3. Bibasilar pulmonary fibrosis, bilateral reticular pattern of linear or lineonodular densities most pronounced in basilar portion of lung on standard chest roentgenogram. May assume appearance of diffuse mottling or honey combing. These changes should not be attributable to primary lung disease.
SSc diagnosed when one major or two or more minor criteria are present.

Klippel JH, Stone JH, Crofford LI, White PH. Primer on th rheumatic diseases, 13th ed, Newyork USA: springerlink, 2008. Pages 670-5.

On further analyzing various lipid fractions; 33.33% (n=26) of patients with RA had disturbed total cholesterol (higher or lower than normal) and this had a significant association with active disease (p= 0.044, Table III).

In SLE, 6 out of 10 patients had dyslipidemia (60%) but this number was too low to look for any specific trend in dyslipidemias or association with disease status. Similarly, there were too few number of other autoimmune diseases to determine the pattern of lipid profile in those patients.

DISCUSSION

Dyslipidemias are a well recognized risk factor for cardiovascular diseases and are very common in patients with autoimmune rheumatic diseases.[2,3] Patients with rheumatologic diseases especially RA and SLE are at increased risk for premature CVD i.e. CVD at a young age. These patients develop atherosclerosis which is now considered as secondary to inflammation rather than primary metabolic alteration.[2] Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in patients with rheumatoid arthritis.[13]

Patterns of dyslipidemias in AIRD have been studied in various international studies but there is no study in Pakistan on this subject. So this study was conducted on local patients that had various types of rheumatologic diseases. Maximum patients had RA (78%). Different types of lipid disorders were observed in 54% of the patients, most common being disturbed total cholesterol (high or low than normal). Disturbed total cholesterol and low HDL had a significant association with disease activity.

Dyslipidemias are common in general population as well. A study conducted by Shah and colleagues on healthy individuals showed increased prevalence of dyslipidemias in obese as well as non-obese individuals.[14] Iqbal and his colleagues did a study in Karachi on healthy civilians between ages 18-60 years in 2004. It showed that 31% of healthy individuals have

dyslipidemias of different types.[15] Other studies by Basit and Estary also showed high frequency of dyslipidemias in otherwise healthy individuals.[16,17]

However, all these studies were done in individuals of age more than 18 years including elderly as well. The present study included only young patients between ages 18 - 45 years to rule out the effect of advancing age on lipid levels.

A study done by Toms and colleagues on dyslipidemias in patients with AIRD showed that patients with RA have decreased total cholesterol, decreased LDL and decreased HDL leading to increased atherogenecity index.[7] The present study also found a high frequency of abnormal lipid profile in patients with RA including low HDL 15.3%, low total cholesterol 13%, high cholesterol 20.5% and raised TG in 15.3% patients. However, these findings are not consistent with the findings of Toms *et al*.[7] They also found low HDL and raised TG to be seen frequently in SLE patients.[7] SLE patients in the present series also had the same findings but number of patients was too low for any significance. Another study by Kowsalya done recently showed that patients with RA have low HDL; increased TC and raised LDL as compared to controls.[11]

Hadda studied the relationship of disease activity of RA with lipid profile.[18] His results showed dyslipidemias in 38.5% patients with low HDL as commonest abnormality (34.3%). Disease activity was negatively related with lipids. The present study has shown that active RA is significantly associated with abnormality in TC i.e. either high or low than normal. Low HDL is not found to be related to disease activity.

Geordiadis *et al*. found that patients with early RA (ERA) exhibited higher TC, LDL and TG, whereas their HDL was significantly low as compared to controls.[19]

Myasoedova *et al*. in a similar study found that lower TC is associated with increased risk for CVD with a 3-fold increased risk for events in patients with TC < 155 mg/dL.[20] Elevated TG is also associated with increased risk for CVD event. They concluded that in RA, association of lipids with CVD events may be different than that in patients without RA.[20]

This study confirms dyslipidemias in AIRD but pattern is not the same as in various international studies. This difference might be due to different race and ethnicity. Cesur and colleagues concluded in their review that patients with RA may have an altered lipoid profile from one country to another.[21] Ethnicity may be a reason for these findings.

This study has a few limitations. First, it has a small sample size so results cannot be generalized. Secondly, there are predominantly patients of RA in this study and other rheumatic autoimmune diseases are not defined well. To determine the true prevalence and pattern of lipid profile in AIRD, much bigger sample size is needed including patients with other diseases like SLE and ankylosing spondylitis.

CONCLUSION

Dyslipidemias are seen frequently in patients with autoimmune rheumatic diseases. When considering different lipid fractions individually, low HDL and deranged cholesterol (either high or low than normal) are the most statistically significant dyslipidemias associated with disease activity. In RA, disturbed total cholesterol has a significant association with disease activity. Lipid levels should be monitored regularly and managed in patients with AIRD to minimize the long-term risk of CVD.

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