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Correlation of lipoproteins with Inflammatory Markers and the risk of cardiovascular events in Rheumatoid Arthritis: Case Control Study

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Keywords
Rheumatoid Arthritis, Lipid profile, ESR, CRP, Iraq patients.

Abstract
Nearly 1% of adults suffer with rheumatoid arthritis (RA), a chronic, systemic, inflammatory illness with unclear causes.Numerous researchers found that RA patients had an elevated rate of cardiovascular morbidity and death.Accelerated atherosclerosis is the main cause of cardiovascular mortality.Strong predictors of atherosclerotic events include increased plasma total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C).

The relationship between blood lipoproteins, particularly total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), and several inflammatory indicators, including erythrocyte sedimentation rate (ESR), C-Reactive protein (CRP), as well as the risk of cardiovascular events in rheumatoid arthritis.

The study's control group consisted of 50 RA patients who satisfied the American College of Rhematology's (ACR) 1987 criteria for rheumatoid arthritis and 50 volunteers who seemed to be in good health.Both the patients' and the control group's lipid profiles (TC,LDL-C,HDL-C), ESR, and C-reactive protein were assessed.

When comparing rheumatoid arthritis patients to the control group, the linear regression analysis of CRP and ESR with the serum lipid profile revealed a statistically significant positive correlation (CRP: r=+0.084, p0.05, ESR: r=+0.082, p0.05) for TC and a significant negative correlation (CRP:r=-0.082, p0.05, ESR:r=-0.081, p0.05) for HDL.

The linear regression analysis of CRP and ESR with the serum lipid profile showed a statistically significant positive correlation (CRP:r=+0.084, p0.05, ESR:r=+0.082, p0.05) for TC and a significant negative correlation (CRP:r=-0.082, p0.05, ESR:r=-0.081, p0.05) for HDL when comparing rheumatoid arthritis patients to the control group.

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1. Introduction

Rheumatoid arthritis (RA) is an autoimmune illness that is chronic, debilitating, and has an unclear cause. It affects approximately 1% of adult population. Accelerated coronary artery disease is responsible for almost 50% of mortality in RA patients (Howard et al., 2006; Kaplan et al., 2006).

In individuals with RA, the risk of sudden mortality from myocardial infraction seems to be higher (Anoze and Nassir, 2008). Cardiovascular disease (CVD) may be exacerbated by systemic inflammation through a variety of pathways, including direct effects on endothelial function and indirect effects on lipoproteins (Toms et al ,.2011).

As a separate risk factor for accelerated atherosclerosis, RA has been thought of. In both conditions, immune-mediated inflammatory processes are crucial, and the pathogenesis of the two illnesses is similar in many ways (Nakkem and Szodory, 2010).

CVD in RA is multi-factorial and results from a complex interaction.

Dyslipidaemia in RA appears to be a result of alterations in endothelial cells, hypercoagulation brought on by circulating immune complexes, inflammatory cytokines including tumor necrosis factor (TNF), interleuken 1 (IL1) and IL6, or C-reactive protein (CRP), as well as disease activity (Nurmohamed et al.2011).

2. Epidemiology

Rheumatoid arthritis (RA) is rather common, with a frequency of 0.5-1.0% in various populations. The Pima Indians, however, have a high frequency of RA (5.3%), according to Silman and Pearson (2002).

The prevalence of RA also varies throughout the world. For instance, the incidence appears to be lower in various European nations than in the UK, ranging from (0.1-0.5%) (Symmons et al. 2002).

In a particular rural Black African community where the illness seems to be rare (0.42%). This shift in RA prevalence raises the possibility that RA is related to the way of life found in urbanized regions (Mody, 2009).

As people get older, the frequency of RA rises, and sex disparities disappear. However, the fourth and fifth decades of life are when the beginning occurs most frequently.Weman are impacted almost three times more frequently than men, and these racial disparities may result from the interplay of genetic make-up and environmental stressors (Fauci et al., 2008; Eftekharian et al, 2011).

Studies on lipid profiles in RA patients are conflictingly available. Studies have shown a TC, LDL-C, and HDL-C increase, decrease, or comparable level when compared to control participants (Nurmohamed, 2007). Numerous variables, such as the presence of an inflammatory illness, limited physical activity due to pain and disability, and medication use are likely to influence dyslipidaemia in RA. Although it appears that RA patients with both and have dyslipidaemia.

The purpose of the current study is to determine whether there is any relationship between TC, HDL, and ESR. The relationship between CRP and the risk of cardiovascular illnesses in RA patients.

3. Patients, Materials and Methods

Case-control research is used in this study. Patients with RA who were treated at AL. Ramadi Teaching Hospital made up the research samples. AL.Anbar.Iraq. Those in the control group appeared to be in good health.

3.1. Patients Categorization

The participants in this study were split into two groups.

Group 1:

This group was made up of (50) RA patients from the AL.Ramadi Teaching Hospital who met the 2010 (Aletaha et al., 2010) American College of Rheumatology (ACR)/European League Against Rheumatism(ELAR) criteria of RA. Rheumatology Outpatient Clinic and Inpatient Department. Their ages varied from 30 to 70, with a mean and standard deviation of (49.7010.40) years. Patients with a history of familial dyslipidaemia, diabetes mellitus, hypothyroidism, liver or renal disease, Cushing's syndrome, cancer, or any other ailment that affects the lipid profile were also excluded.

Patients receiving lipid-altering medications, beta blockers, oral contraceptives including estrogen, progesterone, and thyroxin, as well as vitamin E, were also excluded from the research.

Group 2:

There were (50) persons in this control group who appeared to be in good health. The control subjects were chosen among the family members who were accompanying the patients at the rheumatology department. Their ages varied from 30 to 70 years, with a mean and SD of 47.26 and 7.22 years, respectively. These individuals met the identical requirements for the patients group's exclusion.

The participants in the control group did not have any previous history of coronary heart disease. The control group and the study group were matched for age and sex.

3.2. Materials

Materials used in this study are arranged as follow:

1-Speciments.

2-Instrument.

3-Reagents.

3.3. Speciments

Blood samples from both the control group and RA patients who had fasted were taken. The individuals were told to fast for between 12 and 14 hours at night.

Using sterile, disposable syringes, five milliliters of venous blood were drawn from the anti-cubital vein.

In 3 tubes, blood was extracted. Two milliliters were taken and placed in a tube containing EDTA (Ethylene Diamine Tetraacetic Acid). The tube was gently inverted several times to ensure that the anticoagulant and EDTA were mixed, and it was then maintained at room temperature until it was needed for the measurement of EAR within an hour. A total of 3 milliliters of blood were extracted and allowed to coagulate for 15 minutes at 37 degrees Celsius in a water bath. To ensure full serum separation, centrifugation was used for 15 minutes at 3000 rpm. Each serum sample was separated, and

All patients and controls had laboratory testing including TC, HDL, ESR, CRP, and FBS to rule out diabetes, blood urea, and serum creatinine to rule out renal illness.

ECG readings by a cardiologist and ECHO procedures performed by a cardiologist

In order to rule out coronary heart disease in the control group, researchers investigated coronary heart disease in rheumatoid patients.

3.4. Instuments

1-Spectrophotometer,CECiL(Germany).

2-Centrifuge,KOKUSAN(Japan).

3-Incubater-37oc.Memmet(Germany).

4-ECG-MAC-1200(India).

5-ECHO-LoGiQS6(USA).

3.5. Reagents

The selection of reagent used in this study was based on accuracy, reliability, availability and were purchased askits from the following international suppliers and companies:

1-Reagent for serum HDL-cholesterol measurement were supplied by Bio Labo, France.

2-Reagent for serum total cholesterol measurement were supplied by Bio Merieux, France.

3-Reagent for C-reactive protein were supplied by plasmatec/CRP latex test-010/United Kingdom.

4-ESR was measured by the modified Westergen.

4. Methods

1. Using an enzymatic colorimetric technique with a Shimadzu Micro-Flow MeterCL-720, serum total cholesterol was quantified.

2.Separation of serum HDL and determination of cholesterol bound to this feaction (Greg *et al*.,2010).

3.Atherogenic index is calculated by following equeation:

AI=Total serum cholesterol/HDL-c (Georgiadis *et al*.,2006).

4.C-reactive protein was done by using of latex agglutination test for the estimation pf C-reactive protien in human serum sample.

5. Statistics analyses

The independent two-sample T-Test of unequal variances was used to evaluate all the data by the software program Minitab version 14.0, with (P0.05) being considered a significant difference.

6. The Results

One handered subjects wre included in the syudy, (50) RA patients were 42 women (84%) and 8 men (16%) with mean age of 49.70±10.40 years.

The average age of the 50 control healthy participants was 47.26 7.22 years, with 42 women (84%) and 8 males (16%).Age differences between rheumatoid arthritis patients and healthy controls were not statistically significant (P=0.176), and sex distribution differences were likewise not statistically significant (NS) (P=0.793).

Table 1. Comparison between patients with RA and control group regarding Age and Sex.

Parameter	RA patients Mean ± S.D.	Control group Mean ± S.D,	P -value *
Sex(male/female)	8/42	8/42	NS
Age(year)	49.70±10.40	47.26±7.22	NS

* (p>0.05) as no significant difference.
* Independent Two-Sample T-Test was used.

Table 2. C Comparison between patients with RA and control group regarding ESR and CRP.

Parameter	RA patients Mean ± S.D.	Control group Mean ± S.D,	P- value *
C-reactive protein	25.88±25.04	5.18±6.73	S
ESR(mm/hr)	37.24±23.04	18.18±11.06	S

* (p<0.001) as highly significant difference.

7. Serum Total Cholestrol

In comparison to the control group, the patients' findings demonstrated a high mean blood level of cholesterol with a statistically significant difference (P 0.05). The correlation between the serum total cholesterol levels in RA patients and the control group is shown in Table 3.

Table 3. Serum level of total cholesterol

Gruops	Serum level of total cholesterol(mean ± S.D)	P value*
Pateints with RA	3.22±0.82	0.016
Control group	2.82±0.79	

* Independed Two-Sample T-Test was used.

Serum HDL-C:

Patients with RA had lower mean blood levels of HDL-C than patients in the control group, a result that was statistically significant (P 0.05).

The correlation between the serum HDL-C level in RA patients and the control group is shown in Table 4.

Table 4. Serum level of total cholesterol

Gruops	Serum level of total cholesterol (mean ±S.D)	P value*
Pateints with RA	1.01±0.26	0.017
Control group	1.13±0.23	

*Independed Two-Sample T-Test was used.

Atherogenic ratio:

The mean atherogenic ratio of TC/HDL-C was greater in patients with RA than in the control group with a highly significant difference (P0.0001), as shown in table (5) below. This finding was a result of the results regarding total cholesterol and HDL-C discussed above.

Table 5. Serum level of total cholesterol

Gruops	Serum level of total cholesterol (mean ±S.D)	Pvalue*
Pateints with RA	5.29±1.63	0.0001
Control group	4.20±1.11	

*(P<0.0001) as very highly significant difference.

Comparison of TC, CRP, and ESR:

In patients with RA, there was a substantial direct association between blood TC and CRP (r=0.084, p0.05), as shown in Figure 1, and a strong direct correlation between serum TC and ESR (r==+0.087, p0.05), as shown in Figure 2.

Relationship between HDL-C, CRP, and ESR

Serum HDL-C exhibited a strong association with ESR in RA patients (r=0.081, p0.05) and a substantial correlation with CRP in RA patients (r=0.082, p0.05) with an inverse correlation as seen in (Figures 3 and 4).

Figure 1. Correlation between CRP and TC (P=0.042)

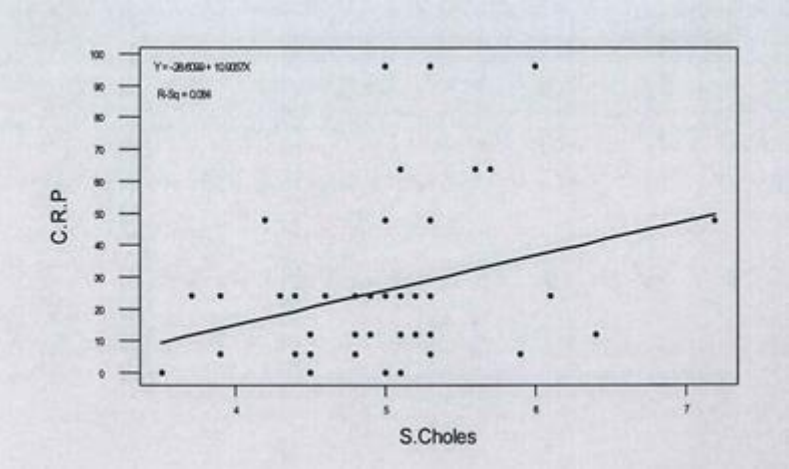


Figure 2. Correlation between ESR and TC (P=0.038)

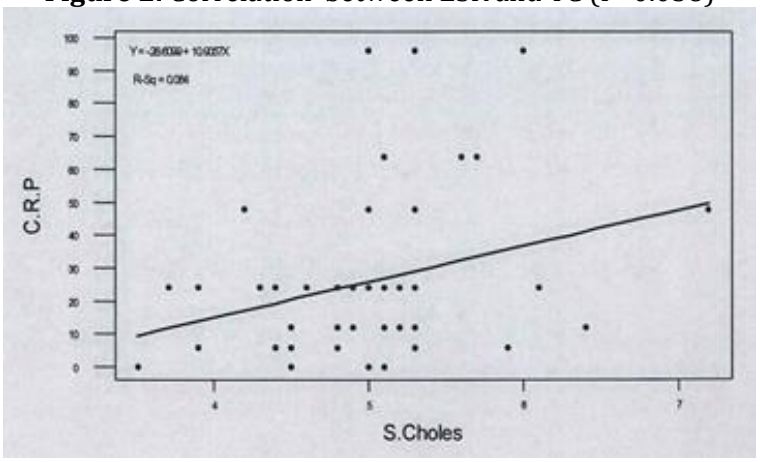


Figure 3. Correlation between CRP and HDL(P=−0.044)

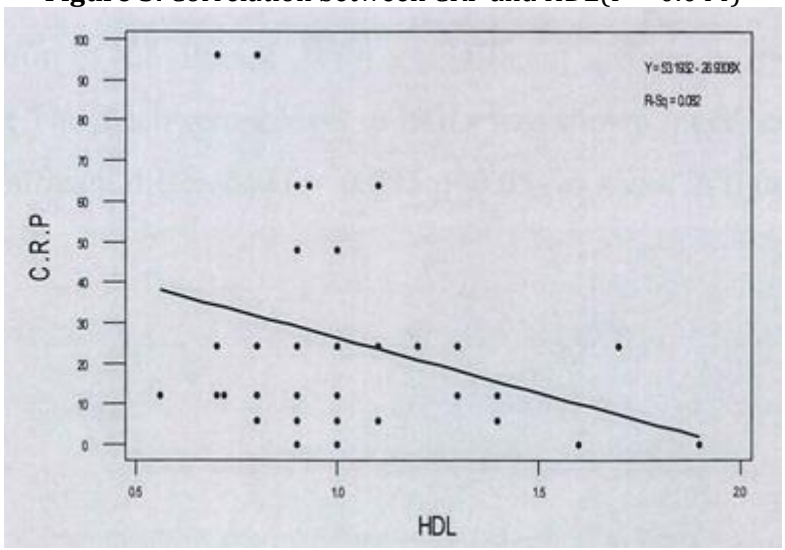
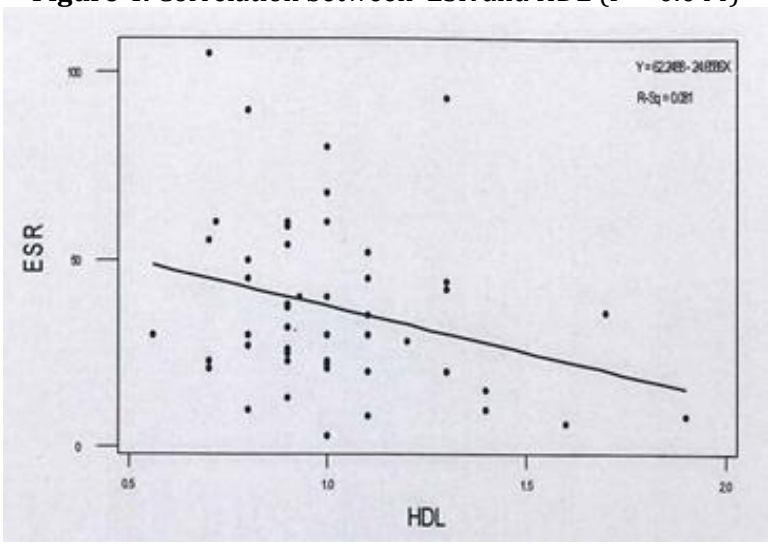


Figure 4. Correlation between ESR and HDL (P=−0.044)



8. Discussion

In this study the ratio of female to male for Rheumatoid Arthritis patients was nearly (5/1). (Table-1), and this agreed with another study (Tore K K *etal*, 2006) reported that the female to male ratio was nearly (5/1). But it disagreed with another one(Fauci *et al.*,2008) reported that the female to male ratio was (2.5/1). The explanation for this difference is that the males were not attending our clinic.

The mean measures for C.reactive protein (CRP) was (25.88±25.04mg/dl) for rheumatoid arthritis patients ranging between (6-128mg/dl) and this result agreed with another study reported that CRP was an inflammatory marker can be followed along with the patient's to monitor disease activity over time (John *et al*., 2008).

When compared to controls, RA patients had higher levels of the inflammatory markers c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR); additionally, ERA patients had a mild dyslipidemia marked by elevated levels of total cholesterol (TC), low density lipoprotein cholesterol (LDLC), and tri glycerides, as well as decreased levels of high density lipoprotein cholesterol (HDLC).Elham A.M. and others (2012(

In several research, the lipid profile of RA patients has been examined.In comparison to the general population, several of these studies have found that patients with active or untreated diseases have lower levels of HDL-C and higher TG/HDL-C ratios.

However, some studies did not find any appreciable differences between lipid levels and those seen in the general population of healthy people, while others reported a general decrease in all lipid sub-fractions in instances with active illness (Georgiadis et al., 2006.(

When RA patients were compared to controls, the current study found a substantial drop in HDL cholesterol levels as well as hypercholesterolemia (P 0.05).(Table-2).Our findings are consistent with those by George Set al. (2008), who found that individuals with RA had significant dyslipidemia in their research.

There is a chance that systemic inflammation contributes to the development of atherosclerosis.In fact, it has previously been established that there has been a rise in acute phase reactant in cardiovascular events.According to Hilal MK et al., there may be a shared predisposing factor for both RA and atherosclerosis.

The fact that RA patients have low HDL serum levels and high TC levels is a significant finding. Figure 1-2 shows a correlation between the increase in TC and the increases in CRP and ESR readings.Figures 3–4 show an inverse relationship between the increase in CRP level and ESR values and the decline in HDL–C; this finding is in line with earlier research (Peters et al., 2010). The correlation between TC with CRP and ESR in active RA patients raises the possibility that cholesterol be used as an activity marker. This finding contrasts with that of another study by Zahra R. et al. (2019), which found that an increase in CRP and ESR levels was associated with a decrease in total HDL-C levels.

Conclusion

The increased cardiovascular risk in rheumatoid arthritis patients may be explained by the fact that our study confirms that RA patients have a more atherogenic lipid profile and that RA-related systemic inflammation influences cardiovascular risk. Furthermore, we demonstrate a link between inflammation and (further) lipid profile degradation. Contrary to predictions, inflammation can only partially account for the observed lipid disparities between rheumatoid arthritis patients and controls. It is still unclear if lipids affect how susceptible people are to developing inflammatory disorders like rheumatoid arthritis.

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