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Serum Adiponectin and Insulin Resistance in Systemic Lupus Erythematosus and Rheumatoid Arthritis Patients

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ABSTRACT

Background: Insulin sensitivity, blood sugar, lipids, and cardiovascular disease (CVD) are all affected by adiponectin. Adiponectin's involvement in the aetiology of autoimmune illness is still debatable.

Objective: To assess the blood level of adiponectin in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), as well as the probable relationship with insulin resistance and disease activity ratings.

Patients and methods: A total of 100 SLE, 100 RA, and 100 matched controls were examined. Both the disease activity score (DAS28) and the SLE disease activity index (SLEDAI) were evaluated. Serum adiponectin, C-peptide, and lipid profile were all measured. Both the homeostasis assessment model of insulin resistance (HOMA-IR) and HOMA-B homeostasis model evaluation indices for beta cell function were evaluated.

Results: In SLE and RA patients, adiponectin (12.27±1.45, 12.05±0.94 vs 4.12±2.03), C peptide (3.97±2.85, 5.66±3.69 vs 1.8±0.9), fasting insulin levels (37.6±13.2, 35.85±13.68 vs 6.55±2.04), HOMR-IR (7.9±3.03, 7.1±3.09 vs 1.33±0.67) were significantly higher compared to control group ($p<0.001$). In patients with SLE and RA, adiponectin had significant positive correlation with ESR and disease activity ($p<0.001$, $p=0.042$ and $p<0.001$, $p=0.015$ respectively) but negative correlation with platelet count ($p=0.003$, $p=0.004$), while C-peptide had significant positive correlation with HOMA-B ($p= 0.019$, 0.041), ESR ($p=0.004$, $p<0.001$), and BMI ($p=0.020$, $p<0.001$)

Conclusion: Adiponectin level, C-peptide and indices of IR are elevated in patients with SLE and RA. Adiponectin positively correlated with disease activity and ESR and C-peptide positively correlated with HOMA-B in SLE and RA patients.

Keywords: Adiponectin, Insulin resistance, Systemic lupus erythematosus, Rheumatoid arthritis.

INTRODUCTION

Obesity is a low-grade inflammatory condition that is characterised by altered adipokine expression and increased production of pro-inflammatory mediators including interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α). Due to the immunomodulatory qualities of adipose tissue and the connection between inflammation and autoimmunity, obesity may raise the risk of developing autoimmune diseases including rheumatoid arthritis (RA) and other immune-mediated illnesses [(1)].

Due to its inflammatory, fibrotic, and antioxidant effects, the adipokine adiponectin plays a critical role in controlling insulin sensitivity, lipid metabolism, and blood sugar levels. Three molecular weights of circulating adiponectin low, medium, and high, each have unique biological characteristics and tissue targets. Anti-proliferation, anti-atherosclerotic, and inhibition of carcinogenesis are further protective properties [(2)]. However, adiponectin, may have a pro-inflammatory impact. It is prevalent in the fluid and synovium that are swollen in RA and causes inflammatory reactions. Additionally, it has been linked to the emergence of bone erosions [(1)]. It's important to note that these variations in adiponectin activity are related to its degree of oligomerization, and contrasting effects have been reported for both low and high molecular isoforms [(3)]. Hence, adiponectin role in autoimmune disease is still a matter of controversy.

Connecting peptide (C-peptide), the cleavage product of proinsulin, is a small linear molecule composed of 31 amino-acids. Its stability and ability to escapes first-pass metabolism by the liver, allow the use of C-peptide as a reliable marker of beta cell function in clinical practice. Many studies had proved that C-peptide is a biologically active molecule acting as an endogenous antioxidant, preventing, in adjunction with insulin, hyperglycemia-induced microvascular dysfunction and nervous damage [(4)].

A complex medley of immunological, environmental, hormonal, and genetic predisposing factors contributes to the development of both SLE and RA. Potential involvement of autoantibodies, immune complexes, and soluble mediators in tissue injury is a common characteristic [(2)].

A particular insulin concentration is associated with a suboptimal glucose response in the clinical condition known as insulin resistance (IR). IR, which is most likely the most significant predictor of type 2 diabetes, may be connected to the inflammatory proteins leptin, adiponectin, TNF-alpha, and resistin released by adipocytes [(5)]. Low-grade inflammatory states have been linked to IR, which may assist to understand how it arises. Inflammation may worsen IR and affect the function of pancreatic cells [(6)]. Additionally, IR has been linked to inflammatory diseases as RA [(7)], and SLE [(5)].

The aim of this work was to compare the level of adiponectin in patients with SLE and RA and to

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evaluate the relation of adiponectin level to IR parameters and disease activity.

PATIENTS AND METHODS

From the out-patient clinics of the rheumatology and internal medicine departments, 100 SLE patients who met the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria [8] for SLE and 100 RA patients who met the 2010 ACREULAR classification criteria [9] were selected. As a control, 100 healthy individuals of similar age and gender were included.

Patients were ineligible if they were less than 18 years old, expecting, or if they had a body mass index (BMI) of more than 30 kg/m2, a history of myocardial infarction, diabetes, liver disease, or renal failure. They were also ineligible if they were taking more than 20 mg of prednisone every day.

Patients' demographics, illness severity, and physical examination were all considered in the evaluation. Fasting blood sugar, complete blood count, erythrocyte sedimentation rate (ESR), cholesterol, triglycerides, urea, and creatinine were all measured at the time of examination for each patient. The clinical records were searched for autoantibodies, antinuclear antibodies (ANA), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP).

The manufacturer's protocol was followed to perform an enzyme-linked immunosorbent assay (ELISA) to determine the serum adiponectin level (g/mL) (MBL International Corp., Woburn, MA, USA). The serum adiponectin range was 3.5-22.4 g/mL.

The quantitative sandwich enzyme immunoassay method was used to measure C-peptide. As instructed by the manufacturer, an antibody specific for C-peptide has been pre-coated onto a microplate (Cusabio Technology LLC., Biotechnology company, Houston, TX, USA). The range of detection was 0.5–8 ng/ml.

The levels of insulin and fasting blood sugar were measured (enzyme immunoassay, ST AIA-PACK IRI, Tosoh corporation, Tokyo, Japan). The formula for HOMA-IR, or homeostasis model assessment of insulin resistance, is fasting plasma insulin (IU/L) x fasting glucose (mmol/L)/22.5. The following formula was used to determine the homeostasis model assessment of ß-cell function (HOMA-B): 20 fasting insulin (IU/L) / fasting glucose (mmol/L) -3.5 [10,11]. The largest relative risk of diabetes is linked to high HOMA-IR and low HOMA-B, with the correlations between HOMA-IR and HOMA-B being independent and additive. HOMA-IR > 1.4 and HOMA-B 81.7 were the median cut thresholds for both indices to signify insulin resistance [12].

At the beginning of the work, disease activity was evaluated using the SLE disease activity index (SLEDAI) [13] for SLE and the disease activity score (DAS28) [14] for RA. The criteria for defining active RA illness were DAS28>2.6 and remission ≤ 2.6.

Ethical approval:

All patients and controls provided informed consent, it was approved by the Menofia University Faculty of Medicine's local ethics committee (IRB Approval number: 11/22 INTM5). The study conforms with the World Medical Association's Declaration of Helsinki on ethical considerations.

Statistical analysis

The statistical programme for the social sciences (SPSS) version 20.0 was used to examine the data. Results were shown as a mean ± standard deviation, or as a number and percentage. For three groups, the Chi square test or one-way analysis of variance (ANOVA) were used to compare the groups. A Spearman correlation test was taken into account. The significance threshold was established at p 0.05.

RESULTS

There was significant difference between the 3 groups as regarding age (p= 0.008) and disease duration (p= 0.000). Characteristics of the patients and control are presented in table 1.

Regarding the disease activity; the mean SLEDAI for SLE patients was 7.36±2.31 while the mean DAS28 for RA patients was 4.45±1.22.

ANA was positive in 90% of SLE patients while rheumatoid factor (RF) was positive in 81% and anti-CCP in 85% of RA patients. 98% of the SLE patients were on low dose steroid (5-10 mg), 90% on azathioprine (100 mg\day), 44 on hydroxychloroquine (HCQ) and 59 were on mycophenolate mofetil (MMF). Regarding RA patients, all were receiving methotrexate (MTX), 30% on low dose steroids, 40 were on HCQ and 39 on leflunomide. IR was present in 90% of SLE patients and 85% of RA compared to 35% control (p<0.001). ß-cell dysfunction was present in 85% SLE and 75% RA compared to 40% of the control (p<0.001). The laboratory investigations are presented in table 2.

Table (1): Demographic data of the studied groups

		SLE (n = 100)	RA (n = 100)	Control (n = 100)	p
Gender	Male	31(31%)	42(42%)	35(35%)	0.26
	Female	69(69%)	58(58%)	65(65%)	
Age (years)	Mean ± SD.	34.35 ± 5.44	34.96 ± 7.9	32.25 ± 5.73	**0.008***
	(Min. – Max.)	(24 – 41)	(23 – 50)	(23 – 44)	
BMI	Sig. bet. Groups	p1=0.51, **p2=0.022* p3= 0.003***			
	Mean ± SD.	25.65 ± 5.16	25.35 ± 3.27	25.5 ± 4.73	0.893
	(Min. – Max.)	(19 – 35)	(20 – 32)	(19 – 35)	
Disease duration	Sig. bet. Groups	p1=0.635, p2= 0.812, p3= 0.812			
	Mean ± SD.	6 ± 1.75	3.83 ± 2.44	–	**0.000***
	(Min. – Max.)	(3 – 10)	(1 – 10)	–	
Disease activity		SLEDAI	DAS28	-----	
	Mean ± SD	7.36 ± 2.31	4.45 ± 1.22		
	(Min. – Max.)	(4-13)	(2.6-6.5)		
Autoantibodies		ANA-positive, %	RF positive	ACCP- positive, %	
		90 %	81%	85%	

p: p value for comparing between the studied groups **,** p_1: p value for comparing between **SLE** and **RA,** p_2: p value for comparing between **SLE** and **Control,** p_3: p value for comparing between **RA** and **Control,** *: Statistically significant at $p \leq 0.05$

Table (2): Comparison between the three studied groups according to laboratory parameters

		SLE (n = 100)	RA (n = 100)	Control (n=100)	P
Adiponectin (ug/ml)	Mean ± SD.	12.27 ± 1.45	12.05 ± 0.94	4.12 ± 1.03	**<0.001***
	Sig. bet. Groups	p_1=0.319, **p_2<0.001*, p_3<0.001***			
ESR	Mean ± SD.	84.1 ± 20.8	83.2 ± 19.4	16.4 ± 4.1	**<0.001***
	Sig. bet. Groups	p_1=0.826, **p_2<0.001*, p_3<0.001***			
CREAT (Mg/dl)	Mean ± SD.	0.75 ± 0.17	0.69 ± 0.17	0.53 ± 0.12	0.5
	Sig. bet. Groups	p_1=0.6, p_2=0.9, p_3=0.6			
FBG (mg/dl)	Mean ± SD.	84.8 ± 10.67	84.6 ± 13.60	79.1 ± 12.1	**0.001***
	Sig. bet. Groups	p1=0.0.912**, p2=0.001*, p3= 0.002**			
Fasting Insulin (mIU/ml)	Mean ± SD.	37.6 ± 9.2	35.85 ± 8.6	6.55 ± 1.4	**<0.001***
	Sig. bet. Groups	p1=0.261, **p2<0.001*, p3<0.001***			
C-peptide (ng/ml)	Mean ± SD.	3.97 ± 0.91	5.66 ± 1.31	1.8 ± 0.44	**<0.001***
	Sig. bet. Groups	p_1=0.06, **p_2<0.001*, p_3<0.001***			
HOMA-IR	≤1.4	10 (10%)	15 (15%)	65 (65%)	**<0.001***
	>1.4	90 (90%)	85 (85%)	35 (35%)	
	Mean ± SD.	7.9 ± 1.9	7.1 ± 7.7	1.33 ± 0.32	**<0.001***
	Sig. bet. Groups	p_1=0.208, **p_2<0.001*, p_3<0.001***			
HOMA -B	≤81.7	85 (85.0%)	75 (75.0%)	40 (40.0%)	**<0.001***
	>81.7	15 (15.0%)	25 (25.0%)	60 (60.0%)	
	Mean ± SD.	52.27 ±12.43	81.04 ± 48.31	84.75 ± 20.22	**0.001***
	Sig. bet. Groups	**p_1=0.003**, **p_2=0.001***, p_3=0.782			
Hemoglobin	Mean ± SD.	11.35 ± 1.46	11.65 ± 1.47	11.26 ± 1.4	0.134
	Sig. bet. Groups	p1=0.138, p2=0.666, p3=0.056			
White blood cells count	Mean ± SD.	5.89 ± 1.02	6.2 ± 1.41	5.09 ± 1.21	0.101
	Sig. bet. Groups	p_1=0.298, p_2=0.72, p_3<0.31			
Platelets count	Mean ± SD.	306.1 ± 75.1	338.7 ± 8.4	355.8 ± 8.3	0.059
	Sig. bet. Groups	p1=0.111, p2=0.508, p3=0.405			

p: p value for comparing between the studied groups**,** p_1: p value for comparing between **SLE** and **RA,** p_2: p value for comparing between **SLE** and **Control,** p_3: p value for comparing between **RA** and **Control,** *: Statistically significant at $p \leq 0.05$ **.**

The correlations of serum adiponectin and C-peptide with the age, disease duration, BMI, laboratory investigations, HOMA-IR, HOMA-B and the corresponding disease activity in SLE and RA patients are presented in table 3 and 4 respectively.

Table (3): Correlation between serum Adiponectin (ug/ml) and various parameters of the systemic lupus erythematosus and rheumatoid arthritis patients

	Adiponectin (ug/ml)			
	SLE (n = 100)		RA (n = 100)	
	r_s	p	r_s	p
Age (years)	0.161	0.109	0.041	0.687
Disease duration	0.069	0.496	0.12	0.46
BMI	0.308	**0.002**	0.087	0.391
ESR	0.582	**<0.001***	0.390	**<0.001***
Hemoglobin	-0.176	0.080	-0.190	0.058
White blood cells	0.096	0.343	0.350	0.070
Platelets	-0.387	**0.003***	-0.285	**0.004***
HOMA-IR	-0.221	**0.160**	-0.280	**0.072**
HOMA -B	-0.104	0.301	-0.104	0.302
Disease activity score	0.681	**0. 042***	0.882	**0.015***

r_s: Spearman coefficient
*: Statistically significant at $p \leq 0.05$

Table (4): Correlation between C- peptide (ng/ml) and various parameters of the systemic lupus erythematosus and rheumatoid arthritis patients

Parameter	C- peptide (ng/ml)			
r , p	SLE(n=100)		RA(n=100)	
Age (years)	0.447	**<0.001***	0.594	**<0.001***
Disease duration	0.286	0.054	0.095	0.350
BMI	0.232	**0.020***	0.382	**<0.001***
ESR	0.288	**0.004***	0.400	**0.000***
Hemoglobin	0.267	0.070	0.242	0.066
White blood cells	-0.281	0.458	-0.484	0.103
Platelets	0.122	0.228	0.401	0.057
HOMA-IR	0.035	0.731	0.061	0.552
HOMA -B	0.076	**0.019***	0.205	**0.041***
Disease activity scores	0.075	0.456	0.327	0.107

r_s: Spearman coefficient *: Statistically significant at $p \leq 0.05$

DISCUSSION

The most prevalent adipokine, adiponectin, is critical with the purpose of preventing and treating metabolic illnesses such as type 2 diabetes, metabolic syndrome, and their associated consequences, particularly cardiovascular diseases [(15)]. Classic chronic inflammatory/autoimmune diseases without significant adipose tissue, such as RA, SLE, inflammatory bowel disease, type 1 diabetes, and cystic fibrosis, have higher levels of adiponectin than lower levels. There was a strong correlation between adiponectin levels and inflammatory markers in these patients [(16)]. Adiponectin has been linked to the occurrence and/or severity of several diseases, including RA, SLE, and osteoarthritis [(15)].

Serum adiponectin was high in both SLE and RA patients in comparison to control (P <0.001). Many studies showed that adiponectin was high in RA patients [(17,18)] and others [(19,20)] showed that adiponectin was high in SLE than control. On the other hand, **Barbosa *et al.* [(21)],** concluded that the level of adiponectin was not high in SLE patients. Another study reported that the mean adiponectin level was significantly lower in SLE patients compared to control [(22)]. Despite having higher amounts of the proinflammatory cytokines IL-6 and TNF-alpha, RA and SLE have higher levels of adiponectin, which may be due to the control of the adiponectin gene [(23)].

Patients with SLE and RA showed significantly substantial positive associations between adiponectin and ESR as well as disease activity. Similar to this, **Minamino *et al.* [(18)]** demonstrated that elevated levels of circulating adiponectin are a separate measure of disease activity in RA patients. According to **Abo-Ragab *et al.* [(17)] and Alkady *et al.* [(24)]** adiponectin levels are connected with RA patients' disease activity scores. Adiponectin was found to promote inflammation in people with autoimmune disorders, according to several recent research. In rheumatoid arthritis, chronic kidney disease, and inflammatory bowel disease, high adiponectin levels were highly linked with the degree of inflammation and the progression of the disorders [(25)].

According to **Fantuzzi [(11)],** indicators of inflammation were favourably linked with circulating and local levels of adiponectin in a variety of inflammatory and immune-mediated diseases. However, **Bustos and associates [(26)],** found no connection between serum adiponectin and RA clinical activity. There was no association between adiponectin levels and disease activity in SLE patients, according to other research [(20, 27)]. While, in individuals with SLE and RA, there was a substantial non-significant inverse relationship between adiponectin and indices of insulin resistance. However, Adiponectin's activity as an insulin sensitizer allows it to perform anti-diabetic, anti-inflammatory, and anti-atherogenic activities, according to research from earlier studies that indicated a

favourable link between circulating levels and insulin sensitivity indicators [23, 28].

In RA sufferers, inflammation makes IR stronger. The criticality of IR, which rises with high RA activity and decreases in the opposite direction, is similarly influenced by the degree of RA inflammation [29]. The patients in this research who had RA and SLE also had IR. In comparison to the control group, they exhibited increased fasting blood glucose, fasting insulin, fasting C peptide, and elevated HOMA-IR readings. **Sánchez-Pérez *et al.*** [30] concurred that SLE patients had higher levels of IR and C peptide compared to controls. **Tejera-Segura *et al.*** [31] demonstrated that individuals with RA exhibited high levels of insulin and C peptide as well as IR. **Shaaban *et al.*[32],** in contrast, discovered that HOMA and insulin levels in SLE patients were equivalent to those in the control group.

In SLE and RA patients, C-peptide correlated favourably with age and BMI. Similar to SLE and RA, obesity has been identified as the primary cause of insulin resistance [33]. In SLE and RA patients, C-peptide demonstrated a statistically significant positive connection with ESR and HOMA-B (P=0.004, P=0.000, and P=0.019, P=0.041, respectively). Additionally, according to **Risti *et al.*** [34], ESR was a standalone predictor of elevated C-peptide concentration (P= 0.133, P = 0.022). According to a recent study **Martín-González *et al.*** [35] on RA patients, hyperglycemia brought on by insulin resistance causes beta-cell malfunction, which manifests as increased insulin and C-peptide production.

CONCLUSION

Patients with SLE and RA had higher serum levels of the hormones C-peptide and adiponectin. In patients with SLE and RA, insulin resistance as measured by HOMA-IR and HOMA-B was elevated. Patients with SLE and RA showed a substantial positive connection between adiponectin and disease activity. C-peptide demonstrated a strong positive association with the HOMA-B measure of insulin resistance in SLE and RA patients.

Limitations: Larger scale longitudinal studies are recommended.

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Competing interests: Nil.

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