

Insulin Resistance: Is it Prevalent in Egyptian Patients with Rheumatoid Arthritis?

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Abstract: *Aim:* to determine the prevalence of insulin resistance in a group of RA patients and to clarify the association between IR and the various disease parameters and the subclinical vascular pathology in those patients.

Subjects and Methods: The present study included 40 patients with RA in addition to 20 healthy age and sex matched controls. The study participants were subjected to careful history taking, thorough clinical examination and laboratory investigations including CRP, RF, ESR and insulin resistance. VAS and Disease activity score were calculated for all patients. Ultrasound assessment of carotid arteries was also performed.

Results: The study included 40 RA patients. The patients comprised 31 females (77.5 %) and 9 males (22.5 %) with a mean age of 42.7 ± 8.3 years and BMI of 28.6 ± 3.2 Kg/m². Patients had significantly higher CIMT when compared with controls. Also, it was found that patients had significantly higher HOMA-IR when compared with control. HOMA-IR was significantly correlated with BMI and CIMT.

Conclusions: Insulin resistance is prevalent in RA patients and significantly contributes to the development of subclinical atherosclerosis in those patients.

Keywords: Rheumatoid arthritis, Insulin resistance, carotid atherosclerosis.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritic characterized by immunologic dysfunction and systemic inflammation [1]. It was declared that patients with RA have a 2-fold higher risk of cardiovascular events than the general population and, in those with 10 years of RA or more, the risk is increased to > 3-fold [2]. The mechanisms behind this higher incidence of cardiovascular disease in RA patients are not fully understood but may be related to vascular inflammation and vascular endothelial injury which is common for RA patients [3].

Moreover, it has been suggested that RA patients had higher risk for the development of subclinical vascular pathology when compared with healthy controls [4].

On the other hand, many studies had shown that hyperinsulinemia is associated with both atherogenic (in pathological concentrations) and anti-atherogenic (in physiological concentrations) effects on the vessels. The latter vasodilatory action might be lost or down-regulated in the insulin resistant state, where increased insulin secretion in combination with hyperglycemia leads to smooth muscle cell hypertrophy and

hyperplasia, and excess synthesis of extra-cellular matrix proteins [5].

Increased prevalence of insulin resistance (IR) has been observed in patients with RA. High-grade systemic inflammation is implicated in the development of insulin resistance in these patients [6].

AIM OF THE STUDY

The present study aims to determine the prevalence of insulin resistance in a group of RA patients and to clarify the association between IR and the various disease parameters and the subclinical vascular pathology in those patients.

SUBJECTS AND METHODS

The present study included 40 patients with RA diagnosed according to the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for RA [7]. In addition, there were 20 healthy age and sex matched controls. Patients were excluded if they had experienced atherosclerotic cardiovascular events before.

RA patients were subjected to careful history taking, thorough clinical examination and laboratory investigations including CRP, RF and ESR. For all patients visual analog scale (VAS) [8], Disease activity

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score (DAS28^{ESR}) [9], tender and swollen joints count were calculated. Assessment of functional status was performed using health assessment questionnaire (HAQ) [10]. Ultrasound assessment of vascular subclinical atherosclerosis in the form of carotid intima media thickness (CMT) of the carotid arteries was achieved according to the technique described by Rundek *et al.* [11].

All subjects were evaluated for serum insulin and glucose levels. Serum insulin was determined by electrochemiluminescence immunoassay. IR was then investigated in all patients at baseline by the homeostasis model for the assessment of IR (HOMA-IR) using the standard formula: fasting Glucose (mg/dl) × fasting Insulin(μU/mL) / 405. Patients were considered insulin resistant if HOMA-IR ≥ 2 [12].

Statistical analysis was performed using SPSS 17. Numerical variables were represented in the form of

mean ± SD where categorical ones are represented the form of number and percent. Comparison between numerical variables was achieved using student t test while Chi-square test was used to compare categorical variables. Correlations were performed using Pearson's correlation coefficient. P value less than 0.05 was considered statistically significant.

RESULTS

Basic demographic, clinical and laboratory characteristics of the studied patients were shown in Table 1. The study included 40 RA patients. It comprised 31 females (77.5 %) and 9 males (22.5 %) with a mean age of 42.7 ± 8.3 years and BMI of 28.6 ± 3.2 Kg/m². The studied patients had a mean disease duration of 9.1 ± 2.9 years, a tender joints count of 4.8 ± 2.9 and a swollen joints count of 2.4 ± 1.5. The VAS score was 2.5 ± 1.0 while DAS28^{ESR} was 4.48 ± 2.05

Table 1: Demographic, Clinical and Laboratory Findings in the Studied RA Patients (n=40)

Age (years)	Range	29.0 - 59.0
	Mean ± SD	42.7 ± 8.3
Sex	Male	9 (22.5 %)
	Female	31 (77.5 %)
BMI (Kg/m ²)	Range	22.9 - 35.7
	Mean ± SD	28.6 ± 3.2
Disease duration (years)	Range	4.0 - 16.0
	Mean ± SD	9.1 ± 2.9
Tender joints	Range	10.0 - 16.0
	Mean ± SD	12.8 ± 2.9
Swollen joints	Range	0.0 - 6.0
	Mean ± SD	2.4 ± 1.5
VAS	Range	4.0 - 8.0
	Mean ± SD	5.5 ± 1.0
DAS28 ^{ESR}	Range	1.53 - 9.87
	Mean ± SD	4.48 ± 2.05
HAQ	Range	3.0 - 20.0
	Mean ± SD	13.1 ± 3.0
ESR (mm/h)	Range	5.0 - 90.0
	Mean ± SD	24.9 ± 21.5

Table 2: Comparison between Patients and Control Regarding CMT, HOMA-IR and Insulin Resistance

	Patients (n=40)	Controls (n=20)	P
CMT*	0.8 ± 0.14	0.64 ± 0.04	0.0001
HOMA-IR*	1.89 ± 0.51	1.02 ± 0.34	0.0001
Insulin resistance**	16 (40.0 %)	-	0.001

*Student t test.

**Chi-square test.

and HAQ was 13.1 ± 3.0 . The laboratory findings in the studied patients included ESR of 24.9 ± 21.5 (mm/h).

The comparison between patients and controls regarding HOMA-IR, insulin resistance and CIMT thickness was demonstrated in Table 2. Patients had significantly higher CIMT when compared with controls (0.8 ± 0.14 vs 0.64 ± 0.04 ; $p=0.0001$). Also, it was found that patients had significantly higher HOMA-IR when compared with controls (1.89 ± 0.51 vs 1.02 ± 0.34 ; $p=0.0001$). The frequency of IR in RA patients was 40.0 % compared to 0 % in controls ($p=0.001$).

Table 3 illustrated the correlations between HOMA-IR, RA parameters and CIMT. HOMA-IR was significantly correlated with BMI and CIMT.

Table 3: Correlations between HOMA-IR, Clinical Parameters and CIMT in RA Patients

	HOMA-IR	
	R	p
Age	0.14	0.38
BMI	0.34	0.031*
Disease Duration	-0.06	0.68
Tender joints	-0.11	0.46
Swollen joints	0.05	0.75
VAS	-0.09	0.54
DAS-28	-0.17	0.26
HAQ	-0.12	0.43
CIMT	0.4	0.009*

DISCUSSION

Rheumatoid arthritis (RA) has long been known to be associated with increased mortality, which is mostly attributable to an increased prevalence of atherosclerosis, particularly ischemic heart disease [13]. Impaired insulin sensitivity has been shown to be an independent cardiovascular risk factor in individuals with [14] and without [15] diabetes.

Accordingly, it has been hypothesized that insulin resistance (IR) may have a role in promoting atherosclerosis in RA [16] and IR has been reported previously among patients with RA [17].

Despite this, the association between IR and atherosclerosis remains under debate. So, the present study aimed to contribute to this issue by determining the prevalence of insulin resistance in a group of RA

patients and to clarify the association between IR and the various disease parameters and the subclinical vascular pathology in those patients.

In the present study, patients had significantly higher CIMT when compared with controls. This is in agreement with the findings of Södergren *et al.* [18] who found that patients with RA had significantly higher CIMT when compared with controls. Also, Stamatelopoulos *et al.* [4] found that CIMT in both femoral and carotid arteries are significantly higher in patients when compared with controls.

In addition, the present study found that RA patients had a significantly higher HOMA-IR when compared with controls. It was also shown that RA patients had IR frequency of 40 % compared to 0 % in controls. These findings are consistent with the conclusions of La Montagna *et al.* [19] who found a significantly higher frequency of IR in RA patients when compared with healthy controls. However, in the study of Pamuk *et al.* [20], no significant differences were found between RA patients and controls regarding IR or HOMA-IR. This is attributed to the high cut-off value this study used to determine IR.

The current study found a significant correlation between HOMA-IR and BMI. This is in accordance with the findings of Chen *et al.* [21] who noted that BMI was significantly and independently associated with HOMA-IR. Also, it was found that HOMA-IR is significantly associated with CIMT in agreement with the results of La Montagna *et al.* [19] In their study, they showed a significant positive relationship between IMT and HOMA-IR ($p<0.001$).

CONCLUSIONS

In conclusion, we can say that insulin resistance is highly prevalent in RA patients. It significantly contributes to the development of subclinical atherosclerosis in these patients.

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