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Assessment of Cardiovascular Risk in Rheumatoid Arthritis and its Relation with Leptin and Interleukin-6

Samar H. Goma[1], Zeinab A. Abd Elhameed[2], Dina A. Mohareb[2], Rania M. Gamal[1], Fatma H. El Nouby[3], Mohamed Raouf Abdel Razek[1], Salma Taha4, Eman H. El-Hakeim[1]

[1]Department of Physical Medicine, Rheumatology and Rehabilitation, Assiut University Hospitals, Assiut, Egypt.
[2]Department of Clinical Pathology, Assiut University Hospitals, Assiut, Egypt.
[3]Department of Physical Medicine, Rheumatology and Rehabilitation, Aswan University Hospital, Aswan, Egypt.
[4]Department of Cardiovascular Medicine, Assiut University Hospitals, Assiut, Egypt.

Abstract—
Objective: In rheumatoid arthritis patients the risk of cardiovascular affection is 2–3 times higher than the general population, with increased morbidity and mortality. This is due to increase in the traditional and nontraditional risk factors. The aim of this study is to determine the cardiovascular risk in patients with RA using four established CV risk algorithms Framingham Risk Score (FRS), Systematic Coronary Risk Evaluation Score (SCORE], Reynolds Risk Score (RRS), Q II Risk Score and there relation with serum levels of leptin and interleukin-6 (IL-6).
Methods: Cross sectional study was conducted during the period between December 2018 and June 2019 Sixty seven RA patients were enrolled in this study. The 10-year CVR for RA patients were calculated using FRS, SCORE, RRS and Q II Risk Score. Serum leptin and IL-6 were estimated.
Results: The results showed a significant difference between higher leptin values and disease activity, obesity, positive RF and longer disease duration, On the other hand, we found a significant difference between higher IL-6 values and disease activity, and hypertriglyceridemia.
As regarding correlations of IL-6 and Leptin with different cardiovascular scores, there were no significant correlations with exception of moderate significant correlation between IL-6 and RRS (r= 0.42, $P< 0.001$).
Conclusion: We found no correlation between CVR scores and leptin or IL-6 except for RRS and IL-6, therefore new models of CVD risk prediction incorporating RA specific variables or imaging techniques are needed.

Keywords— Rheumatoid arthritis (RA), cardiovascular disease (CVD), leptin, interleukin-6 (IL-6).

Introduction

Rheumatoid arthritis (RA) is an autoimmune, chronic inflammatory disease, characterized by destruction to the cartilage and bone due to inflammation and hyperplasia of the synovial membrane and the production of antibodies such as rheumatoid factor (RF), and anti-cyclic peptide antibodies citrullinate. Also, there is systemic affectation, mainly of cardiovascular and pulmonary type[1]. In RA patients the risk of cardiovascular affection is 2–3 times higher than the general population [1, 2], with increased morbidity and mortality[1]. This is due to increase in the traditional and nontraditional risk factors[3].

Risk algorithms which are usually used are developed for the general population and do not give the accurate risk in RA patients and may underestimate the increased risk in RA[4]. In this study we used the frequently used risk algorithms to estimate the cardiovascular risk in RA patients which are; the Framingham risk score (FRS)[5], the Systematic Coronary Risk Evaluation score (SCORE) [6], the Reynolds risk score (RRS)[7], and the Q II risk score[8]. SCORE and FRS are based on traditional risk factors, so, may underestimate the CV risk in RA [9] asinflammation may account for the extra risk[10]. Modified SCORE is a score recommended by the European League Against Rheumatism (EULAR) in which the risk factor of the SCORE is multiplied by 1.5 when a patient fulfils two out of three criteria; disease duration >10 years, rheumatoid factor or ant cyclic citrullinated peptide positivity and presence of extra-articular manifestations[11], but this M-SCORE has not been validated and there are studies that shown that this multiplication factor does not significantly improve the prediction risk[12-14]. Also, modified SCORE overestimate the CVD of RA patients which may be harmful as patients receive unnecessary treatment. However, overestimation of CVD risk mostly affect intermediate-risk to high-risk patients, in which case overestimation would only confirm treatment indication[15].

The RRS included high-sensitivity C reactive protein (hs-CRP) inflammatory marker in addition to traditional risk factors [7]. However, it is not clear if adding hs-CRP to the algorithm improves the prediction of the risk as patients with RA may retain high levels of CRP during the course of the disease[4]. Hippisley-Cox et al. have updated a version of the Risk algorithm where RA is included as an independent risk factor it is called Risk II[8].

Pro-inflammatory cytokines such as leptin and interleukin-6 [IL-6] play an important role in the development of cardiovascular risk[16]. Adipokines secreted by adipose tissue e.g. leptin are involved in inflammation and endothelial damage which plays a role in the development of CVD, independently associated with the development of atherosclerosis[3]. Also, IL-6 levels cause increase in triglycerides and lipolysis of adipose tissue which affects the lipid profile[17].

The aim of this study is to determine the cardiovascular risk in patients with RA using four established CV risk algorithms (FRS,SCORE, RRS and QII Risk) and their relation with serum levels of leptin and IL-6.

Material and Methods

This cross sectional study was conducted at department of Physical Medicine, Rheumatology and Rehabilitation, Assiut University Hospitals, Assiut, Egypt.

Sixty seven RA patients were enrolled in this study during the period between December 2017 and June 2018 diagnosed according to ACR/EULAR 2010 criteriafor the classification of RA[18].

All patients gave informed written consent and the study was approved by Ethical Medical Committee of Assiut University Hospitals, Assiut, Egypt according to the guidelines of the Helsinki Declaration.

Inclusion criteria included adult patients <18 years with disease duration >1 year. Exclusion criteria included patients with history of CV affection before the start of the study.

Data collection

History of age (years), gender, smoking status, family history of CVD, history of diabetes mellitus, history of hypertension and use of statins and/or antihypertensive medication was taken. Also history of the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) [methotrexate, hydroxychloroquine] and corticosteroids was taken. Measurement of blood pressure (mm Hg), height (m), weight (kg).Body mass index [BMI] was calculated using the formula weight/height2 (kg/m2) were the underweight range< 18.5

kg/m2, normal range 18.5–24.9 kg/m2, overweight range 25–29.9 kg/m2, and obese range > 30 kg/m2
Positive rheumatoid factor, ESR, hs-CRP were estimated for all patients. Disease activity score 28-joints using ESR was calculated. Lipid profile was measured where total cholesterol (mmol//L), high-density-lipoprotein, low-density-lipoprotein and triglycerides were measured.

Risk algorithms

The 10-year CVR for RA patients were calculated using the 4 frequently used algorithms FRS, SCORE, RRS4 5 and QII Risk score.

Laboratory investigations

Blood samples:

Six ml blood was withdrawn after 12-14 hours fasting and was divided into:

■ Two ml blood into EDTA tube, for peripheral haemogram and ESR.

■ Four ml blood for separation of serum, was divided into aliquots for routine and special investigations

I.Routine investigations:

Serum blood glucose level, kidney function test and complete lipid profile.

II.Special investigations:

1. High sensitive C reactive protein (hsCRP)
2. Human interleukin 6 (IL-6)
3. Leptin

hsCRP:

Was done by ELISA test with Oxis International Inc. and normal level considered from 0.068 to 8.2 mg/L.

IL-6:

Was done by ELISA test with SinoGeneClon Biotech co.and normal level considered from 0.2 -0.8 ng/L.

Leptin

Was done by ELISA test with Diagnostics Biochem Canada Inc. and normal level considered from 3.7-11.1 ng/ml for women and 2.0-5.6 ng/ml for men.

Principle:

ELISA based on the principle of a sandwich immunoassay. The assay uses two highly specific monoclonal antibodies for detection of tested antigen; one antibody is immobilized into the micro plate and the other one is labeled to form a sandwich complex (Ab-Ag-labeledAb).Absorbance is measured spectrophotometrically at 450 nm.

Statistical analysis

Data was collected and analyzed those using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in form of mean ± SD or median (range) while nominal data was expressed in form of frequency (percentage).

Chi²-test was used to compare the nominal data of different groups in the study while student t-test was used to compare mean of different two groups and ANOVA test for more than two groups in case of normally distributed data while Mann-Whitney and Kruskal Wallis tests were use in case of not- normally distributed data. Spearman correlation was used to determine the correlation between IL- 6, Leptin and different scores with other continuous variables in the current study. *P* value was considered significant if < 0.05.

Results

Sixty seven patients with rheumatoid arthritis were enrolled in this study. Mean age of studied patients was 47.94 ± 10.58 years with range between 30 and 73 years and majority (92.5%) of them were females. As regarding smoking status, 36 (53.7%) of the patients were passive smoker. Mean body mass index was 28.13 ± 6.36 kg/m^2 while mean waist circumference was 94.34 ± 18.64 cm. Normal body mass index presented in 19 (28.2%) patients, while 27 (40.3%) patients were overweight and 21 (31.3%) patients were obese.

As regarding disease activity; 4 (6%), 36 (53.7%) and 26 (38.8%) patients had low, moderate and high disease activity respectively while only one patient was on remission. Disease duration ranged between 1.5 and 30 years with median duration was 8 years.

The most frequent traditional risk factors for CVD were age> 40 years (74.6%) and body mass index> 30 kg/m^2 followed by passive smoking (53.7%). It was noticed that majority of patients had DAS-28 ESR>2.3, positive RF, IL-6 ≥ 5 pg/ml and leptin ≥ 17 ng/ml. Other characteristics of patients were summarized at Table 1. Laboratory data of RA patients were summarized in table 2.

Serum leptin concentrations and CVR factors were compared. The results showed a significant difference between higher leptin values and disease activity, obesity, positive RF, smoking, male sex, and longer duration, similarly, a significant association was found between lower concentrations of leptin and consumption of hydroxychloroquine. Details of the baseline laboratory were shown at Table 3.

On the other hand, serum IL-6 concentrations and CVR factors were compared, finding a significant difference between higher IL-6 values and disease activity, and hypertriglyceridemia. Likewise, a significant difference was found between lower concentrations of IL-6 and the use of hydroxychloroquine as shown in table 4.

As regarding correlations of IL-6 and Leptin with different cardiovascular scores, there were no significant correlations with exception of significant correlation between IL-6 and RRS (r= 0.42, *P*< 0.001) table 5 and figure 1.

Discussion

Cardiovascular disease in RA patients is 30% higher than general population[19] with increased mortality rate 30-50%[20]. Our study showed that age ranged from 30-73 years with a mean ±SD 47.94±10.58. Age is considered an important predictor of CVD mortality in the general population. Most models include patients over 40 years old but it should be noted that for RA the age of onset is usually lower[21], also there is an evidence that CVD events are more often seen within the first 7 years of the disease onset and mortality is higher in the elderly [22].

Although RA is a chronic disease and cachexia is highly prevalent, most of our patients were overweight (40.3%) and obese (31.3%). There is evidence that a high body mass index is linked to a lesser disease burden[23]. Our results showed that there was significant correlation between serum level of leptin and BMI (p<0.02). RA is a disease which is associated with loss of body cell mass or rheumatoid cachexia.[24]. However, researches on body composition has drawn attention to excess fat mass or obesity in RA[25]. In fact, the loss of body cell mass is usually accompanied by increased fat mass, leading to a type of cachectic obesity in RA [26]. There is altered fat distribution in body composition measurements in patients with RA with clear shift to the abdominal region and a parallel decrease in lean mass [27].

In a case–control study they found that women with RA have increased visceral (intra-abdominal) adipose tissue[28]. Fat accumulation in the android or abdominal region refers to abdominal fat that can be subcutaneous or visceral fat[29]. It is well demonstrated that visceral fat, rather than subcutaneous fat, is a major predictor of adverse CVD[29,30].

Our study showed correlation between leptin and patients with positive rheumatoid factor. This was also found by (Batún-Garrido, 2018)[16] and (Abdalla, 2014)[31] who found that seropositive patients were 51.5 and 25.27 respectively while seronegative patients were 23.5 and 24.57 respectively. On the other hand another two studies found no significant correlation [32,33].

Our results showed that there was significant correlation between serum leptin levels and DAS 28($p<0.04$). These results were similar to that found by 2 meta-analyzes who reported association between leptin and disease activity [34,35].

We found inversely proportional association between serum leptin levels and hydroxychloroquine ($p<0.02$). This was also reported by[16], but (Engvall, 2010)found that leptin concentrations increased in patients treated with hydroxychloroquine; these results are opposite to ours[36].

As regarding IL-6 we found significant correlation between it and hypertriglyceridemia ($p<0.02$) and DAS28 ($p<0.001$). These results similar to that found by (Batún-Garrido, 2018)[16]. Also we found positive correlation between IL-6 and hydroxychloriquine ($p<0.02$). Similarly, (Silva, 2013) found that hydroxychloroquine decreased levels of proinflammatorycytokines such as IL-1, TNF, and IL-6 in patientswith lupus systemic erythematosus and RA[37]. As regarding correlations of IL-6 and Leptin with different cardiovascular scores, there were no significant correlations with exception of significant correlation between IL-6 and RRS ($P< 0.001$).

In a study on European RA patients, there was an overestimation of (Risk II) and underestimating (SCORE, FRS, RRS) the risk of future CV events[4]. This underestimation was most pronounced in the lower two-thirds of predicted CV risk, in line with the underestimation of CV events by FRS and RRS in patients with RA from northern America[38]. Under estimation of CVD is probably because RA is considered chronic multisystem disease[39,40]. This underestimation is presented in low and intermediate risk groups[41]. In high-risk patients, control of risk factors is recommended [11, 42] as the traditional risk factors eg. BMI, lipid profile, smoking, diabetes or hypertension or risk factors related to RA eg. Inflammation, disease activity, RF or ACCP positivity and treatment related risk factors[41].

Another study published in 2013concluded that the SCORE, RRS, FRS and QRisk II algorithms tend to either underestimate or overestimate CV risk in alarge portion of the RA population and provide less accuratepredictions of CV risk in the RA population, compared withresults reported in the general population. Underestimating CVrisk may lead to insufficient treatment of (traditional) CV risk factors[15].

Conclusion

We did not find correlation between CVR scores and leptin or IL-6 except for RRS and IL-6. Current evidence suggests that addressing CVD risk in rheumatoid arthritis with general population models of prediction is of limited interest. New models of CVD risk scores prediction incorporating RA specific variables or imaging techniques are needed to develop risk algorithm specific to RA patients by adding factors that is related to disease pathogenesis and inflammation e.g. carotid ultrasound.

Conflict of interest

Authors declare that there is no conflict of interest.

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Table 1: Characteristics of the cardiovascular risk factors of studied patients

Variables	Frequency (percentage)
Traditional cardiovascular risk factors	
Age > 40 years	50 (74.6%)
Body mass index> 30 kg/m^2	46 (68.7%)
Diabetes mellitus	7 (10.4%)
Hypertension	17 (25.4%)
Male sex	5 (7.5%)
Glucose ≥ 100mg/dl	25 (37.3%)
Cholesterol ≥ 200 mg/dl	16 (3.9%)
LDL ≥ 130 mg/dl	14 (20.9%)
HDL (< 40 mg/dL women or < 50 mg/dL men)	25 (37.3%)
Triglyceride≥ 150 mg/dl	14 (20.9%)
Passive smoking	36 (53.7%)
Disease related cardiovascular risk factors	
DAS-28 ESR> 2.3	41 (61.2%)
Duration of illness > 10 year	30 (44.8%)
Use of glucocorticoids	17 (25.4%)
Positive RF	36 (53.7%)
IL-6≥5 pg/ml	37 (55.2%)
Leptin≥17 ng/ml	37 (55.2%)
Use of methotrexate	
Use of hydroxychloroquine	20 (29.8%)
	47 (70.1%)

Data was expressed in form of frequency (percentage).**LDL,** low density lipoproteins; **HDL**, high density lipoproteins; **DAS-28 ESR**, disease activity score-28 Erythrocyte Sedimentation Rate; **RF**, rheumatoid factor; **IL**, interleukin- 6

Table 2: Laboratory data of RA patients

	N= 67
Red blood cells (x10^9/l)	4.49 ± 0.51
Total leucocytic count (x10^9/l)	6.55 ± 2.31
Hemoglobin	11.47 ± 1.38
Platelets	84.52 ± 79.48
ESR	39.61 ± 24.37
HsCRP	7.27 ± 4.91
RBS	5.6 ± 1.98
Positive RF	36 (53.7%)
Urea	4.51 ± 1.81
Creatinine	59.32 ± 15.32
Lipid profile	
Cholesterol	180.64 ± 30.61
LDL	103.91 ± 33.67
HDL	46.05 ± 13.14
TG	116.41 ± 68.05
Cholesterol/ HDL ratio	4.17 ± 1.35
Leptin (ng/ml)	20.8 (2.5- 160)
IL- 6 (pg/ml)	8 (0.5- 41)

Data was expressed in form mean (SD), median (range), frequency (percentage). **ESR**, erythrocyte sedimentation rate;**HsCRP**, high sensitive C- reactive protein; **RBS**, random blood sugar; **RF**, rheumatoid factor; **LDL**, low density lipoprotein; **HDL,** high density lipoprotein; **TG**, triglyceride; **IL-6;** interleukin- 6

Table 3: Relationship betweenserum leptin levels andcardiovascular risk factors

Variables	**Serum concentrations of leptin (ng/ml)**		***P***
	Yes	**No**	
Age > 40 years	25.25 (2.50-160)	9.8 (2.7-116)	0.05
Body mass index> 30 kg/m^2	39.1 (2.50-160)	18.15 (3-116)	**0.02**
Diabetes mellitus	28.40 (10.60-120)	20.30 (2.50-160)	0.29
Hypertension	28.40 (4- 120)	19.3 (2.50-160)	0.26
Male sex	4 (2.50- 24.80)	23.8 (2.70-160)	**0.02**
Glucose ≥ 100 mg/dl	19.8 (2.50-116)	23.8 (2.70-160)	0.66
Cholesterol ≥ 200 mg/dl	31.75 (8.60-98.50)	18.10 (2.50-160)	0.05
LDL ≥ 130 mg/dl	28.75 (2.70-98.50)	18.8 (2.50-160)	0.34
HDL*	28.40 (28.40-160)	20.30 (2.50-160)	0.83
Triglyceride≥ 150 mg/dl	30.1 (6.60-120)	18.8 (2.50-160)	0.06
Passive smoking	21.35 (2.70-160)	19.80 (2.50-130)	**0.01**
DAS-28 ESR > 2.3	31.20 (2.70-160)	18.8 (2.50-130)	**0.04**
Duration of illness > 10 year	31.50 (2.70-130)	17 (2.50-160)	**0.04**
Use of glucocorticoids	25.25 (3- 160)	16.40 (2.50-116)	0.32
Positive RF	25.70 (2.70-160)	18.95 (2.50-120)	**0.03**
Use of methotrexate	22.80 (2.70-71.10)	18.80 (2.50-160)	0.76
Use of hydroxychloroquine	18.20 (2.70-130)	28.40 (2.50-160)	**0.02**

Data was expressed in form of median (IQR).*P* value was significant if < 0.05. * HDL< 40 mg/dL in case of women or < 50 mg/dL in case of men. **LDL,** low density lipoproteins; **HDL**, high density lipoproteins; **DAS-28 ESR**, disease activity score-28Erythrocyte Sedimentation Rate; **RF**, rheumatoid factor; **IL**, interleukin- 6

Table 4: Relationship between IL- 6 levels andcardiovascular risk factors

Variables	Serum concentrations of IL- 6		*P*
	> 5 pg/ml (n= 37)	< 5 pg/ml (n= 30)	
Age > 40 years	31 (83.8%)	19 (63.3%)	0.05
Body mass index> 30 kg/m^2	24 (64.9%)	22 (73.3%)	0.31
Diabetes mellitus	4 (10.8%)	3 (10%)	0.61
Hypertension	9 (24.3%)	8 (26.7%)	0.52
Male sex	2 (5.4%)	3 (10%)	0.40
Glucose ≥ 100 mg/dl	15 (40.5%)	10 (33.3%)	0.36
Cholesterol ≥ 200 mg/dl	12 (32.4%)	4 (13.3%)	0.06
LDL ≥ 130 mg/dl	9 (24.3%)	5 (16.7%)	0.32
HDL*	12 (32.4%)	13 (43.3%)	0.83
Triglyceride≥ 150 mg/dl	12 (32.4%)	2 (6.7%)	**0.02**
Passive smoking	19 (51.4%)	17 (56.7%)	0.42
DAS-28 ESR> 2.3	28 (75.7%)	13 (43.3%)	**<0.001**
Duration of illness > 10 year	14 (37.8%)	16 (53.3%)	0.15
Use of glucocorticoids	7 (18.9%)	10 (33.3%)	0.14
Positive RF	18 (48.6%)	18 (60)	0.25
Use of methotrexate	13 (35.1%)	7 (23.3%)	0.21
Use of hydroxychloroquine	24 (64.9%)	23 (76.7%)	**0.02**

Data was expressed in form of frequency (percentage).*P* value was significant if < 0.05. * HDL< 40 mg/dL in case of women or < 50 mg/dL in case of men. **LDL,** low density lipoproteins; **HDL**, high density lipoproteins; **DAS-28 ESR**, disease activity score-28Erythrocyte Sedimentation Rate; **RF**, rheumatoid factor; **IL**, interleukin- 6

Table 5: Correlations of different scores with IL-6 and leptin

Scores	Il- 6		Leptin	
	r	*P*	r	*P*
FRS	0.16	0.23	-0.03	0.79
RRS	**0.42**	**< 0.001**	0.03	0.78
QRisk II	0.07	0.52	-0.01	0.91
SCORE	0.06	0.62	-0.15	0.21

Data was expressed in form of r (indicated to strength of correlation), *P* (indicated to significance of correlation). **FRS**, Framingham risk; **RRS**, Reynolds risk score; **SCORE,** Systematic Coronary Risk Evaluation

Figure 1: Correlation of RRS with IL-6