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ORIGINAL ARTICLE

Dyslipidemia in cohorts of rheumatoid arthritis presented at Independent University Hospital Faisalabad.

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ABSTRACT… Objective: To determine the frequency of dyslipidemia in RA patients and its association with different factors i.e., age, gender, disease duration and disease score. **Study Design:** Cross Sectional study. **Setting:** Independent University Hospital Faisalabad. **Period:** January 2022 to December 2023. **Methods:** 200 consecutive RA patients fulfilling inclusion and exclusion criteria, of either sex between age of 20 and 60 years were enrolled. The selection technique was non-probability convenient in this study. Frequency of dyslipidemia was assessed by the National Education Cholesterol Program 2004. The Chi square test was used to compare the frequency of dyslipidemia among different disease scores, different disease duration groups, age groups and gender. A p-valve of < 0.05 was considered statistically significant. **Results:** The frequency of dyslipidemia in RA patients was assessed. It was more common in female gender and age group of 36-50 years and of moderate disease score, also negative association of dyslipidemia was found when compared with different gender groups. **Conclusion:** Dyslipidemia, which is an important risk factor for CV diseases, was more prevalent in RA patients. High disease activity and more chronic disease are important association factors in dyslipidemia in RA patients.

Key words: Cardiovascular, Dyslipidemia, Disease Modifying Anti-rheumatic Drugs, Methotrexate, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disease, it is autoimmune and inflammatory in nature, mostly involving the joints having synovium, also leads to systemic inflammation as well.[1] Its prevalence varies from 0.5-1% in the general population worldwide. If not treated properly it leads to joint deformities and permanent joint damage. This disease affects both articular and extra articular organs as well, sometimes leading to severe co-morbidities like metabolic syndrome, cardiovascular diseases, chronic infections and malignancies as well.[2]

Because of severe joint destruction and disability, specific disease modifying antirheumatic drugs (DMARDs) were introduced to prevent joint destruction and disability.[3] So, in the past 20 years, disease has attained a bit milder course, less destruction of joints, also fewer extra articular manifestations and less co-morbidities, and ultimately lower morbidity and mortality.[4,5] But still patients with RA exhibit 2-fold higher mortality as compared to the non-RA patients.[6]

Pathogenetic mechanisms associated with RA, extra articular manifestations, and co-morbidities are very complex. However systemic inflammation has a critical role in the occurring of these.[7] Although a lot of other precipitating factors have also been observed like malnutrition, physical inactivity, corticosteroids use, and some DMARDs as well.[8]

Dyslipidemia is one of comorbidities that has a direct impact on the illness and death associated with RA. Inflammatory burden in systemic circulation have a critical role in the occurrence of dyslipidemia. Systemic inflammation produces pro-inflammatory cytokines which directly affects oxidative stress and leads to dyslipidemia.[9] Prevalence of dyslipidemia contributes almost

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55-65% in RA patients which even present in early RA and pre-RA in which the clinical symptoms of RA are not evident yet. At this stage of disease immune mechanisms like rheumatoid arthritis factor (RAF), anti-cyclic citrullinated peptide antibodies (Anti-CCP) and inflammation are at a high level.[10] Important inflammatory mediators like tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) have vital importance in development of dyslipidemia which increases the risk of atherosclerosis and increased cardiovascular morbidity.[11]

Atherogenic dyslipidemia usually occurs in active or untreated RA, and it is due to abnormal levels of total cholesterol (TC) and triglyceride (TG) levels.[12] High density lipoprotein (HDL) cholesterol is essentially low while low density lipoprotein (LDL) cholesterol and TG levels are increased. High disease activity leads to Low level of HDL cholesterol which usually leads to high ratio of TC/HDL which represents an atherogenic index in RA patients and is a prognostic factor for the cardiovascular disease in RA patients.[13] It is also noted in different studies that cholesterol is paradox in active RA as compared to general population having low total cholesterol and HDL.[14]

Singh and colleagues showed that there are importantly low levels of HDL-C, TC and high levels of LDL-C in RA. It was seen that the TC reduction was significantly less than the HDL-C levels, again leading to high level of both TC/HDL (atherogenic index) and LDL/HDL ratios.[15] Similarly, another study showed that there is significant reduction of TC, LDL-cholesterol, TG, and dyslipidaemic index in RA patients who have a disease in remission or minimum activity as compared to the patients who have a severe disease.[13] Another study conducted in Pakistan showed prevalence of dyslipidemia was 45%.[16] Erum and colleagues showed that 53.5% of Karachi population have abnormal lipids with predominant finding was low HDL level, seen in 41.5% of the patients.[14]

Above discussion clearly showed that there is high inflammation in untreated and highly active disease and this inflammation is clearly associated with co-morbidities like dyslipidemia which is very notorious for early presentation of cardiovascular diseases. So, our main rationale is to find out the frequency of dyslipidemia in RA cohorts presenting at my institution and to determine the correlation of dyslipidemia and duration and activity of disease in RA. This study will give benchmark for treating physicians to assess dyslipidemia at very initial level of disease, and if present then timely intervention with proper anti rheumatic and lipid lowering drugs will improve the disease and patient life status and decreases the burden of chronic illness and death related to dyslipidemia and cardiovascular diseases.

METHODS

This study which is cross-sectional was conducted in Independent University Hospital Faisalabad from January 2022 to December 2023. A total of 200 adult cohorts who have fulfilled the baseline criteria of American rheumatology association (ACR) of RA 2010[17], visiting outpatient department of IUH. All these patients have fulfilled the entry criteria. The selection technique was non-probability convenient in this study. This study was approved by the Institutional review board of this hospital on the date of December 13, 2021, with ethical approval letter no. IUH/IRB/000036.

All the selected patients, both males and females have ages 18 years to 60, have been labeled previously or newly as a case of RA fulfilling the ACR 2010 criteria. Inflammatory arthritis of other autoimmune diseases like SLE, ankylosing spondylitis, Sjogren's disease and Seronegative Arthritis were clearly excluded. Also, patients with metabolic syndrome and joint disease were excluded from this study as well. 200 patients were selected having confidence level of 95%, margin of error was 5%. All the selected patients were told about the purpose of this research. Also, have been briefed about any harm or benefit and written consent was taken from all patients selected for this study. Patients were explained about the aim, risk/benefit of the study and informed consent was taken. Basic information about the patient like age, sex was noted. Information about the disease onset, for how long patient is suffering from this disease and drugs used for treatment were also noted. Severity of the disease was

determined by Disease activity score (DAS-28), a computerized formula which includes number of painful joints, number of swollen joints and general condition of the patient.

All the blood samples were taken in early morning having at least 12 hours of over night fast. Aseptic technique was applied for sampling. A minimum of 10 ml venous blood was obtained from each patient. BD vacutainer (red topped) bottles were used sampling. Cobas C III (Roche) through Photo Spectrometry method was used for analysis of all samples. abnormal values of lipid levels used for all samples were TG of 150 mg/dl or more, serum HDL-C less than 40 mg/dl for males and less 50 mg/dl for females. Serum cholesterol of 200mg/dl or more was considered abnormal in both males and females.[18]

RESULTS

A total of 200 patients who were diagnosed as RA were enrolled in this study. Patients enrolled have a mean age of 45 ± 10 yrs, having a range between 20 to 60 yrs. Females were 161(80.5%) and males were 39 (19.5%) seen in Figure-1.

Median with inter-quartile range of age, disease duration, fasting TG and HDL-C level in RA patients were shown in Table-I. The median disease duration was 4 (2 – 8) years. Other factors like age were 45 (35 – 52) years, fasting TG level was 140 (116– 180) mg/dl, and HDL-C was 52 (40 – 59) mg/dl and total cholesterol was 167 (145-232.5) mg/dl.

Figure-2 shows the age distribution of all patients. A larger proportion of patients 94 (47.0%) belongs to age group of 36-50 yrs. A lesser proportion 55 (27.5%) belongs to > 50 years of age while only 51 (25.5%) belongs to 20-35 yrs.

Table-II shows 100% of patients in this study were using treatment for arthritis especially anti-rheumatic drugs. 56.5% were treated with methotrexate (MTX) 28.5% were treated with leflunomide, 15% were using different add on drugs i.e. HCQ, MTX, LFN, SSZ, tofacitinib, or rituximab.

Table-II also shows that Most of the of RA patients 49.5% in this study were of moderate disease activity and 29% were of severe disease activity score. Only 8.5% of patients were fully controlled with treatment or of minimum disease activity.

Association of dyslipidemia in arthritis patients were significantly seen with age, severity of disease, and duration of arthritis as seen by Chi square test shown in Table-III while gender difference was not significantly associated with dyslipidemia in RA patients. Dyslipidemia was more common in the age group of 36-50 years. It was also found that the Proportion of dyslipidemia was less in mild disease score as compared to moderate and severe disease score.

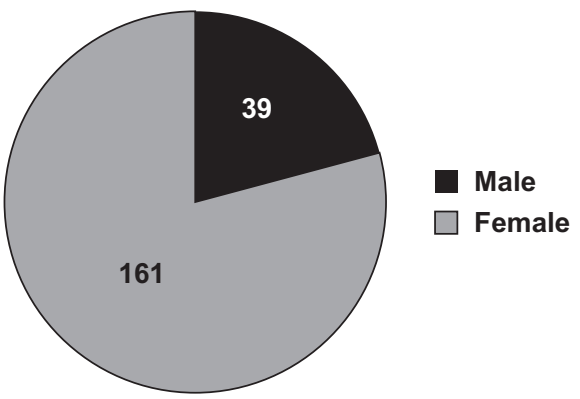

Figure-1

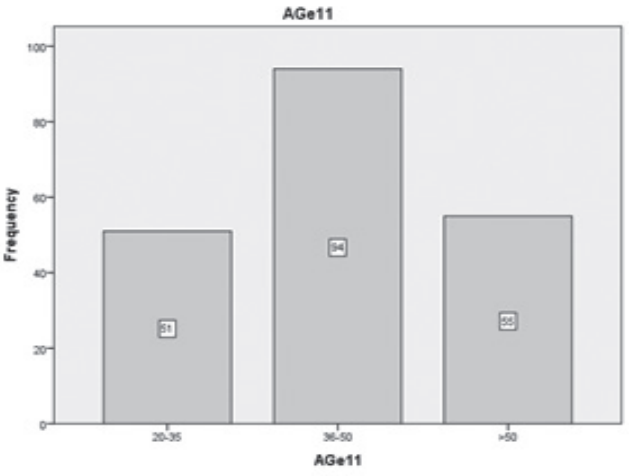

Figure-2

	Median (IQR)	Minimum	Maximum
Age	45 (35– 52)	20	60
Disease Duration	4 (2 – 8)	1	30
Total cholesterol	167 (145 – 232.5)	80	345
Triglycerides	140 (116– 180)	63	397
HDL Level	52 (40 – 59)	20	190
Current disease score	2	1	4

Table-I. Descriptive statistics for age, disease duration, disease score, total cholesterol, triglycerides and HDL level n:200

Variable	Group	Frequency	Percentage*
Age	20-35 years	51	25.5
	36 – 50 years	94	47
	> 50 years	55	27.5
Disease duration	≤ 10 years	156	78
	11-20 years	36	18
	>20 years	8	4
Treatment	MTX	113	56.5
	LFN	57	28.5
	Combination drugs	30	15
Disease score	Remission	17	8.5
	Mild	26	13
	Moderate	99	49.5
	Severe	58	29
Dyslipidemia	Total	157	78.5
	HDL	62	31
	Cholesterol	68	34
	Triglycerides	101	50.5

Table-II. Distribution of RA patients according to age, disease duration and treatments n:200

Variable	Group	Dyslipidemia		P-Value
		Yes	No	
Gender	Male	17	22	0.112
	Female	51	110	
Age	20-35 years	34	17	0.047
	36 - 50 years	76	18	
	> 50 years	47	8	
Disease Duration	≤ 10 years	128	28	0.018
	11-20 years	22	14	
	> 20 years	7	1	
Disease Score	Mild	21	5	0.015
	Moderate	86	13	
	Severe	39	19	

Table-III. Group comparisons for dyslipidemia. n:200

DISCUSSION

It is very clear now a days that both dyslipidemia and RA have increased CV diseases and even deaths. So, in the last decade researchers were strongly addressing the need to assess the prevalence of dyslipidemia in arthritis.[19] Evidence of this morbidity and mortality is multifactorial, but dyslipidemia and cardiovascular risk is mostly due to endothelial dysfunction and vascular damage leading to cardiovascular diseases.[20]

Our study showed the frequency of dyslipidemia was 78.5%, with higher prevalence of triglycerides which is 50.5%, followed by cholesterol and HDL

abnormalities. Grover S et al.[21] clearly showed high total cholesterol levels in India while Hadda et al.[22] also demonstrated in their study that 38.5 % of the 96 patients have abnormal lipid profile, more common one is low HDL-C, which is in 34.3 %. The results of these studies were comparable to my study which shows 31% abnormalities in HDL-C. similarly another study conducted in India showed dyslipidemia in RA with predominant HDL-C reduction which is 37.1% which is comparable with my study that showed 31% abnormality of HDL-C I RA patients.[23]

A study conducted in Pakistan showed prevalence of dyslipidemia was 45%.[16] In Pakistan, Erum and colleagues showed 53.5% of their patients were dyslipidaemic, the predominant finding was low HDL level, seen in 41.5% of the patients.[14] These studies have different results as compared to my study, which showed total dyslipidemia of 78.5%. reason for these differences is, my study was done on all RA patients which itself is pro-arthritogenic and most of our patients are in moderate and high disease activity which promotes dyslipidemia while Erum and colleagues and other study was not done on similar population to evaluate dyslipidemia.

Severe disease showed significant association with dyslipidemia (p value: 0.015) in my study. Patients with moderate disease activity have greater dyslipidemia as compared to mild and severe disease. Other studies[18,24] showed similar results in which moderate to high disease activity have significant dyslipidemia while a study[25] showed significant improvement of dyslipidemia after treatment with DMARDs. A Swedish study showed higher disease activity was significantly associated with dyslipidemia and acute coronary syndrome[26] as compared to low disease activity. Similar results were obtained from a US cohort study which showed lower CVD risk factors like dyslipidemia in controlled disease or minimally active disease after treatment as compared to patients who have highly active disease.[27] Dyslipidemia was significantly associated with the age of the patients, more profound in age group of 36-50 years in my study. Most of the patients presenting with disease at young age group usually ignore the disease and not taking any anti-rheumatic drugs that leads to high inflammatory burden and causing significant dyslipidemia. Similarly, patients in my study with less than 10 yrs of disease duration have significant association with dyslipidemia as compared to patients who have more chronic disease of more than 10 years. Again, the reason for this significant abnormality is that patients usually do not approach the rheumatologist or physicians for mild to moderate disease that leads to high disease burden and causing significant dyslipidemia.

There are few limitations in my study that should be addressed. We cannot compare our results with the controls because of its cross-sectional design. The sample size of my study was small, so results of this study were not compared with larger design studies, bigger trials so generalization is not possible. Similarly, dyslipidemia in other autoimmune inflammatory diseases and generative articular diseases was not compared with dyslipidemia in RA patients in my study. Also, in this study dyslipidemia was assessed first time in pure RA patients in Pakistan so it is not possible to have exact comparison of our results with similar local studies.

CONCLUSION

All above discussion had a significant advance to understand the relationship between dyslipidemia and RA. In short, the prevalence of dyslipidemia in RA in Pakistani population was matchable to the rest of the community. Major issues like ethnicity, financial status, social behaviors, demographic features of patients, co-morbidities in different study populations have a significant impact on the on the dyslipidemia in RA patients. After all this work and discussion, it is clearly determined that dyslipidemia is one of major risk factors for CVD in RA population. So, working up for dyslipidemia is very important in RA patients and if it is found significantly abnormal then better treatment options should be applied to control both inflammatory disease and CVD risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Oude Voshaar MAH, Das Gupta Z, Bijlsma JWJ, Boonen A, Chau J, Courvoisier DS, et al. **International consortium for health outcome measurement set of outcomes that matter to people living with inflammatory arthritis: Consensus from an international working group.** Arthritis Care Res (Hoboken). 2019; 71:1556-65.

2. Firestein GS, Budd RC, Gabriel SE, **McInnes IB editors in: Kelly's textbook of rheumatology.** 9th ed. Philadelphia: WB Saunders. 2013; 1059-1181.

3. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. **Rheumatoid arthritis.** Nat Rev Dis Primer. 2018; 4:18001.

4. Kerschbaumer A, Sepriano A, Smolen JS, Heijde DV, Maxime Dougados M, Vollenhoven RV et al. **Efficacy of pharmacological treatment in rheumatoid arthritis: A systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis.** Ann Rheum Dis. 2020; 79:744-759.

5. Ebina K, Hirano T, Maeda Y, Yamamoto W, Hashimoto M, Murata K, et al. **Drug retention of 7 biologics and tofacitinib in biologics-naïve and biologics-switched patients with rheumatoid arthritis: the ANSWER cohort study.** Arthritis Res Ther. 2020; 22:142.

6. Bartels CM, Bell CL, Shinki K, Rosenthal A, Bridges AJ. **Changing trends in serious extra-articular manifestations of rheumatoid arthritis among United State veterans over 20 years.** Rheumatol Oxf Engl. 2010; 49:1670-1675.

7. Letarouilly JG, Flipo RM, Cortet B, Tournadre A, Paccou J. **Body composition in patients with rheumatoid arthritis: A narrative literature review.** Ther Adv Musculoskelet Dis. 2021; 13:1759720X211015006.

8. Engvall I-L, Brismar K, Hafström I, Tengstrand B. **Treatment with low-dose prednisolone is associated with altered body composition but no difference in bone mineral density in rheumatoid arthritis patients: A controlled cross-sectional study.** Scand J Rheumatol. 2011; 40:161-168.

9. Phull A.-R., Nasir B., ul Haq I., Kim S.J. **Oxidative stress, consequences, and ROS mediated cellular signaling in rheumatoid arthritis.** Chem. Biol. Interact. 2018; 281:121-136.

10. Kavanaugh A. **Dyslipoproteinaemia in a subset of patients with rheumatoid arthritis.** Ann. Rheum. Dis. 1994; 53:551-552.

11. Svenungsson E., Fei G.Z., Jensen-Urstad K., De Faire U., Hamsten A., Frostegård J. **TNF-α: A link between hypertriglyceridaemia and inflammation in SLE patients with cardiovascular disease.** Lupus. 2003; 12:454-461.

12. Bag-Ozbek A., Giles J.T. **Inflammation, adiposity, and atherogenic dyslipidemia in rheumatoid arthritis: Is there a paradoxical relationship?** Curr. Allergy Asthma Rep. 2015; 15:1-10.

13. Ferreira HB, Melo T, Paiva A, do Rosário Domingues M. **Insights in the role of lipids, oxidative stress and inflammation in rheumatoid arthritis unveiled by new trends in lipidomic investigations.** Antioxidants (Basel). 2021 Jan; 10(1):45.

14. Erum U, Ahsan T, Khowaja D. **Lipid abnormalities in patients with rheumatoid arthritis.** Pak J Med Sci. 2017 Jan-Feb; 33(1):227-230.

15. Singh H.V., Shrivastava A.K., Raizada A., Singh S.K., Pandey A., Singh N., Yadav D., Sharma H. **Atherogenic lipid profile and highly sensitive C-reactive protein in patients with rheumatoid arthritis.** Clin. Biochem. 2013; 46:1007–1012.

16. Nisar A, Rasheed U, Aziz W, Farooqi AZ. **Prevalence of dyslipidemias in autoimmune rheumatic diseases.** J Coll Physicians Surg Pak. 2012 Apr; 22(4):235-9.

17. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DJ, Bingham C, et al. **Rheumatoid arthritis classification criteria.** Arthritis Rheum. 2010; 62(9):2569-81.

18. **Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel - ATP-III) IV- General Approach to treatment goals and thresholds.** Circulation. 2002; 106(25):3143-3421.

19. Lee SG, Kim JM, Lee SH, Kim KH, Kim JH, Yi JW, et al. **Is the frequency of metabolic syndrome higher in South Korean women with rheumatoid arthritis than in healthy subjects?** Korean J. Intern. Med 2013; 28(2):206-15.

20. Prashanth R. **Cardiac and vascular complications in rheumatoid arthritis.** Reumatologia. 2019; 57(1):27-36.

21. Grover S, Sinha RP, Singh U, Tewari S, Aggarwal A, Misra R. **Subclinical atherosclerosis in rheumatoid arthritis in India.** J Rheumatol. 2006; 33(2):244-47.

22. Hadda V, Handa R, Aggarwal P, Lakshmy R, Kumar U, Pandey RM. **Disease activity and lipids in rheumatoid arthritis: A prospective study.** Indian J Rheumatol. 2007; 2(4):137-40.

23. Ghosh UC, Roy A, Sen K, Kundu AK, Saha I, Biswas A. **Dyslipidemia in rheumatoid arthritis in a tertiary care center in Eastern India--a non-randomized trial.** J Indian Med Assoc. 2009 Jul; 107(7):427-30.

24. Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Therneau TM, Gabriel SE. **Lipid paradox in rheumatoid arthritis: The impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease.** Ann. Rheum. Dis. 2011; 70:482–487.

25. Choy E, Ganeshalingam K, Semb AG, Szekanecz Z, Nur mohamed M. **Cardiovascular risk in rheumatoid arthritis: Recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment.** Rheumatology. 2014; 53:2143-54.

26. Mantel Ä, Holmqvist M, Nyberg F, Tornling G, Frisell T, Alfredsson L, et al. **Risk factors for the rapid increase in risk of acute coronary events in patients with new-onset rheumatoid arthritis: A nested case-control study.** Arthritis Rheumatol. 2015; 67:2845-54.

27. Solomon DH, Reed GW, Kremer JM, Curtis JR, Farkouh ME, Harrold LR, et al. **Disease activity in rheumatoid arthritis and the risk of cardiovascular events.** Arthritis Rheumatol. 2015; 67:1449-55.

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2	Ammad Asghar	Data interpretation.	
3	Aqib Rehman	Introduction.	
4	Badar Bashir	Review.	
5	Tauseef Anwar	Result compilation.	