Research Article

The Relationship between Insulin resistance and Disease Activity in Rheumatoid arthritis patients

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Abstract
Background: chronic inflammatory disorders such as rheumatoid arthritis are associated especially active disease are associated with disturbed glucose and lipid metabolism, this underlying metabolic disorders such as insulin resistance. **Objectives**: The aim of this study was to determine insulin resistance and its relation to disease activity in patients with RA. **Methods:** Sixty RA patients fulfilling the 2010 ACR/EULAR RA Classification Criteria were included in the study. Thirty age- and sex-matched healthy volunteers were enrolled as the control group. All subjects underwent full history taking, clinical examination. BMI was calculated. Waist/hip ratio was measured. RA disease activity was assessed by DAS28-ESR. The following laboratory investigations were done for all patients and control: HbA1c, lipid profile and insulin. Insulin resistance was assessed with the HOMA Index. Echocardiography for cardiac abnormalities. **Results**: The frequency of cardiovascular (CV) involvement in our RA patients was 11.6% with echocardiography. Patients had higher insulin resistance than controls with no statistically significant difference. RA patients with CV involvement showed increased disease activity in comparison with patients without CV involvement, and no significant difference in insulin levels nor resistance between them. **Conclusions:** Rheumatoid arthritis has higher insulin resistance than controls, with no correlation to disease activity.
Key words: Rheumatoid arthritis, insulin resistance

Introduction
Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease that affects the small joints of the body. It is primarily characterized by bilateral symmetrical poly-articular arthritis, which is often erosive[1].

Rheumatoid arthritis (RA), especially active disease, is associated with considerable changes in body composition, lipid profile, adipokines and insulin sensitivity. Metabolic changes, such as increased total cholesterol, LDL cholesterol and triglyceride levels, occur even in preclinical RA. Active RA is associated with decreased lipid levels, BMI, fat and muscle mass, as well as altered lipid profiles[2].

Epidemiologic studies suggest that RA is an independent risk factor for CVD[3] RA increases the risk of cardiovascular (CV) mortality by up to 50% compared with the general population. Inflammation has consistently been shown to be a major CV risk factor. Thus, compared with the general population, the increase in CV events in RA appears to be a feature of the systemic inflammation associated with RA disease activity A 'lipid paradox' has been

described, such that low total cholesterol and LDL cholesterol levels in patients with RA are associated with increased cardiovascular risk[4].

Aim of the work
The aim of this study was to assess insulin resistance in patients with rheumatoid arthritis and to evaluate its relation to disease activity.

Patients and methods
This study included 60 adult rheumatoid arthritis patients 53 female patients (88.3%) and 7 male patients (11.7%) males. Control and RA patients with known atherosclerotic compli-cations such as stroke and MI, those undergoing hemodialysis, patients with peripheral vascular disease, malignancy, or infections; hyper-tensive, diabetic patients, and smokers were excluded. RA patients group subdivided accor-ding to CV involvement into two groups:

Group1A patients with CV involvement and Group 1B patients without CV involvement.

The nature of the study was explained to all patients. The laboratory procedures represent standard care and pose no ethical conflicts. A consent was obtained from all patients.

All patients were subjected to detailed medical history and complete physical examination. Laboratory investigations were performed for all patients including CBC, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), RF, anti CCP antibodies, lipid profile and serum insulin level. Insulin resistance will be assessed with the Homeostasis Model Assessment (HOMA) Index (plasma glucose (mol/l) x plasma insulin (mU/l)/22.5)[5]. Echo-cardiograph will be performed by a cardiologist. Disease activity was assessed using DAS28-ESR.

Statistical analysis

Analysis of data was done by personal computer using SPSS (Statistical program for social science) version 20. The data of all software patients and controls were fed into an IBM personal computer. Data were expressed as mean ± SD for parametric variables and as number and percent for non-parametric variable. Comparison between groups for parametric data was done by independent samples t-test (unpaired t-test). Chi – square ($\chi 2$) test was used to compare qualitative variables. The difference was expressed as probability of value (P value). The difference was considered significant if $P < 0.05$. Pearson and Spearman correlation coefficients (r) were calculated for detection of parametric and non-parametric correlations respectively.

Results

Demographic data of the studied patients:

This study included 60 adult rheumatoid arthritis patients 53 female patients (88.3%) and 7 male patients (11.7%) males**.** Their age ranged from 24 to 64 years with a mean of 47.0 ± 9.5 years. the duration of illness ranged from 1 to 25 years with a mean of 6.27 ± 5.89. Age at onset ranged from 18 to 61 years with a mean of 40.92 ± 10.28. Thirty healthy age and sex matched persons (73.3% females, the mean of age was 45.50 ± 8.72 years) were recruited to serve as controls.

Demographic characteristics of all the studied RA patients are shown in (Table 1).

Anthropometric measurements (Table 2):

Body Mass Index (BMI) of RA patients ranged from 18.6 to 48.8 with a mean of 27.41 ± 4.84 and was classified into: 0 (0%) underweight, 19 (31.7%) normal patients, 26 (43.3%) over-weight patients, 11 (18.3%) obese patients and 4 (6.7%) extremely obese patients (figure 3.3). Waist / hip ratio ranged from 0.6 to 1.0 with a mean of 0.73 ± 0.12 in female patients (normal value 0.8) and ranged from 0.6 to 0.9 with a mean of 0.72 ± 0.11 in male patients (normal value 0.9).

Clinical characteristics of RA patients:

The most frequent joints involved were MCP joints in 43 patients (71.6%) and PIP joints in 30 patients (50%). The least prevalent one was acromioclavicular joints in 2 patients (3.33%) and sternoclavicular joints in 1 patient (1.66%). Morning stiffness was present for more than one hour in 9 (25%) patients. Constitutional symptoms were present as fever in 18 (30%) patients, myalgia in 35 (58.3%) patients and weight loss > 10% in 4 (6.7%) patients. Extra-articular manifestations in the form of gastritis in 14 (23.3%) patients, dysuria in 4 (6.7%) patients, dry eyes in 31 (51.7) patients, chest pain in 2 (3.3%) patients, dyspnea in 18 (30%) patients and palpitation in 15 (25%) patients. Disease activity score 28 ranged from 1.2 to 7.00 with a mean of 3.75 ± 1.48 (Table 3).

Laboratory data for the studied RA patients (Table 4):

Erythrocyte sedimentation rate 1st hour ranged from 10 to 66 mm/ hour with a mean of 33.75 ± 15.08. Serum C-reactive protein (CRP) ranged from 1.4 to 11.5 mg/l with a mean of 7.51 ± 2.8. Rheumatoid factor (RF) was positive in 43 patients (71.6%), while Anti-citrullinated peptide antibody (ACPA) was positive in 11 patients (18.3%). Hemoglobin A1c was within the normal range in all RA patients, it ranged from 4.1 to 5.8 % with a mean of 4.86 ± 0.47. Insulin level ranged from 4.4 to 81 uIU/ml with a mean of 13.83 ± 12.44. There was an increasing in insulin resistance in 34 (72.3%) female patients, that were above the upper normal value of homeostatic model assessment of insulin resistance level (HOMA-IR) with a mean of 4.32 ± 5.05 {normal value < 2.5}. There were 5 (55.6%) male patients that were above the upper normal level of HOMA-IR with a mean of 3.56 ± 2.17 {normal value < 2}.

As regard the lipid profile: there was slight increase in cholesterol levels as they ranged from 105 – 239 mg/dl with a mean of 150.83 ± 30.08, triglyceride levels ranged from 40 to 244 mg/dl with a mean of 84.37± 38.94. The level of LDL ranged from 44 to 161 mg/dl with a mean of 96.80 ± 24.44. There was a marked decrease in HDL level as its range was 24-55 mg/dl with a mean of 35.3 ±7.49.

Echocardiographic findings of RA patients (Table 5):
Cardiovascular involvement detected in 7 patients (11.6%), mild increase in pulmonary artery systolic pressure (PASP) detected in 4 patients (6.6 %) and valvular heart diseases found in 3 patients (5%). Pericardial effusion or regional wall motion abnormalities (RWMA) could not be detected. The ejection fraction was normal in all patients.A comparison of serum Resistin between patients and controls showed a high significant difference between the patients and the controls (P< 0.001).

Comparison between RA patients (group 1A) and control group (group 1B):
There was a statistically significant difference between RA patients and control group as regards HbA1c (P <0.05) while, not in insulin resistance.

Comparison between patients' subgroups according to cardiovascular involvement:
Patients of group 1A had longer duration of illness and more active disease. There was no a significant difference in HbA1C and insulin level. According to lipid profile there was no statistical significant between two groups apart from HDL (P < 0.05*). We found an insulin resistance in 18 (66.7%) in patients of group (1A) and in 21 (63.6%) patients of group (1B) with no statistically significant difference (P = 0.807)

Conclusion
Rheumatoid arthritis especially active disease associated with increased insulin resistance. However, before finale judgment we recommend further studies with larger study population. Also add more parameters for assessment of cardiovascular involvement such as carotid intimal medial thickness for more accurate correlation with insulin resistance.

Table 1: Demographic data

	RA patient (N=60)
	Mean ± SD N (%)
Age (years)	47.03 ± 9.52
Sex	Females 53 (88.3%)
	Males 7 (11.7%)
Duration of illness	6.27 ± 5.89
Age at onset	40.92 ± 10.28

Table 2: Anthropometric measurements of RA patients

BMI (kg/m^2)	**Range**		18.6 – 48.8
	Mean ± SD		27.41 ± 4.84
	BMI Classification	**Under weight (N, %)**	0
		Normal (N, %)	19 (31.7%)
		Overweight (N, %)	26 (43.3%)
		Obese (N, %)	11 (18.3%)
		Extreme obese (N, %)	4 (6.7%)
Waist / hip ratio	**Range**	**Male**	0.6 – 0.9
		Female	0.6 – 1.0
	Mean ± SD	**Male**	0.72 ± 0.11
		Female	0.73 ± 0.12

Table 3: Clinical characteristics of RA patients

		Patients (No = 60)
Morning stiffness > 1 hour	**(N, %)**	9 (25%)
Constitutional symptoms	**Fever (N, %)**	18 (30%)
	Myalgia (N, %)	35(58.3%)
	Weight loss by 10% (N,%)	4 (6.7%)
Extra-articular manifestation	**Gastritis (N, %)**	14 (23.3%)
	Dry eyes (N, %)	31 (51.7%)
	Dysuria (N, %)	4 (6.7%)
	Chest pain (N, %)	2(3.3%)
	Dyspnea (N, %)	18 (30%)
	Palpitation (N, %)	15 (25%)
DAS 28-ESR	**Range**	1.2 - 7.00
	Mean ± SD	3.75 ± 1.48

Table 4: Laboratory finding of RA patients

		Patient (n=60)
ESR 1st hour (mm/h)	**Range**	10 – 66
	Mean ±SD	33.75 ± 15.08
CRP	**Range**	1.4 – 11.5
	Mean ±SD	7.51 ± 2.8
RF	**Positivity (N, %)**	43 (71.7%)
ACPA	**Positivity (N, %)**	11 (18.3%)
HbA1c	**Range**	4.1 - 5.8 %
	Mean ±SD	4.86 ± 0.47
Insulin	**Range**	4.4 - 81
	Mean ±SD	13.83 ± 12.44
HOMA-IR (N, %) Mean ±SD	**Female**	34(72.3%)
		4.32 ± 5.05
	Male	5 (55.6%)
		3.56 ± 2.17
Cholesterol (mg/dl)	**Range**	105 – 239
	Mean ±SD	150.83 ± 30.08
Triglyceride (mg/dl)	**Range**	40 – 244
	Mean ±SD	84.37± 38.94
HDL (mg/dl)	**Range**	24 - 55
	Mean ±SD	35.3 ±7.49
LDL (mg/dl)	**Range**	44 - 161
	Mean ±SD	96.8 ± 24.44

ACPA= Anti citrulinated peptide antibody, CRP= C-reactive protein, ESR= Erythrocyte sedimentation rate, HBA1c = hemoglobin A1C, HDL = high density lipoprotein, HOMA-IR= homeostatic model assessment of insulin resistance, LDL = low density lipoprotein, RF= Rheumatoid factor.

Table 5: Echocardiographic findings of RA patients

		R.A patient	
		N=60	**%**
pericardial effusion	**No**	60	100.0
RWMA	**Normal**	60	100.0
Valvular heart disease	**Present**	3	5.0
PASP	**Abnormal**	4	6.7

PASP = pulmonary artery systolic pressure, RWMA = regional wall motion abnormalities.

Discussion

Diagnosis of rheumatoid arthritis (RA) is based upon symmetrical polyarthritis characteristically involving small joints of the hands. It is characterized by progressive destruction of affected synovial joints. RA especially active disease, is associated with considerable changes in body composition, lipid profile, adipokines and insulin sensitivity. Metabolic changes, such as increased total cholesterol, LDL cholesterol and triglyceride levels, occur even in preclinical RA. Active RA is associated with decreased lipid levels, BMI, fat and muscle mass, as well as altered lipid profiles[2].

The aim of this study was to assess insulin resistance in patients with rheumatoid arthritis and to evaluate its relation to disease activity.
In our study we found that, insulin resistance (HOMA-IR > 2 in males and > 2.5 in females) were defined in 39 patients (23.4%) of our study. There was no statistically significant difference between patients and control group according to insulin resistance. In accordance to [6] who studied 403 early diagnosed RA patients to explore the prevalence of IR in RA, they found 85 patients (21.1%) of RA were defined to have IR (HOMA-IR ≥ 2.40).

The 'lipid paradox' phenomenon -reduction in serum lipids– mainly LDL level- associated with increased CVD risk- was described by[7] in a study pooled RA patients from cohort studies of cardiovascular disease.

However, in our study there was increasing in level of total cholesterol triglyceride, LDL and decreasing in HDL level with no statistically significant difference with control group, this was in accordance with[8] who studied RA patients to investigate the relationship between inflammation and disturbed lipid and gluscose metabolism in these patients, however, they showed no statistically significant difference between patients and control group. This corresponds to the results of another study of RA patients done by[9] to assess the relationship between physical activity and the RA-associated lipoprotein profile and they found that, triglycerides and HDL did not differ between RA and controls, while, both total cholesterol and LDL were lower in persons with RA.

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