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Relation of Tumor Necrosis Factor-Alpha with Insulin Resistance in Rheumatoid Arthritis Patients

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ABSTRACT

Background: rheumatoid arthritis (RA) is a chronic inflammatory arthropathic with multiorgan involvement. Increased prevalence of insulin resistance (IR) has been observed in patients with RA. High-grade systemic inflammation is implicated in the development of IR in these patients. Tumor necrosis factor-alpha (TNF-α) is a potent proinflammatory cytokine that plays a role in initiation and progression of inflammation and the mechanisms associated with accelerated atherosclerosis in RA. **Aim of the work:** this study aimed to investigate the relation between TNF-α and IR in RA patients and its relation to disease activity. **Patients and methods:** 40 RA patients were included as the patient group and 40 healthy subjects as the control group. Both groups were subjected to full history, clinical examination including body mass index (BMI) and lab investigation, fasting blood glucose, fasting insulin and TNF-α. **Results:** the sex distribution was the same in patients and the control groups, 82.5% females and 17.5% males. The disease activity (DAS score) was 4.57 ± 1.35. TNF-α median was 240 with IQR 190-510. RA patients had significantly higher serum TNF-α than controls (p value = 0.001). BMI and Waist Circumference among RA patients and controls showed no significant difference. TNF-α has significantly positive correlations with fasting serum insulin, HOMA-IR and disease activity in RA patient group (p value < 0.001).
Conclusion: serum TNF-α level was significantly higher in RA patients than the control groups with positive correlation in fasting serum insulin, HOMA score and disease activity.
Keywords: rheumatoid arthritis (RA), TNF-α, HOMA-IR, insulin resistance (IR).

INTRODUCTION

RA is chronic inflammatory, immune mediated disease with prevalence of 0.5-1% in the developed countries. In RA, chronic synovial inflammation and hyperplasia drive articular destruction and bone erosion, leading to functional decline and disability [(1)]. Disease hallmarks are synovial inflammation, progressive bone erosion, joint destruction and subsequent weakness of surrounding tissues and muscles. Systemic manifestations also occur. Presentations ranged from mild to severe, although the typical patient had a progressive course leading to functional limitations [(2)].TNF is a pleiotropic cytokine that is transcriptionally activated in response to a variety of stimuli during inflammation, infection and stress. Excessive TNF activity contributes to the complex pathogenesis of RA, associated with pro-inflammatory cascade that includes production of IL-1 and IL-6 and drives tissue destruction [(3)]. Increased prevalence of IR has been observed in patients with RA. High-grade systemic inflammation was implicated in the development of IR in these patients[(4)]. This study aimed to investigate the relation between TNF-α and IR in RA patients and its relation to disease activity.

PATIENTS AND METHODS

This study was a cross sectional patient control study; it involved 40 RA patients following ACR 1987 revised criteria [(5)] as the patient group and 40 healthy subjects as the control group. Patients were selected from outpatient clinic and inpatient Rheumatology Department of Ain Shams University Hospitals and informed written consent taken from all subjects approved by ethical committee of Ain Shams University. Both groups were subjected to full history taking, clinical examination included body mass index (BMI) and lab investigation; fasting blood glucose (FBG), fasting serum insulin and TNF-α. RA patients only were subjected to full rheumatological examination, assessment of disease activity using Disease Activity Score 28, erythrocyte sedimentation rate (DAS28-ESR) [(6)] and other lab investigations (Complete blood count (CBC), ESR, serum C-reactive protein (CRP), rheumatoid factor (RF), aspartate transaminase (AST), alanine transaminase (ALT) and serum creatinine). CBC performed on 5 parts differential automated cell counter; Sysmex Hematology Autoanalyzer (©2012 Sysmex America, Inc.), CRP level using dimension clinical chemistry system (Siemens Health Care Diagnostic Products GmbH, Malburg, Germany) based on particle enhanced turbidimetric immunoassay technique (Cut off value 3.0 mg/L), ESR by using Westergren's method. AST, ALT, FBG and S-creatinine were done using AU 680 chemistry autoanalyzer, (Beckman Instruments.,

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Inc., Fullerton, California USA). RF was quantitatively determined by Roche/Hitachi Cobas C311 Analyzer based on latex bound immune turbidimetric assay. A positive result was defined as a level of >14.0 U/mL. Measurement of fasting plasma insulin level by Enzyme-Linked Immunosorbent Assay (ELISA) kit (Chemux-Bio-Science, Inc, USA) according to manufacturer's instructions with the following ranges: 0.7- 9.0 IU/ml for normal adult and 0.7 – 25.0 IU/ml for diabetic (Type II). IR was evaluated using the Homeostasis Model Assessment of insulin resistance (HOMA)**.** HOMA-IR was calculated using the following formula: HOMA-IR (mg/dL x μU/ml) = [fasting blood sugar (mg/dL) x fasting serum insulin (μU/ml)] /405[(7)].

Serum TNF-alpha was assayed by ELISA technique, using ELISA kit (PELO-BIOTECH, GmBH- Am Klopferspitz 19, Germany). It is used according to the manufacturer's instructions with the assay range of 3-900 ng/L.

Statistical analysis: the present data were analyzed using SPSS (version 20) statistical software package under Windows 7 operating system for IBM compatible PC. Data were presented and suitable statistical tests were done according to the type of data obtained for each parameter. The level of significance was at p value ≤ 0.05.

RESULTS

This study was a cross sectional patient control study; it was involved 40 RA patients following ACR 1987 revised criteria as the patient group and 40 healthy subjects as the control group. The sex distribution was the same in both patient and control groups, 33 (82.50%) females and 7 (17.5%) males. The control group age mean ± SD was 33.90 ± 11.14 years and the age mean ± SD of RA patients was 36.50 ± 11.62 years. On comparing the patient and control groups regarding age, sex and other anthropometric measures (Height, weight, BMI and Waist Circumference), there was no statistically significant difference between both groups.

In RA patients, the mean disease duration ± SD was 4.56 ± 3.47 years, while mean disease activity (DAS28-ESR score)± SD was 4.57 ± 1.35.Three patients (7.5%) were in remission (DAS28-ESR Score was ≤ 2.6), two patients (5%) had low disease activity (DAS28-ESR Score was (> 2.6 - ≤ 3.2), 18 patients were (45%) in moderate activity (DAS28-ESR Score was > 3.2 - ≤ 5.1) and 17 patients (42.5%) had high disease activity (DAS28-ESR Score was > 5.1). As regard treatment, 35 of RA patients used corticosteroids and hydroxychloroquine, meanwhile 26, 21and 15 of RA patients were on methotrexate (MTX), NSAIDS and leflunomide respectively.

Table 1: description of the laboratory results among the patient group

		Patients	
		Mean/ Median	**SD/ IQR**
CBC	**RBCs (10^6/cmm)**	4.41	0.40
	Hb (g/dl)	12.10	1.19
	MCV (fl)	81.64	4.95
	Hct (pg)	35.62	7.93
	WBCs (10^3/cmm)	8.00	2.75
	PNL (%)	64.00	9.94
	Lymph (%)	28.13	8.94
	PLT (10^3/cmm)	289.18	65.72
ESR (mm/hr)		50.00	23 - 63
CRP- titre (mg/L)		12.00	0 - 26
AST (U/L)		18.00	16 - 25
ALT (U/L)		23.50	15 - 32
S.Cr. (mg/dl)		0.80	0.6 - 0.9
RF (IU/ml)		22.00	0 - 40
TNF-α (ng/L)		240	190-510
Fasting serum sugar (mg/dl)		98.78	7.80
Fasting serum insulin (IU/ml)		17	8-38

CBC = complete blood count, **RBCs** = red blood cells, **Hb** = hemoglobin, **MCV** = mean corpuscular volume, **Hct** = hematocrit, **WBCs** = white blood cells, **PNL** = polymorphonuclear leukocytes, **Lymph** = lymphocytes, **PLT** = platelet count, **ESR** = Erythrocyte Sedimentation rate, **CRP- titre** = C-reactive protein titre, **AST** = Aspartate aminotransferase, **ALT** = Alanine aminotransferase, **S.Cr**. = Serum Creatinine, **RF** = rheumatoid factor, **TNF-α** = tumor necrosis factor alpha.

RF of RA patients was positive in 28 pts (70%) and its median was 22 and IQR was (0-40).

Table 2: comparison between patients and controls regarding fasting blood sugar, fasting serum insulin, TNF-αand HOMA score.

		Controls		Patients		T: t test Mann Whitney test	
		Mean / Median	SD / IQR	Mean / Median	SD / IQR	p value	sig.
Fasting Blood Sugar (mg/dl)		76.93	11.11	98.78	7.80	**<0.001$^{(T)}$**	**HS**
Fasting Serum Insulin (IU/ml)		13	12-18	17	8-38	0.063$^{(M)}$	NS
TNF-α (ng/L)		140	110-189	240	190-510	**<0.001$^{(M)}$**	**HS**
HOMA Score		3.06	2.14-3.49	3.8	1.88-9.2	0.078$^{(M)}$	NS
IR	**No IR (HOMA score <1.9)**	6	15.0%	11	27.5%	0.154$^{(M)}$	NS
	Early IR (HOMA score >1.9 - <2.9)	11	27.5%	5	12.5%		
	Significant IR (HOMA score >2.9)	23	57.5%	24	60.0%		

There was a statistically high significant difference between RA patients and the controls as regard fasting blood sugar and TNF-α**(**p value <0.001**)**. While, there were relatively higher fasting serum insulin and HOMA score in RA patients than the control, but without statistically significant difference **(**p value > 0.05) as shown in table 2. Since the number of patients who were in remission and those with low disease activity were very low, they were added together and considered as one group.

Five (12.5%) patients had remission and low disease activity (DAS28 < 3.1), 18 patients (45.0%) had moderate activity (DAS28 > 3.2 - ≤ 5.1) and 17 patients (42.5%) had high disease activity (DAS28 > 5.1).

Table 3: comparative study between RA patients with different disease activities as regard fasting blood sugar, fasting serum insulin, serum TNF-α and IR.

		DAS28-ESR score "Disease activity"						ANOVA K: Kruskal Wallis	
		Remission & low		Moderate		High			
		Mean / Median	SD / IQR	Mean / Median	SD / IQR	Mean / Median	SD / IQR	value	sig.
TNF-α (ng/L)		210.00	75-240	200.00	170-345	540.00	480-900	**<0.001$^{(K)}$**	**HS**
F. blood sugar (mg/dl)		88.40	7.23	99.50	7.19	101.06	6.36	**0.003$^{(A)}$**	**HS**
F. serum insulin (IU/ml)		8.00	7-11	10.50	7.5-27.5	25.00	22-42	**0.030$^{(K)}$**	**S**
HOMA score		1.59	1.56-2.31	2.73	1.83-7.19	7.16	5.27-10.04	**0.015$^{(K)}$**	**S**
IR	**No IR (HOMA score <1.9)**	3	60%	6	33.3%	2	11.8%	**0.020$^{(A)}$**	**S**
	Early IR (HOMA score >1.9 - <2.9)	1	20 %	4	22.2%	0	0%		
	Significant IR (HOMA score >2.9)	1	20%	8	44.5%	15	88.2%		

There was a high statistically significant difference between the three groups regarding fasting blood sugar and TNF-α level as they were higher in those who had high disease activity more than moderate disease activity, more than remission and low disease activity (p value < 0.001).

Also, there was a statistically significant difference as regard fasting serum insulin and HOMA score in RA patients being higher in those who had high disease activity more than moderate disease activity, more than remission and low disease activity group **(p value < 0.05)** as shown in table 3.

Table 4: comparison between IR regarding (TNF-α, DAS, BMI, WC) among RA patients

	Patient						A: ANOVA / K: Kruskal Wallis test	
	No IR (HOMA score < 1.9)		Early IR (HOMA score >1.9 - < 2.9)		Significant IR (HOMA score > 2.9)			
	Mean / Median	SD / IQR	Mean / Median	SD / IQR	Mean / Median	SD / IQR	p value	sig.
TNF-α (ng/L)	165.00	135-175	240.00	210-270	442.50	210-662.5	0.001(K)	HS
DAS28-ESR Score	3.75	1.27	4.50	1.18	5.13	1.13	0.010(A)	S
BMI	25.87	1.02	25.40	0.25	26.33	1.15	0.157(A)	NS
Waist Circum. (cm)	85.91	10.77	94.20	11.58	90.92	9.78	0.262(A)	NS

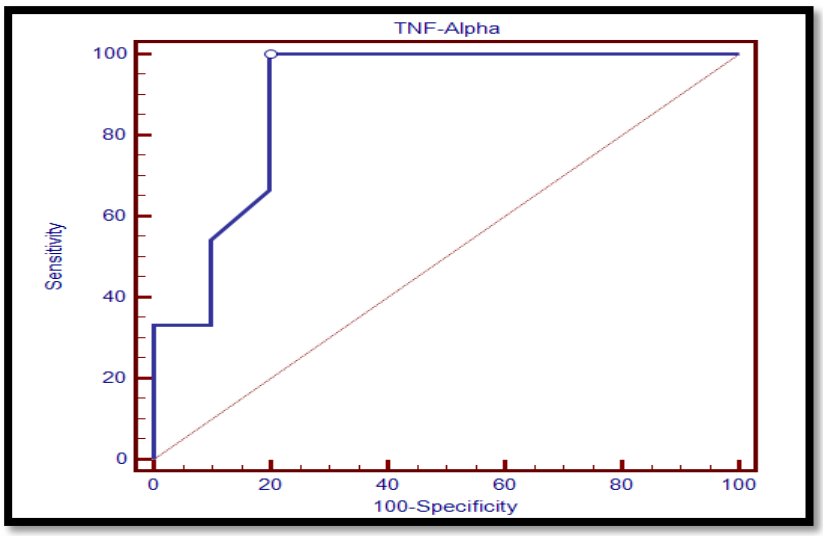
There was a highly statistically significant increase in TNF-α (p value = 0.001) which was higher in those had significantly IR and a statistically significant increase in disease activity DAS28-ESR (p value = 0.010) which was higher in those had significant IR group. However, there were no statistically significant differences as regard BMI and waist circumference (p value > 0.05) as shown in table 4.

TNF-α had a highly statistically significant positive correlation with DAS28-ESR in RA patients (p value < 0.001). There was also a significant positive correlation with fasting serum insulin and IR in RA patients and the control group (p value >0.001). There was no statistically significant correlation as regard other parameters (p value > 0.05) as shown in table 5.

Table 5: correlation between TNF-α and BMI, waist circumference, fasting blood sugar, fasting insulin, HOMA-score and DAS-ESR28 score in the different patients

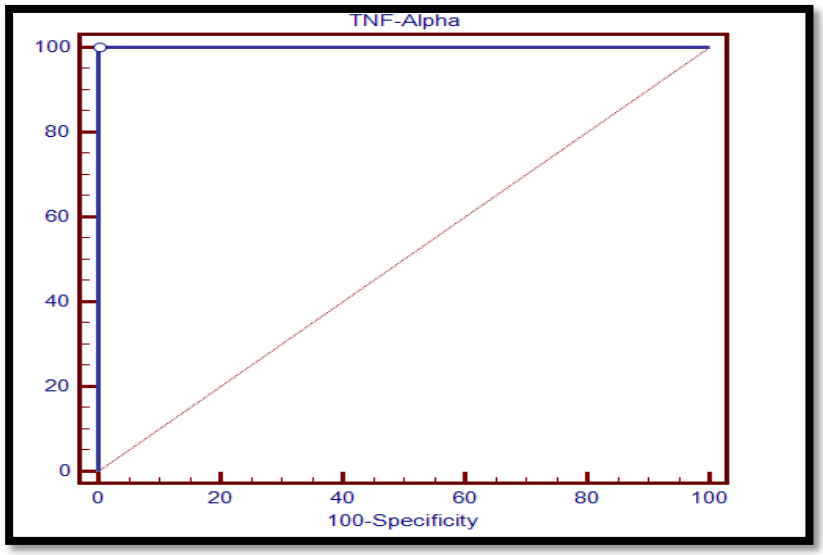
	TNF-α					
	Patients			Control		
	R	P	Sig.	R	P	Sig.
BMI (kg/m^2)	-0.020	0.905	NS	-0.048	0.770	NS
Waist circum. (cm)	-0.186	0.251	NS	-0.045	0.783	NS
F. blood sugar (mg/dl)	0.172	0.288	NS	0.217	0.178	NS
F. serum insulin (IU/ml)	0.420	**0.007**	**S**	0.512	**0.008**	**S**
IR (HOMA score)	0.380	**0.016**	**S**	0.410	**0.020**	**S**
DAS28—ESR	0.539	**<0.001**	**HS**	---	---	

ROC curves were constructed to determine sensitivity and specificity of TNF-α in predicting IR in RA patients. The curves showed that at cut point of TNF-α (>195 ng/L), early significant IR in RA patients sample was detected with sensitivity 93.7% and specificity 85.1%. And, at cut point of TNF-α (>88 ng/L), early and significant insulin resistance among the control sample with sensitivity 100% and specificity 100% was detected as shown in figures 1 and 2.



Area unde curve	Standard Error	95% CI	Cut off point	Sensitivity	Specificity	p value
0.814	0.076	0.740 to 0.943	>195	93.7	85.1	0.001

Fig. 1: ROC curve of TNF to predict early and significant insulin resistance among the patients.



Area under the curve	Standard Error	95% CI	Cut off point	Sensitivity	Specificity	p value
1	0.000	.877 TO 1	>88	100	100	<0.001

Figure 2 : ROC curve of TNF to predict early and significant insulin resistance among the controls

DISCUSSION

RA is a common chronic autoimmune systemic inflammatory disease and it leads to the development of synovitis, joint damage and structural bone damage. A number of extra articular manifestations and comorbidities were present in patients with RA, which resulted in increased mortality [(8)]. Increased prevalence of IR in patients with RA had been potentially correlated with the degree of RA disease activity [(9)]. TNF-α is an adipocytokine involved in systemic inflammation, stimulates the acute phase reaction and involved in the pathogenesis of IR. It plays an important role in the induction and perpetuation of the chronic inflammatory processes in rheumatoid joints as well as in the systemic manifestations of this disease [(10)].This study was designed to investigate the relation between TNF-α and IR in RA patients and its relation to disease activity.

Among the 40 RA patients sex distribution was 33 (82.50%) females and 7 (17.50%) males. Therefore, the ratio of female to male was 4:1 ; it is nearly agreed with results of **Kavanaugh**[(11)] which showed that RA was significantly more common in females than in males (about 3:1 female: male ratio).The RA patients age ranged

from 20 to 59 years with the mean ±SD (36.50±11.62). **Majithia and Greraci** [12] study showed similar data concerning age of the patients; RA onset was most frequent between the ages of 40 and 50, but people of any age can be affected.

As regard treatment of RA patients, 35 (87.5%) patients were on corticosteroids and hydroxychloroquine, 26 (65.5%) patients had MTX therapy, 21 (52.5%) patients had NSAIDS and 15 (37.5%) patients had leflunomide.

MTX therapy had been a major advance in the treatment of RA and it is now the cornerstone of therapy;it is the most popular drug worldwide for the treatment of RA. Low-dose, weekly MTX (10 to 25 mg/wk) used as either monotherapy or in combination with other drugs has a superior efficacy [13].

In their study on 12526 RA patients, **Roberts *et al.*** [14] found that the most commonly prescribed cDMARD was methotrexate (76% patients).Also, **Rannio *et al.*** [15] found that at baseline, 68% of their studied RA patients used methotrexate-based combination therapy.

In our study, RF of RA patients was positive in 28 pts (70%) and its mean ± SD was 49.82 ± 59.27. This was strongly agreed with results of **Aletaha *et al.*** [16] which showed that RF could be found in up to 75 % of RA patients. **Hakal *et al.*** [17] studied 95 RA patients and they found that 75% of the patients were RF positive. And their results were slightly agreed with those of **Humphreys *et al.*** [18] who mentioned that approximately 80% of adult RA patients test positive for RF.

IR is defined as impaired ability of insulin to stimulate glucose utilization and it is a major characteristic of diabetic patients. [19]

In RA patients, fasting blood sugar mean ± SD was 98.78 ± 7.80, fasting serum insulin mean ± SD 17.70 ± 16.31 and consequently HOMA score calculation mean ± SD was 3.96 ± 3.14. By comparing fasting blood sugar, fasting serum insulin and HOMA score between RA and the control group there was only highly significant difference between them as regard fasting blood sugar but no significantly difference as regard fasting serum insulin and HOMA score, even they were higher in RA patient than in the control **(**P value = 0.667, P value = 0.083).

The results obtained in this study agreed with those of **Bilecik *et al.*** [20], they showed that there was no significant difference between the RA patients and the control group patients regarding fasting serum insulin. The serum insulin levels and IR as calculated by HOMA-IR of the RA patients were higher than for the control group values, however the difference was not significant (P = 0.103, P = 0.132).However, our result didn't agree with those of **Giles *et al.*** [9], since they found that mean HOMA-IR levels were significantly higher in the RA patients group compared to the control group. This difference could be explained by the different demographic features of their studied subjects since, they had more number of subjects (393 vs 80), higher age range (45-84 vs 18-60) years and different BMI index (up to 35 vs < 30) kg/m^2.

TNF-α is a pleiotropic cytokine that is transcriptionally activated in response to a variety of stimuli during inflammation, infection and stress [21].

As regard serum TNF-α level, its median was 240 and IQR was 190-510 which was higher in RA patients than control (median 140 and IQR 110-189). Serum TNF-α level was significantly higher in RA patients than in the control.

Hadinedoushan *et al.* [22] study demonstrated that the serum level of TNF-α was 5.21 ± 1.69 Pg/mL in the control group and 62.4 ± 27.1 Pg/mL in the RA group (P value< 0.0001)**.** There was a significant difference in terms of serum TNF-α level in RA group **(**p < 0.05).In addition, **Wei *et al.*** [23] studied 890 patients with RA and 441 healthy people as the control and they mentioned that serum TNF-α level of RA patients was significantly higher than in the control (P value < 0.001).And also, **Gheita *et al.*** [24] study concluded that serum TNF-a levels was higher in RA patients than in controls **(**P value = 0.036**)** and it might be predicted by disease activity.

We used DAS28-ESR score to assess disease activity in RA patients. We further classified RA patients according to disease activity, where 3 patients (7.5%) were in remission, 2 patients (5.0%) had low disease activity group, 18 patients (45.0%) had moderate disease activity group and 17 patients (42.5%) had high disease activity.

And by comparing them according to fasting blood sugar, fasting serum insulin and HOMA score we found that there was a high statistically significant difference between the 3 groups regarding fasting blood sugar being higher in the high disease activity group (p value < 0.001). And a there was statistically significant difference as regard fasting serum insulin and HOMA score in RA patients which being higher in the high disease activity group **(P value < 0.05).** This result agreed with **those of Muller *et al*.** [25] who studied 92 RA patients to assess relation between IR and RA disease activity, they found that IR developed in the early stage of the disease and associated with RA disease activity. Also, **Stagakis *et al.*** [26]

studied 61 patients with RA, they found that elevation HOMA score was accompanied with elevated fasting blood sugar, fasting serum insulin level and disease activity. They cleared strong link between degree of inflammation and IR among RA patients.

In this study, TNF-α level showed that there was a high statistically significant difference between the three groups. TNF-α was higher in the high disease activity group (P value < 0.001). This result agreed with **those of Costa *et al.*** [27] they showed that patients with RA had significantly increased TNF-α and it was associated with increasing disease activity. This is different from results of **Chung *et al.*** [28] who studied 124 patients with RA. Compared TNF-α in the different disease activity groups, they found no significant difference. Yet, after eight weeks of medical treatment in patients with high disease activity, a decrease in DAS28-ESR was associated with a significant decrease in the serum TNF-α.

We further subdivided our RA patients according to the degree of IR into 3 groups:11 patients (27.5%) had no IR (HOMA score <1.9), 5 patients (12.5%) had early IR(HOMA score >1.9 - <2.9) and 24 patients (60.0%) had significant IR (HOMA score >2.9).

In RA patients comparative study between the 3 groups revealed high significant increase in TNF-α in the significant IR group **(**P value = 0.001**)** and significantly high disease activity in those patients with significant IR also **(**P value = 0.010), however there was no significant difference as regard BMI and waist circumference (P value > 0.05).This result agrees with those of **Muller *et al.*** [25] who found increased IR which was associated with increased RA disease activity and a highly statistically significant increase in TNF-α level with increasing IR. **Şahin *et al.*** [29] also found that HOMA-IR was positively significant correlated with TNF-α and RA disease activity.

In addition, **Castillo-Hernandez *et al.*** [30] found that insulin resistance was significantly higher in rheumatoid with normal weight than in overweight. As expected, levels of TNF-α, IL6 and IL1B were significantly higher in RA patients. Also, **Costa *et al.*** [27] evaluated the involvement of TNF-α and insulin resistance (IR) in the inflammatory process, oxidative stress and disease activity in patients with rheumatoid arthritis (RA). The presence of insulin resistance was strongly associated with both oxidative stress and TNF-α level. This also agreed with results of **Gonzalez-Gay *et al.*** [31] who explained that TNF-α had a role in the pathogenesis of IR in RA patients independent of the contribution of age, race, sex and BMI in RA patients. Those results had also proved by the presence of highly statistically significant positive correlation between TNF-α and DAS28-ESR. Also, positive significant correlation had been found between TNF-α, fasting serum insulin and HOMA-IR in RA patients. Our results agree with those of **Gwozdziewiczova *et al.*** [32] they showed a positive significant correlation between TNF-α and IR in RA patients and concluded that TNF-α plays an important role in the development of IR in men and women with early symptoms of IR in a different way. **Chung *et al.*** [28] study mentioned that HOMA index was also significantly positively correlated with TNF-α**(**P value = 0.05) in RA patients and TNF-α plays a role in the development of IR. Also, **Giles *et al.*** [9] proved that TNF-α was positively correlated with the HOMA-IR and serum insulin independently of BMI in RA patients.

We also found that among the control group, there was a highly significant increase in serum TNF-α especially in significant IR group **(**p value < 0.001). There was no statistical significance as regard BMI and waist circumference **(**p value > 0.05**).**We also found that serum TNF-α level among the control group was significantly positive correlated with HOMA-IR and fasting serum insulin independently of BMI. Our result agrees with those **Agarwal *et al.*** [33] study that showed positive significant correlation between TNF-α and HOMA-IR in normal population (male and female) and also with those of **Rajarajeswari *et al.*** [34] who studied 100 RA patients and control as regard serum level of TNF-α, fasting blood sugar and fasting serum insulin; they found that serum level of TNF-α had strong correlation with fasting blood sugar and fasting serum insulin in RA patients and control groups.

Using ROC curve this study showed that among RA patients, TNF-α >195 ng/L there was early significant IR with sensitivity 93.7% and specificity 85.1%. And the cut off value of TNF-α >88 ng/L among control group showed early significant IR with sensitivity 100% and specificity 100%. **Lee *et al.*** [35] study concluded that serum cutoff value of TNF-α among subjects was 4.52 Pg/ml (sensitivity 67%; specificity 79%).And **Chen *et al.*** [36] study showed that by the ROC curve among RA patients the optimal cutoff value of TNF-α was 1.27 (AUC of 0.791, sensitivity of 94.2%).

CONCLUSION

TNF-α plays a role in development of IR in rheumatoid arthritis patients or normal control. Higher disease activity was associated with increased IR, one of the pathogenic mechanism may be due to higher level of TNF-α in those patients.

REFERENCES

1. **Sridhar R, Ramya S S and Sowjanya S (2016):** Rheumatoid Arthritis Review. World Journal of Pharmacy and Pharmaceutical Sciences, 5(10): 1283-1302.
2. **Paul B J, Kandy H I and Krishnan V (2017):** Pre-rheumatoid arthritis and its prevention. Eur J Rheumatol., 20(17): 1-5.
3. **Byng-Maddick R, Turner C T, Pollara G, Ellis M, Guppy N J, Bell L C K and Noursadeghi M (2017):** Tumor necrosis factor (TNF) bioactivity at the site of an acute cell-mediated immune response is preserved in rheumatoid arthritis patients responding to anti-TNF therapy. Frontiers in Immunology, 8: 1-13.
4. **Gonzalez-Gay M A, Gonzalez-Juanatey C, Vazquez-Rodriguez T R, Miranda-Filloy J A and Llorca J (2010):** Insulin resistance in rheumatoid arthritis: the impact of the anti-TNF-α therapy. Ann. N.Y. Acad. Sci., 20(10): 153–159.
5. **Arnett F C, Edworthy S M, Bloch D A, McShane D J, Fries J F, Cooper N S, Healey L A, Kaplan S R, Liang M H and Luthra H S (1988):** The American rheumatism association1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum., 31(3): 315-324.
6. **Goswami R P, Basu K, Das S, Mondal S, Ghosh P and Ghosh A (2016):** Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann. Rheum. Dis., 12(3): 236–247.
7. **Ghaffari M A, Payami S, Payami S, DamoonAshtary-Larky D, Nikzamir A and Mohammadzadeh G (2016):** Evaluation of insulin resistance indices in type 2 diabetic patients treated with different anti-diabetic drugs. Open Journal of Endocrine and Metabolic Diseases, 20(6): 95-10.
8. **Gibofsky A (2012):** Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am. J. Manag. Care, 18(13): 295-302.
9. **Giles J T, Danielides S, Szklo M, Post W S, Blumenthal R S, Petri M, Schreiner P J, Budoff M, Detrano R and Bathon J M (2015):** Insulin resistance in rheumatoid arthritis disease-related indicators and associations with the presence and progression of subclinical atherosclerosis.Artheritis and Rheumatology, 67(3): 626-636.
10. **Swaroop J J, Rajarajeswari D and Naidu J N (2012):** "Association of TNF-α with insulin resistance in type 2 diabetes mellitus. Indian J. Med. Res., 135(1): 127–130.
11. **Kavanaugh A F (2005):**Macromolecule tumor necrosis factor inhibitors: are they more better?." J. Rheumatol., 32(5): 2285-87.
12. **Majithia V and Geraci S A (2007):** Rheumatoid arthritis: diagnosis and management. Am. J. Med., 120(11): 936-945.
13. **Weinblatt M E (2013):** Methotrexate in rheumatoid arthritis. Trans. Am. Clin. Climatol. Assoc., 124(13): 16–25.
14. **Roberts L, Tymms K, Jager J D, Littlejohn G, Griffiths H, Nicholls D, Bird P, Young J, Hill J and Zochling J (2017):** The CEDAR study: a longitudinal study of the clinical effects of conventional DMARDs and biologic DMARDs in Australian rheumatology practice. Int. J. Rheumatol., 20(17*)*:460-468.
15. **Rannio T, Asikainen J, Hannonen P, Yli-Kerttula T, Ekman P, Pirilä L, Kuusalo L, Mali M, Puurtinen-Vilkki M, Kortelainen S, Paltta J, Taimen K, Kauppi M, Laiho K, Nyrhinen S, Mäkinen H, Isomäki P, Uotila T, Aaltonen K, Kautiainen H and Sokka T(2017):** Three out of four disease-modifying anti-rheumatic drug-naïve rheumatoid arthritis patients meet 28-joint Disease Activity Score remission at 12 months: results from the FIN-ERA cohort. Scand. J. Rheumatol., 20(3): 1-7.
16. **Aletaha D and Smolen J S (2015):** Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges.Nat. Rev. Rheum., 11(5): 276–89.
17. **Hakala M, Sajanti E, Ikäheimo I and Aho K (2009):** High prevalence of rheumatoid factor in community-based series of patients with rheumatoid arthritis meeting. Scandinavian Journal of Rheumatology, 27(5): 368-372.
18. **Humphreys J H, Nies J A B V, Chipping J, Marshall T, Mil A H M, Symmons D P M and Verstappen S M (2014):** Rheumatoid factor and anti-citrullinated protein antibody positivity, but not level, are associated with increased mortality in patients with rheumatoid arthritis: results from two large independent cohorts. Arthritis Research and Therapy, 16(6): 483-90.
19. **Rashidi H, Kasiri A, Latifi S M, Zaman F, Shabazian H and Moravej A (2014):** Comparison of established risk factors among type 2 diabetic patients with or without retinopathy in Golestan Hospital, Ahvaz 2010. Open Journal of Endocrine and Metabolic Diseases, 14(4): 225-229.
20. **Bilecik N A, Tuna S, Samancı N, Balcı N and Akbaş H (2014):** Prevalence of metabolic syndrome in women with rheumatoid arthritis and effective factors. International Journal of Clinical and Experimental Medicine, 7(8): 2258-2265.
21. **Byng-Maddick R, Turner C T, Pollara G, Ellis M, Guppy N J, Bell L C K and Noursadeghi M (2017):** Tumor necrosis factor (TNF) bioactivity at the site of an acute cell-mediated immune response is preserved in rheumatoid arthritis patients responding to anti-TNF therapy. Frontiers in Immunology, 8: 1-13.

22. **Hadinedoushan H, Noorbakhsh P and Soleymani-Salehabadih H (2016):** Tumor necrosis factor alpha gene polymorphism and association with its serum level in Iranian population with rheumatoid arthritis. Arch Rheumatol., 31(4): 306-313.
23. **Wei S-T, Sun Y-H, Zong S-H and Xiang Y-B (2015):** Serum levels of IL-6 and TNF-α may correlate with activity and severity of rheumatoid arthritis. International Medical Journal of Experimental and Clinical Research, 21(4): 4030-4038.
24. **Gheita T A, Azkalany G S, Gaber W and Mohey A (2015):** Clinical significance of serum TNFα and -308 G/A promoter polymorphism in rheumatoid arthritis. The Egyptian Rheumatologist, 37(2): 49-54.
25. **Müller R, Mart Kull M, Lember M, Põlluste K, Valner A and Kallikorm R (2017):** Insulin resistance in early rheumatoid arthritis is associated with low appendicular lean ass.BioMed. Research International., 20(17): 1-5.
26. **Stagakis I, BertsiasG, Karvounaris S, Kavousanaki M, Virla D, Raptopoulou A, Kardassis D, Boumpas D T and Sidiropoulos P I (2012):** Anti-tumor necrosis factor therapy improves insulin resistance, beta cell function and insulin signaling in active rheumatoid arthritis patients with high insulin resistance. Arthritis Research and Therapy, 14 (3): 141-147.
27. **Costa N T, Iriyoda T M V, Kallaur A P, Delongui F, Alfieri D F, Lozovoy M A B, Amin R B, Delfino V D A, Dichi I and Simão A N S (2016):** Influence of insulin resistance and TNF-α on the inflammatory process, oxidative stress and disease activity in patients with rheumatoid arthritis. Oxidative Medicine and Cellular Longevity, 20(16): 1-9.
28. **Chung C P, Oeser A, Solus J F, Gebretsadik T, Shintani A, Avalos I and Stein C M (2008):** Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. Arthritis and Rheumatism, 58(7): 2105–2112.
29. **Şahin M, Ugan Y, Tunç S E, Akın S, K◌roğlu B, Kutlucan A, Sütçü R and Yeşildağ-AandKılbaş A (2014):** Potential role of interleukin-18 in patients with rheumatoid arthritis associated carotid intima-media thickness but not insulin resistance. Eur. J. Rheumatol., 14(4): 135-144.
30. **Castillo-Hernandez J, Maldonado-Cervantes M I, Reyes J P, Patiño-Marin N, Maldonado-Cervantes E, Solorzano-Rodriguez C, de la Cruz Mendoza E and Alvarado-Sanchez B (2017):** Obesity is the main determinant of insulin resistance more than the circulating pro-inflammatory cytokines levels in rheumatoid arthritis patients.Rev. Bras. Reumatol. Engl., 57(4): 320-329.
31. **Gonzalez-Gay M A, Gonzalez-Juanatey C, Vazquez-Rodriguez T R , Miranda-Filloy J A and Llorca J (2010):** Insulin resistance in rheumatoid arthritis: the impact of the anti-TNF-α therapy. Annals of the New York Academy of Sciences, 11(93): 153–159.
32. **Gwozdziewiczova S, Lichnovska R, Yahia R B, Chlup R and Hřebiček J (2005):** "TNF-α in the development of insulin resistance and other disorders in metabolic syndrome. HDL. Biomed. Papers, 149(1): 109–117.
33. **Agarwal N, Chitrika A, Bhattacharjee J and Jain S K (2011):** Correlation of tumor necrosis factor-α and interleukin-6 with anthropometric indices of obesity and parameters of insulin resistance in healthy North Indian population.JIACM., 12(3): 196-204.
34. **Rajarajeswari D, Ramalingam K and Naidu J N (2011):** Tumor necrosis factor- alpha in the development of insulin resistance in type 2 diabetes mellitus.International Journal of Applied Biology and Pharmaceutical Technology, 4(2): 55-60.
35. **Lee J S, Shin J H, Lee J O, Lee K M, Kim J H and Choi B S (2010):** Serum levels of interleukin-8 and tumor necrosis factor-alpha in coal Worker's Pneumoconiosis: one-year follow-up study. Safety and Health at Work, 2(1): 69-79.
36. **Chen L, Chen R, Wang H and Liang F (2015):** Mechanisms linking inflammation to insulin resistance. Int. J. Endocrinol.,409: 1-9.