Serum Lipid in Early Rheumatoid Arthritis

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Abstract

Background: Several investigators reported an excess of cardiovascular morbidity and mortality among RA patients. The majority of cardiovascular deaths results from accelerated atherosclerosis.

Elevated plasma total cholesterol (TC) and low –density lipoprotein cholesterol (LDL-C), decreased high – density lipoprotein cholesterol (HDL-C) are strong factors for atherosclerotic events.

Objectives: This study was done to:

1- Show the changes of serum lipid profile in patients with ERA.

2- Explain the pathological role of changing lipid profile in ERA and to demonstrate the changes of atherogenic ratio in ERA patients.

3- Presenting the correlation between lipid profile and different inflammatory markers especially ESR and CRP.

Method: Twenty five patients with ERA who met the American college of rheumatology (ACR) 1987 criteria for rheumatoid arthritis (RA) had early disease with disease duration of less than one year without prior use of disease modifying antirheumatic drugs (DMARDS) and or systemic steroids were examined for their lipid profile level and the relation of the atheroganic ratio to their disease were investigated during the period between March –December 2006 in the department of rheumatology at Al –Kadymia teaching hospital .Lipid profil (TC,LDL-C,HDL –C and TG)ESR and C-reactive protein were determined for both the patients and control groups.

Results: The results of the study revealed that ERA patients exhibited higher serum levels of total cholesterol (TC) low- density lipoprotein cholesterol (LDL) and triglycerides (TG) .Where as their serum high –density lipoprotein cholesterol (HDL –C) levels were significantly lower compared to control .As a consequence the atherogenic ratio of TC /HDL –C as well as that of LDL-C/HDL –C was significantly higher in ERA patients compared to controls and these changes were correlated with laboratory changes especially GRP and ESR .

Conclusion: ERA patients are characterized by an atherogenic profile in comparision with the healthy control subject .Recognition and treatment of early rheumatoid arthritis and reduction of these and other cardiac risk factor has greater impact on the course of the diseases.

Keywords: Lipid profile – rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves joints. Extra – articular features of RA including anemia fatigue subcutaneous (rheumatoid) nodules pleuropericarditis neuropathy sclerities splenomegaly sjogrens syndrome vasculitis and renal disease may occur during the course of the disease [(1)].

There is an increased risk of premature death due to coronary artery disease in patients with RA and there may be an increase risk of heart failure [(2)]. The risk for decreased life expectancy and early cardiovascular mortality in particular, among people with rheumatoid arthritis is increasingly recognized. The increased

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risk of coronary heart disease may precede the onset and diagnosis of RA [3].

The risk in RA for cardiovascular death, thought to be increased more than tow folds over the general population, appears to be independent of the known cardiac risk factors. 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), and decreased high – density lipoprotein cholesterol (HDL-C), high blood pressure, smoking and diabetes mellitus[4].

The risk of sudden death of myocardial infraction appears to be increase in patients with RA. Athermatous plaques in the carotid artery and greater intima – media thickness are two markers that suggest the presences of generalized atherosclerosis.

By these measures, patients with RA have a greater burden of atherosclerotic disease than control .The prevalence of carotid plaques as detected ultrasonographically in patients with RA is correlated with the duration of disease.

- Changes in the endothelium due to circulating immune complexes, cytokines or C-reactive protein [5].
- Ahypocoagulable state due to increased plasma levels of fibrinogen ,von willebrand factor ,plasminogen activator inhibitor -1, and/or other acute phase reactants that correlate with the ESR[6].
- Direct vascular injury due to the dyslipidemia associated with glucocorticoid therapy or rheumatoid vasculitis [7].
- Depletion of circulating endothelial cell progenators [8].

Continued active inflammation as provided by repeated elevation of the erythrocyte sedimentation rate (ESR) to 60mm/hr may be an independent risk factor for cardiovascular death in patients with RA [9, 10].

A concentration of C reactive protein (CRP) 5mg/L may also be an independent risk factor for cardiovascular death [11, 12].

In general, and with some variations between different studies, the lipid profile of patient with active or untreated RA is primarily characterized by a decrease in serum levels of HDL-C where as contrasting result have been published on the serum levels of TC and LDL-C importantly, the reduction in HDL-C has as a consequence the increase in the TC/HDL-C ratio [13, 14]. This ratio represents an atherogenic index which is an important prognostic marker for cardiovascular disease indeed the risk of myocardial infarction increases considerably when this ratio is higher than five and it should ideally be four or less. The serum TC and HDL-C levels in RA are inversely correlated with disease activity suggesting potential role for inflammation in the atherogenic profile and the higher atherosclerotic risk observed in RA [15, 16].

Use of methotrexate and anti-tumor necroses factor (anti-TNF) agents may have a beneficial effect upon cardiovascular morbidity and mortality [17]. Because an increased prevalence of coronary atherosclerois may contribute to the elevated mortality rates of patients with RA the combination of lipid –lowering and anti-inflammatory would be a compelling rationale for the use of statins [18].

Methods

Inclusion criteria: Twenty five patients who met the American college of rheumatology (ACR) 1987 criteria for rheumatoid arthritis (RA) had early disease with duration of less than one year without prior use of disease

modifying antirheumatic drugs (DMARDs) and or systemic steroids were investigated during the period between March –December 2006 in the department of rheumatology at Al Kadhimiya Teaching Hospital.

Smokers or patients suffering from conditions that affect the lipid profile such as diabitus mellitus ,hypothyrodisim liver or kidney disease ,Cushing's syndrome ,obesity (body mass index >30)and a history of familial dyslipidemia ,were excluded . In addition patients receiving medication affecting lipid metabolism such as lipid –lowering drugs,beta blockers ,oral contraceptives estrogen ,progesterone ,thyroxin and vitamine E were excluded from the study . Twenty five apparently healthy, non smoking subjects also participated in the study and were considered as a control group. These subjects fulfilled the same exclusion criteria reported for the patient group. None of the subjects participating in the control group had a history of coronery heart disease. The control group was proportionally matched for age and sex to the patient group.

Overnight fasting blood samples were obtained from both ERA patients and the control groups. Serum lipids were determined within six hours of blood sampling .TC-, triglycerides and HDL –C were determined with enzymatic colorimetric method using shimadzu micro –flow meter CL-720 .LDL-C was estimated using the friedewald formula.

Friedewald formula=serum TC [serum HDL+Serum TG/5] [22]**.**

IgM rheumatoid factor was measured by EELIZA method. ESR was measured by the modified Westergen method. In addition complete blood count with differential, as well as serum glucose, liver and kidney function tests, were performed for all patients.

All data were analyzed by excel programme using the independent t-test of unequal variances considering ($p<0.05$) as significant difference.

Results

During the selection period (March –December 2006),twenty –five patients were included in the study .There were 22 women and 3 men with a mean age of 54.2=\9.6 years and mean disease duration of 0.5+-0.3 years ,The clinical characteristics and lipid profiles of patients and control are described in (Table 1).

1-Serum Total Cholesterol LDL-C and TG

The results of the patients had shown a high mean serum level of cholesterol in comparison to control group with a significant difference ($p<0.05$) as shown in (Table 2).

The mean serum level of LDL-C in patients was higher than the mean serum level of LDL-C in control group .But a non –significant difference ($p>0.05$) as shown in (Table 3).

On the other hand the mean serum TG level in patients was higher than the mean serum TG level in control group. There was a non-significant difference between serum cholesterol level of patients in comparison to that in control group ($p>o.o5$) as shown in (Table 4).

2- Serum HDL-C

The mean serum level of HDL-C in patients with ERA was lower than the mean serum level of control group. With a significant difference ($p<0.05$) as shown in (Table 5) .

3-The Atherogenic ratio

As a consequence of the above mentioned results regarding total cholesterol LDL-C , HDL-C and TG the mean atherogenic ratio of TC HDL-C was higher in patients with ERA than in control group with

significant difference ($p<0.05$) m as shown in (Table 6) .

The LDL-C, HDL-C was also higher in patients with ERA than the control group with a significant difference ($p<0.05$) as shown in (Table 7).

4- Correlation of TC , CRP , HDL-C , ESR

There was a significant direct correlation between serum TC and CRP in patients with ERA ($p<0.05$).

Serum HDL-C had shown a significant correlation in relation to CRP in patients with ERA ($p<0.05$), with an inverse correlation.

Serum TC had a significant correlation to ESR in patients with ERA ($p<0.05$), with a direct correlation as shown in (Figure 3).

Serum HDL-C had a significant correlation with ESR in patients with ERA ($p<0.05$), with an inverse correlation.

Table 1: Comparison between mean values ± standard deviation of patients with ERA and control group

Parameter	Control values ± S.D.	ERA patients values ± S.D.
Sex (male / female)	5/20	3/22
Age (year)	5504 ± 10.4	54.2 ± 9.6
Body mass index (BMI) (Kg/m^2)	25.3 ± 1.8	25.2 ± 2.4
IgM Rheumatoid factor (+/-)	0/0	21/4
C – reactive protein	2.1 ± 0.7	24.4 ± 10.8
ESR (mm/hr)	501 ± 1.7	49.9 ± 11.2
TC (mg/dl)	192.2 ± 18.5	217.9 ± 37.5
LDL (mg/dl)	125.7 ± 14.7	141.2 ± 24.2
HDL (mg/dl)	52.0 ± 5.5	40.5 ± 7.9
TG (mg/dl)	98.3 ± 13.4	133.4 ± 27.5
TC/HDL	3.74 ± 0.7	5.69 ± 1.37
LDL/HDL	205 ± 0.57	4.04 ± 0.9

Table 2: The relationship between Serum Total Cholesterol level in ERA patients and control group

Groups	Serum level of total cholesterol (mean ± S.D.) mg/dl	P value
Patients with ERA	217.9 ± 37.5	0.004
Control group	192.2 ± 18.5	

Table 3: The relationship between Serum LDL level in ERA patients and control group

Groups	Serum level of LDL (mean ± S.D.) mg/dl	P value
Patients with ERA	141.2 ± 24.2	0.07
Control group	125.7 ± 14.7	

Table 4: The relationship between Serum TG level in ERA patients and control group

Groups	Serum level of TG (mean ± S.D.) mg/dl	P value
Patients with ERA	133.4 ± 27.5	1.72
Control group	98.3 ± 13.4	

Table 5: The relation ship between Serum HDL-C level in ERA patients and control group

Groups	Serum level of HDL (mean ± S.D.) mg/dl	P value
Patients with ERA	40.5 ± 7.9	0.009
Control group	52.0 ± 5.5	

Table 6: Atherogenic ratio in ERA patients and control group

Groups	TC/ HDL (mean ± S.D.)	P value
Patients with ERA	5.6 ± 1.3	0.004
Control group	3.7 ± 0.7	

Table 7: LDL/HDL in ERA patients and control group

Groups	LDL/ HDL (mean ± S.D.)	P value
Patients with ERA	4.04 ± 0.9	0.004
Control group	2.5 ± 0.5	

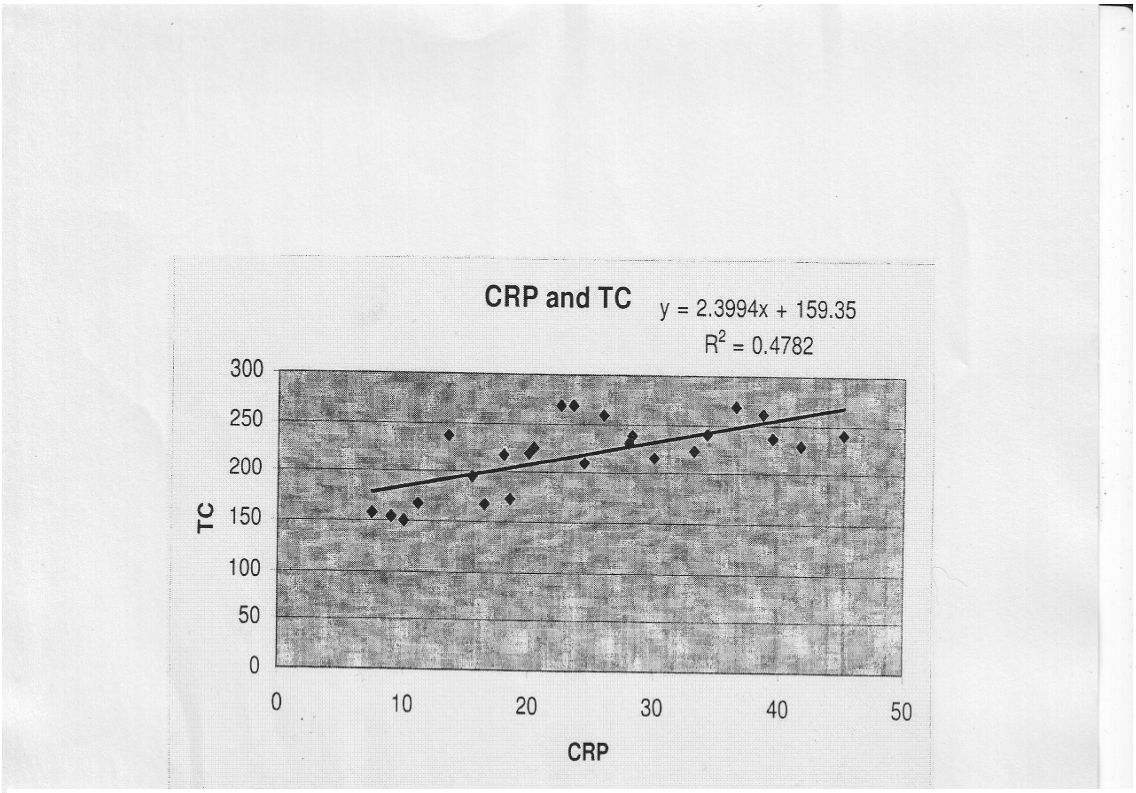

Figure 1: The correlation between CRP and TC in ERA patients.

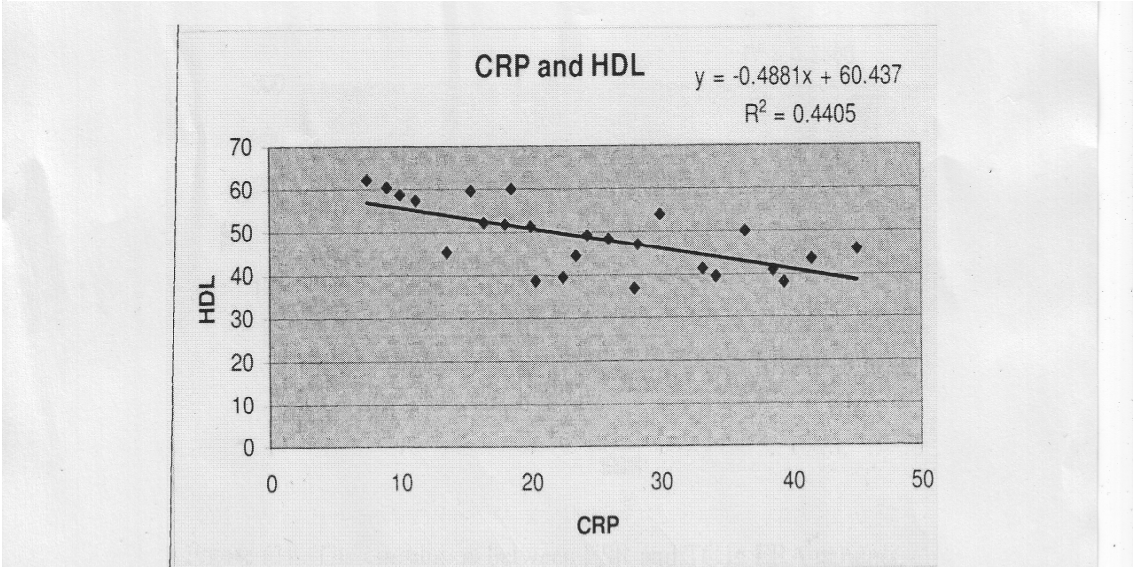

Figure 2: The correlation between CRP and HDL in ERA patients.

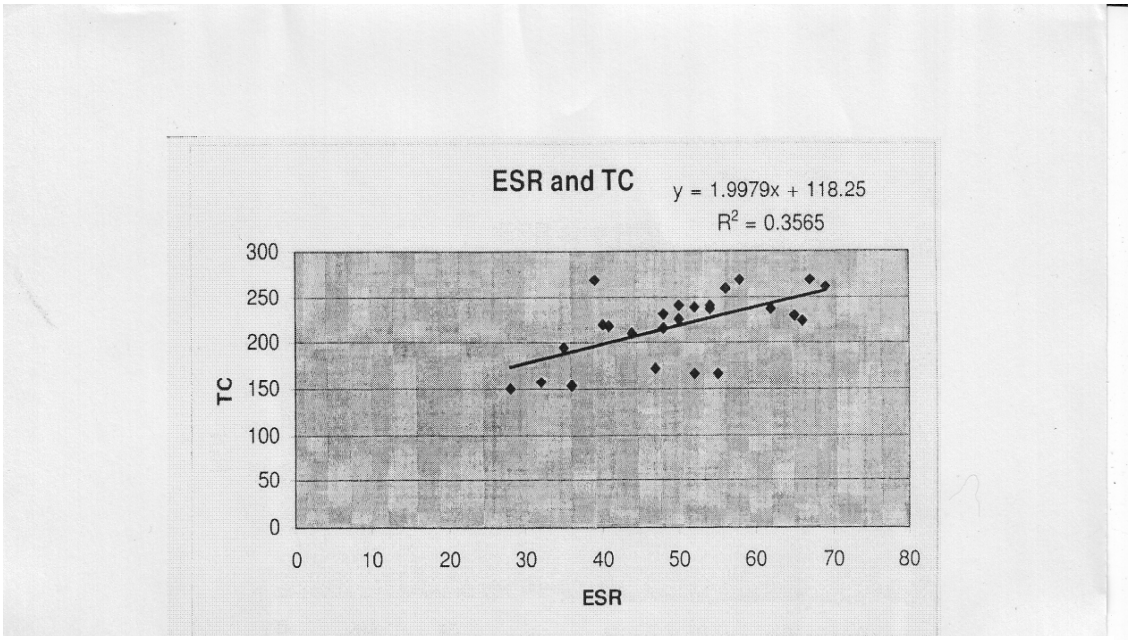

Figure 3: The correlation between ESR and TC in ERA patients.

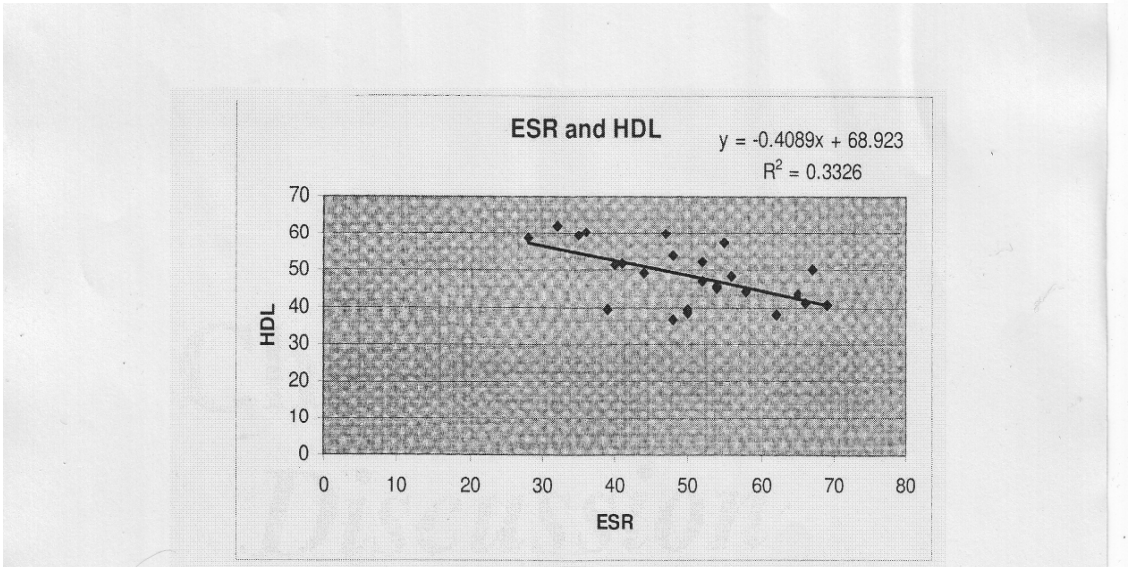

Figure 4: The correlation between HDL and ESR in ERA patients.

Discussion

The objective of this study was to determine the lipid profile of ERA patients had to investigate whether this could be influenced by disease activity in the early stages of rheumatoid arthritis. According to the results, patients with ERA exhibited an atherogenic lipid profile characterized by a significantly reduced serum level of HDL-C and as a sequence an increase in the atheroginic ratio of TC/HDL-C or LDL-C/HDL-C was observed in ERA patients, suggesting that these patients are possibly exposed to a higher risk of atherosclerosis.

The lipid profile of patients with ERA has been evaluated in several studies. Some of these studies have reported lower levels of HDL-C and TC, higher TC/HDL-C and LDL-C/HDL-C ratios in active and/or untreated disease than in general population [19, 20]. On the other hand other studies did not show significantly different lipid levels from those observed in the healthy population [21, 22], while others referred to an overall reduction in all lipid sub-fractions in cases of active disease [23].

These contrasting results may be attributed to the size of the sample, the type of the study (prospective or cross-sectional) and difference in the disease type (established or early) or to difference in disease activity. Patients in remission or with controlled disease show an increase in HDL-C levels and a reduction in the atherogenic index compared to patients with active disease.

Systemic inflammation may also play a role in the development of atherosclerosis [24]. In fact the increase in acute phase reactants in cardiovascular events has already been documented [25]. It has even been suggested that RA and atherosclerosis may share a common predisposing factor [26, 27].

CRP is the common denominator for both diseases CRP which increase in active disease may contribute to atherosclerosis because it stimulates macrophages to produce tissue factor, a procoagulant that is found in atherosclerosis plaques [28, 29]. The presence of CRP in atheromatic lesions also suggests a (cause and effect) relationship between this acute phase reactant and coronary events [30].

An important observation is that ERA patients exhibit low HDL serum levels. The decrement in HDL-C was inversely correlated with the increment of either CRP levels or ESR values. This suggests that inflammation is an important determinant for the reduced HDL-C levels observed in ERA patients. It is possible that RA patients may have some classic risk factors for atherosclerosis development [33, 34]. However it is not correct to attribute the increase prevalence of atherosclerosis observe in RA patients to those factors. In our study, we tried to exclude patients with classic risk factors for atherosclerosis and we found that ERA patients with high disease activity showed an adverse lipid profile before the commencement of therapy.

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