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Insulin Resistance in Patients with Lupus Nephritis: Association to Cardiovascular Risk Factors, Disease Activity, and Subclinical Atherosclerosis

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Abstract

Background: Insulin resistance is one of the crucial risk factors for cardiovascular disease (CVD) insystemic lupus erythematous (SLE). Lupus nephritis represents one of the most serious complications of SLE with increased risk of CVD. No previous studies evaluated insulin resistance in Lupus nephritis patients.

Aim of Study: The study aimed to evaluate insulin resistance in patients with lupus nephritis and assess its relationship to traditional cardiovascular risk factors, disease activity, damage index and subclinical atherosclerosis.

Material and Methods: We enrolled 90 patients had SLE including 10 males and 80 females. SLE patients were divided into 45 patients had lupus nephritis based on renal biopsy and 45 patients had no evidence of lupus nephritis. One hundred healthy subject sex and age matched was served as the control group. Patients were recruited from the Rheumatology and Immunology Clinic of the Internal Medicine Department, Kasr Al-Ainy Hospital, Faculty of Medicine, Cairo University. Fasting (blood sugar, serum lipids, oxLDL, and insulin) were measured. Homeostasis model assessment of insulin resistance (HOMA-IR) were calculated and Carotid intima media thickness (CIMT) was measured in all patients. Our data was expressed as mean ± SEM, The correlation between variables was evaluated using Spearman's rank correlation coefficient test. Linear regression analysiswas done to explore the associated factors with insulin resistance.

Results: There was significant increase in HOMA-IR in lupus nephritis patients with mean (11.7±1.1) compared to non-nephritis patients (4.4±0.4), $p<0.001$. HOMA-IR was significantly correlated to BMI ($p=0.01$), FBS ($p=0.001$), TC ($p=0.001$), TG ($p=0.003$), LDL-C ($p=0.01$), oxLDL ($p=0.03$), CRP ($p=0.04$), serum creatinine ($p<0.001$), urine albumin creatinine ratio ($p<0.001$), CIMT (P= 0.03), lupus activity index (SLEDAI) ($p=0.02$), damage index (SLICC/ACR) ($p=0.04$) and negatively correlated to albumin ($p=0.04$) and HDL-C ($p<0.001$). After linear regression analysis, serum creatinine ($p=0.04$), and SLICC/ACR ($p=0.02$) were still significantly associated to insulin resistance in lupus nephritis patients.

Conclusion: Patients with lupus nephritis were at increased risk of insulin resistance than non-nephritis SLE patients andsignificantly associated to traditional CVD risk factors, subclinical atherosclerosis, disease activity and damage index. Increase in serum creatinine and disease damage index were significant associated factors for insulin resistance in lupus nephritispatients. Early introduction for the suitable treatment modality in patients with lupus nephritis could ameliorate cardiovascular disease progression.

Key Words: *Insulin resistance – Cardiovascular disease – Lupus – Atherosclerosis.*

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Introduction

SYSTEMIC lupus erythematosus is an autoimmune chronic inflammatory disorder that commonly affects young women. It has been obvious that patients with SLE have increased morbidity and mortality due to premature cardiovascular disease (CVD) [1]. SLE patients havetwice greater risk of developing CVD than the general population that could be related to traditional atherosclerotic risk factors as (older age, male sex, dyslipidemia, hypertension and smoking),and SLE disease related factors as disease duration, disease activity, and other related disease manifestations [2]. However, asymptomatic premature CVD has been significantly documented in patients with SLEregardless traditional atherosclerotic risk factors or SLE disease activity, or corticosteroid treatment [3]. Lupus nephritis (LN) represents one of the most serious complications of SLE [4], affecting 7%-31% of SLE patients at diagnosis and 31%-48% within 5 years after diagnosis [5] and accounting for significant morbidity and mortality [6]. Previous studies documented increased risk of CVD in SLE patients with lupus nephritis compared to SLE patients without nephritis [7,8]. This finding supports that other SLE related factors could increase the risk of CVD independently from traditional atherosclerotic risk factors.

Insulin resistance has been defined as decreased sensitivity or responsiveness of insulin-sensitive tissues to insulin [9]. Insulin resistance,calculated

by Homeostasis Model Assessment Index (HOMA-IR), has been establishedas an independent risk factor for CVD in nondiabetic individuals [10]. Insulin resistance can accelerate the cellular process of atherosclerosis and plaque progression through various possible mechanismsincluding its effect on the endothelium leading to endothelium dysfunction enhancing the migration of the inflammatory cells into the plaque and via promoting the apoptosis of the endothelial cells, the vascular smooth muscle cells, and macrophages which promotes plaque progression and rapture and acute vascular occlusion [11]. Previous reports demonstrated significantincrease of insulin resistance in SLE patients compared to healthy population [12-14]. Moreover, significant insulin resistancehas been documented in SLE patients with inactive and mild disease manifestations when compared with healthy controlswhich was observed despite normal levels of fasting glucoseand pancreatic beta cell function [15]. Thus, identifying the underlying pathophysiological causes and the SLE disease related risk factors for CVD in SLE patients is a subject of interest for studying. Previous studies assessed insulin resistance in SLE patients through the evaluation of metabolic syndrome which relied on other risk parameters [16].

To our Knowledge, no previous studies assessed insulin resistance in lupus nephritis patients one of the crucial SLE related factors that increase the risk for CVD. Thus, we assessedthe presence of insulin resistance in SLE patients with lupus nephritis in comparison to lupus non-nephritis patients, and weinvestigated the relationship of insulin resistance in lupus nephritis patients to cardiovascular risk factors, disease related parameters, and subclinical atherosclerosis.

Patients and Methods

Patients:

We enrolled in our study 90 SLE patients including 10 males and 80 females aged from 19 to 57 years with a mean age of (29.9 ±0.86 years). SLE patients were divided into 45 patients had lupus nephritis based on renal biopsy and 45 patients had no evidence of lupus nephritis. One hundred healthy subject sex and age matched was served as the control group including 12 males and 88 females, aged from 18 to 56 years with a mean age of (31.2±0.75 years). Patients were recruited during the interval from November 2020 to March 2021 from the Rheumatology and Immunology Clinic of the Internal Medicine Department, Faculty of Medicine, Cairo University. The patients were recruited according to the American College of Rheumatology (ACR) revised criteria for SLE (1982) [17]. The diagnosis of lupus nephritis was assessed by the ACR 2012 guidelines [18]. Patients on lipid lowering treatment or renal replacement therapy, had recent infection, thyroid gland disorders and pregnancy were excluded from the study. Informed voluntary oral consent to participate in the study was taken from patients and control subjects according to the protocol approved by the local ethics committee andin accordance with the ethical standard laid down in the Helsinki declaration. The study was approved by the Research Ethics Committee of Internal Medicine Department, Faculty of Medicine, Cairo University, Egypt. The medical records were reviewed to obtain the data of the blood picture, liver functions and to confirm the medication history. Our patients were receiving steroid therapy at the time of the study. Additionally, all patients were receiving immuno suppressive therapy such as cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, and sulphasalazine and some patients were receiving an antimalarial drug (chloroquine or hydrochloroquine).

II- *Methods:*

Clinical examinations:

The severity of the disease was assessed using Systemic lupus erythematosus diseases activity index (SLEDAI) [19]. Organ damage was assessed according to Systemic Lupus International Collaborating Clinics (SLICC) damage index [20]. Patients were considered hypertensive if the measured systolic blood pressure of at least 140mmHg or the diastolic blood pressure of at least 90mmHg repeatedly or they were known hypertensive on antihypertensive drugs. Obesity was defined as BMI more than 30. Hypercholesterolemia was defined as total cholesterol level (TC) >200mg/dl or Low density lipoprotein cholesterol (LDL-C) level of >150mg/dl. The reference intervals were obtained according to the National Cholesterol Education Program [9]. The prevalence of metabolic syndrome was evaluated according to the International Diabetes Federation criteria [21]. The patients and controls were subjected to carotid duplex using HDI 5000 machine using 7.5 MHz linear transducer. Internal carotid artery was imaged in a longitudinal and cross-sectional view. Carotid intima media thickness (CIMT) was measured in the common carotid artery from the carotid bulb.

Blood sampling and biochemical analysis:

Venous blood samples were withdrawn under aseptic conditions from patients at least 24 hours after the last dose of immunosuppressive treatment.

Then blood was divided to separate both plasma and serum and kept at –80ºC for further analysis. Fasting insulin, oxidized low-density lipoprotein (ox LDL) were estimated using commercial ELISA kits. Serum creatinine, urea, total cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured using colorimetric kits according to the manufacturer's instructions. Low density lipoprotein cholesterol (LDL-C) levels were measured by Friedewald's formula **[22]**. Complement 3 (C3), complement 4 (C4) and high-sensitivity C-reactive protein (CRP), were measured by immunoturbidimetry. Homeostasis model assessment of insulin resistance (HOMA IR) was calculated as Insulin * Fasting blood glucose level /22.5 **[23]**.

Statistical analyses:

Data was analyzed using Graph Pad Prism version 5.0 software (USA). The normally distributed data was expressed as mean ± SEM, whereas variables with a skewed distribution were presented as median (interquartile range). Statistical differences between two groups were analyzed using Student's *t*-test for parametric data and Mann-Whitney U test for non-parametric data. Categorical data was represented by frequency and percentage, and was compared by chi square (χ^2) test. The correlation between variables was evaluated using Spearman's rank correlation coefficient test (two-tailed). Linear regression was done to explore the associated factors with insulin resistance. The level of significance was identified at $p<0.05$.

Results

The demographic and laboratory data of SLE patients compared to control subjects:

Table (1) shows the demographic and laboratory data of SLE patients and control subjects. In the SLE group, eighty patients were females (89%) and 10 patients were males (11%). The mean age was (29.9±0.86 years). From the 90 SLE patients, 68 werehypertensive(75%), 67 were diabetic (74%), 50 were obese (56%), 56 had (62%) dyslipidemia and 54 patients (60%) met the criteria of metabolic syndrome. In the control group, 88 were females (88%) and 12 were males (12%), with a mean age of (31.2±0.75 years). There were significance elevation in the fasting blood glucose and lipid profile of SLE patients compared to control group ($p<0.001$). OxLDL significantly increased in SLE patients compared to the control group ($p<0.001$). There was significant increase in the CIMT as a diagnosis for subclinical atherosclerosis in SLE patients compared to control group ($p<0.001$). Fasting insulin and calculated HOMA IR were significantly elevated in SLE patients compared to control group ($p<0.001$).

Table (1): Demographic and laboratory data of SLE patients and control subjects.

Groups / Parameters	SLE patients (n=90)	Control subjects (n=100)	*p*-value
Age (years)	29.9±0.86	31.2±0.75	0.07
Sex, no (%):			
Female	80 (89%)	88 (88%)	0.8
Male	10 (11%)	12 (12%)	
Weight (kg)	68.5±0.89	69.2±1.2	0.64
Height (Cm)	160.8±0.51	159.2±0.92	0.09
BMI (kg/m^2)	26.8±0.31	25.9±0.5	0.13
FBG (mg/dl)	160±12.4	108.5±6.5	<0.001**
Hb (g/dl)	11.6±0.2	14.5±0.7	<0.001**
WBCs ($x10^3$/microl)	6.7±0.3	9.5±0.5	<0.001**
Platelets ($x10^3$/microl)	249.3±0.3	220.2±0.1	<0.001**
ds-DNA antibodies positive	100%		
ANA positive	100%	–	–
C3 (mg/dl)	20.6±2.6	–	–
C4 (mg/dl)	88.6±4.8	–	–
SLEDAI	19.6±0.89	–	–
SLICC/ACR	4.2±0.18		
AST (IU/l)	38.3±4.1	25.2±1.5	<0.01**
ALT (IU/l)	26.1±2.1	22.5±1.2	0.12
Albumin (gm/l)	3.5±0.1	5.2±0.3	<0.001**
Creatinine (mg/dl)	1.6±0.13	1.1±0.8	0.045*
Urine A/C ratio (mg/mmol)	13.3±0.16	2.1±0.06	<0.01**
TC (mg/dl)	246±9.8	142.6±8.1	<0.001**
TG (mg/dl)	165±7.2	122.8±3.5	<0.001**
HDL-C (mg/dl)	47.1±2.2	78.1±2.9	<0.001**
LDL-C (mg/dl)	167.2±10.2	76.4±4.2	<0.001**
oxLDL (ng/ml)	208±18	76.9±8.6	<0.001**
Left CIMT (mm)	0.07±0.001	0.06±0.002	<0.001**
Right CIMT (mm)	0.07±0.006	0.05±0.003	<0.001**
ESR (mm/hr)	62.2±3.5	42.6±4.1	<0.001**
C-reactive protein (mg/l)	18.2±0.8	7.2±0.6	<0.001**
Fasting Insulin (mU/l)	25.4±3.5	20±2.1	<0.001**
HOMA-IR	7.5±1.3	1.5±0.08	<0.001**

Data are represented as mean ± SE. Significant difference at $p<0.05$*, at $p< 0.01$**, BMI, body mass index, FBG, fasting blood glucose, C3, complement 3, ANA, antinuclear antibodies, urine A/C ratio, urine albumin creatinine ratio, CIMT, carotid intima media thickness, SLEDAI, systemic lupus erythematosus disease activity index; SLICC, Systemic Lupus International Collaborating Clinics, oxLDL, oxidized low-density lipoprotein, HOMA-IR, Homeostasis model assessment of insulin resistance.

The demographic and laboratory data of lupus nephritis compared to lupus non nephritis patients:

Fasting blood glucose, lipid profile and renal function tests were significantly increased in lupus nephritis patients compared to lupus non nephritis patients. There were significant increase in TC, TG, LDL-C and oxLDL (p=0.02, 0.008, 0.03, 0.00) respectively, with significant decrease in HDL-C (p=0.04) (Table 2). Also there was significant elevation in ESR ($p<0.01$), CRP ($p<0.001$), lupus activity index (SLEDAI) and damage index (SLICC/ACR) ($p<0.001$) associated with significant decrease in C3 and C4 ($p<0.01$) in lupus nephritis patients compared by non-nephritis patients (Table

2). CIMT as a measure to subclinical atherosclerosis was significantly increased in lupus nephritis patients compared to non-nephritis patients (p<0.03). Fasting insulin and HOMA-IR were significantly elevated in lupus nephritis patients compared to non-nephritis (p<0.001) (Table 2).

Table (2): Comparison of demographic and laboratory parameters between lupus nephritis and lupus non-nephritis patients.

Groups Parameters	Lupus nephritis (n=45)	Lupus non-nephritis (n=45)	p-value
Age (years)	31.2±1.3	28.6±1.1	0.1
Sex, no (%):			
Female	40 (89%)	41 (89%)	1
Male	5 (11%)	5 (11%)	
Weight (kg)	70.5±1.2	68.5±1.4	0.2
Height (Cm)	161.2±0.75	160.3±0.69	0.3
BMI (kg/m^2)	27.1±0.47	26.4±0.4	0.2
FBG (mg/dl)	184.6±11.8	132.1±6.3	<0.001 **
Hb (g/dl)	10.5±0.27	10.7±0.31	0.6
WBCs (x10^3/microl)	5.9±0.4	7.6±0.4	0.003 *
Platelets (x10^3/microl)	244.8±13.2	254.1±15.8	0.6
ds-DNA antibodies positive	345 (100%)	45 (100%)	1
ANA positive	45 (100%)	45 (100%)	1
C3 (mg/dl)	14.1±1.8	26.6±4.6	0.01 *
C4 (mg/dl)	81.6±5.7	96.1±7.7	0.01 *
SLEDAI	24.6±0.99	15.7±1.1	0.001 * *
SLICC/ACR	4.8±0.24	3.7±0.25	<0.001 **
AST (IU/l)	43.2±7.5	33.1±5.9	0.2
ALT (IU/l)	28.5±3.2	24.1±2.4	0.27
Albumin (gm/l)	3.7±0.1	4.2±0.3	0.1
Creatinine (mg/dl)	2.2±0.45	0.8±0.09	0.003 * *
Urea (mmol/l)	3.9±0.13	3.2±0.14	<0.001 **
Urine A/C ratio (mg/mmol)	24.7±2.9	12.2±2.3	0.001 * *
TC (mg/dl)	292.4±14.9	247.9±13.3	0.02*
TG (mg/dl)	212.3±12.7	168.3± 9.9	0.008**
HDL-C (mg/dl)	40.9±3.2	50.1±3.1	0.04*
LDL-C (mg/dl)	209.6±15.2	168.3±9.9	0.03 *
oxLDL (ng/ml)	292.6±28.1	119.1±15.2	<0.001 **
Average CIMT (mm)	0.075±0.002	0.069±0.002	0.03**
ESR (mm/hr)	75.5±5.1	57.9±5.4	0.01 *
C- reactive protein (mg/l)	16.7±1.9	10.3±1.3	<0.001 **
Fasting insulin (mU/l)	27.5±1.9	21.2±0.96	<0.001 **
HOMA-IR	11.7±1.1	4.4±0.4	<0.001 **

- Data are represented as mean ± SE. Significant difference at p<0.05*, at p<0.01 * *.

Metabolic risk factors and metabolic syndromein lupus nephritis compared to non-nephritis patients:

There were significant elevations in the metabolic risk factors as diabetes and obesity in lupus nephritis patients compared to non-nephritis (p= 0.02, 0.03), however, there were no significant differences regarding hypertension and dyslipidemia (p=0.32, 0.19). Metabolic syndrome wasdetected in 32 (71%) lupus nephritis patients and 22 (49%) non-nephritis patients with significant difference, (p<0.03) (Table 3).

Table (3): Comparison between metabolic parameters between lupus nephritis and lupus non-nephritis patients.

Groups Parameters	Lupus nephritis (n=45)	Lupus non-nephritis (n=45)	p-value
Hypertension	36 (80%)	32 (71%)	0.32
Metabolic syndrome	32 (71%)	22 (49 %)	0.03 *
Diabetes mellitus	38 (84%)	29 (65%)	0.02*
Obesity	32 (71%)	22 (49%)	0.03 *
Dyslipidemia	31 (68%)	25 (56%)	0.19

Data are represented by percentage. Significant difference at p<0.05*.

The associations between HOMA-IR and cardiovascular risk factors, disease activity, disease damage and CIMT in lupus nephritis patients:

HOMA-IR was positively correlated to age (p=0.002), BMI (p=0.01), FBS (p=0.001), CRP (p=0.04), TC (p=0.001), TG (p=0.003), LDL-C (p=0.01), oxLDL (p=0.03), and negatively correlated to HDL (p=0.001). Also HOMA-IR strongly correlated to serum creatinine (P<0.001) and urine A/C ratio (p<0.001) and negatively correlated to albumin (p=0.04). HOMA-IR was positively correlated to CIMT (p=0.03), SLEDAI (p<0.02) and SLICC/ACR (p<0.04) (Table 4). After regression analysis was done to explore the associated renal factors to insulin resistance, we found serum creatinine (p=0.04) and damage index (SLICC/ACR) (p<0.02) were significantly associated to insulin resistance (Table 5).

Table (4): The correlation between insulin resistance and different parameters among patients with lupus nephritis.

Parameter	r	p
Age (years)	0.44	0.002*
BMI (kg/m^2)	0.38	0.01 *
FBS	0.47	0.001 **
CRP	0.3	0.04*
C3 (mg/dl)	-0.32	0.03 *
C4 (mg/dl)	0.19	0.2
SLEDAI	0.34	0.02*
SLICC/ACR	0.29	0.04*
Serum Albumin (g/l)	-0.29	0.04*
Serum Creatinine (mg/dl)	0.54	<0.001**
Urine A/C ratio (mg/mmol)	0.7	<0.001**
TC (mg/dl)	0.47	0.001 **
TG (mg/dl)	0.43	0.003 **
HDL-C (mg/dl)	-0.48	0.001 **
LDL-C (mg/dl)	0.36	0.01 *
Average CIMT (mm)	0.32	0.03 *
oxLDL (ng/ml)	0.32	0.03 *

r = Spearman correlation co-efficient, * p<0.05 is significant.

Table (5): Linear regression analysis to explore the associated factors with HOMA-IR among lupus nephritis patients.

Model	Unstandardized Coefficients		Standardized Coefficients	*p*-value
	B	Std.Error	Beta	
SLICC	12.822	5.668	2.22	0.02*
SLEDAI	8.4	2.6	0.02	0.915
Creatinine	9.5	3.24	1.8	0.04*
Albumin	–.255	0.741	–0.05	0.733
Urine AC ratio	.000	0.065	–0.002	0.991

*p<0.05 is significant; SLEDAI, systemic lupus erythematosus disease activity index; SLICC, Systemic Lupus International Collaborating Clinics; Urine AC, ratiourine albumin creatinine ratio.

Discussion

There are several mechanisms that could contribute to altered insulin sensitivity in SLE. These include obesity andsteroid usewhich are commonly present in SLE patients. In addition, insulin resistance is associated with a state of chronic low-grade inflammation, and several mediators released from various cell types, including immune cells and adipocytes, have been identified as being involved in the development of insulin resistance **[24]**. From available studies, insulin resistance has been found significantly elevated in SLE patients compared to healthy controls which significantly associated to increased risk of CVD in SLE patients **[12-14]**. Similarly, in our study we found significant increase in insulin resistancein SLE patients compared to control group. Moreover, insulin resistancewas significantly elevated in lupus nephritis patients compared to non-nephritis patients.

Metabolic syndrome represents a crucial factor for the development of CVD in SLE patients which associated with organ damage complications **[25]**. Insulin resistance represents one of the main criteria to define metabolic syndrome by the World Health Organization definition **[26]**. Thus, previous studies used to evaluate the association of insulin resistancein SLE patients through the evaluation of metabolic syndrome in their patients **[16,27]**. In a meta-analysis included 86 studies in SLE patients had metabolic syndrome reported twice increase in CVD risk and 1.5 increase in all-cause mortality **[28]**. In our study metabolic syndrome was detected in 60% of SLE patients that correlated to previous studies **[16,29]**. In addition, metabolic syndrome in our patients was significantly elevated in lupus nephritis patients 71% compared to 48% non-nephritis patients. Our findings correlated with a previous study by Zhang et al., **[30]**, and a recent study by Jin et al., **[31]**. In a large cohort study included 30 centers, metabolic syndrome was found in 38% SLE patients mostly in patients had active lupus nephritis, thrombocytopenia or on large doses of corticosteroids and immunosuppressive drugs **[32]**.

Dyslipidemia is one of the crucial risk factors for accelerated CVD **[33]**. Various studies documented significant dyslipidemia in SLE patients **[34,35]** which usually characterized by elevation in TC, LDL,TG, and decrease in HDL **[36]**. In our study we found significant dyslipidemia in SLE patients compared to control group. Dyslipidemia was significant in lupus nephritis compared to non-nephritis patients. In addition, insulin resistance was significantly associated with dyslipidemia in lupus nephritis patients. Different pathogenic factors are related to dyslipidemia in SLE patients. Elevation in the inflammatory markers as CRP and ESR have been involved in loweringthe HDL-C levels and increasing TG levels. Also,autoantibodies in SLE can decrease the lipoprotein lipase activity results in elevation in TG levels **[36]**. Moreover, autoantibodies to HDL-C can decrease the paraoxanase activity, an antioxidant enzyme which renders the HDL its antioxidant protective effect **[37]**. In addition, functional impairment in the anti-atherogenic HDL property has been established in SLE **[38]**.

In addition to dyslipidemia, ox LDL represents one of the important atherogenic peroxidation products **[39]**. OxLDL has been shown to be immunogenic, autoantibodies against ox-LDL are found elevated in SLE patients which facilitate oxLDL uptake by macrophages **[40]**. In our study, we found significant increase in oxLDL in SLE patients compared to control group and it was significantly elevated in lupus nephritis patients versus non nephritis patients. This finding was in line with Frostegård J et al., **[41]** who found the plasma oxLDL significantly elevated in SLE patients and significantly associated with lupus nephritis patients which supports the theory of increased lipid peroxidation in SLE especially in lupus nephritis patients **[40]**. Moreover, we found a significant association between insulin resistance and oxL DL in lupus nephritis patients. This finding was similar with the study by El Magadmi et al., who supposed that insulin resistance was not related to the steroid use in SLE patients but was closely related to oxLDL which represent an additional CVD risk factor in SLE patients **[12]**. Thus, the significant elevation in oxLDL and the positive association to insulin resistance supports the finding that pa-

tients with lupus nephritis are more susceptible to CVD.

Regarding the relation between insulin resistance and other traditional CVD risk factors in lupus nephritis patients, we found strong positive significant correlations between insulin resistance-with age, BMI, and fasting blood sugar in lupus nephritis patients. These were in line with the study Chung et al., who found the same associations in SLE patients and showed that BMI was the most significant contributor for insulin resistance in SLE patients [42].

CIMT has been established to be a reliable non-invasive method to identify subclinical atherosclerosis in SLE patients. Significant increase in CIMT has been reported in SLE patients compared to healthy subjects [43]. Similarly, we found significant increase in the CIMT in SLE patients compared to control group. In addition, CIMT was significantly higher in lupus nephritis patients compared to non-nephritis patients. Also we found a strong positive association between insulin resistance and CIMT in lupus nephritis patients.Our study correlated with Zhang et al., who found significant correlation between lupus nephritis and CIMT [30]. However, our finding did not correlate with Sharma et al., [44] who found that CIMT values did not significantly differ in patients with lupus nephritis compared to non-nephritis patients. They explained this to the early age group of their included patients and the effective treatment they had received with immunosuppressive agents that might contributed in delaying the process of atherosclerosis [44].

Measurement of CRP is widely used as a marker of inflammation, and it is pro-atherogenic [45]. CRP levels are associated with the presence of atherosclerosis in SLE patients [46]. In our study we found CRP significantly elevated in lupus nephritis versus non nephritis patients. In addition, insulin resistance was significantly correlated to CRP in patients with lupus nephritis. This finding supports the importance of inflammation in the pathogenesis of insulin resistance in addition to traditional CVD risk factors in lupus nephritis patients. In a previous large multicenter population study reported the significant relationship between insulin resistance and CRP in healthy subjects and suggested that chronic subclinical inflammation involved in the pathogenesis of insulin resistance [47].

Moreover, insulin resistance was significantly associated to serum creatinine, A/C ratio, low C3, SLICC, and SLEDAI in lupus nephritis patients. After linear regression analysis serum creatinine and SLICC were still the significant associated factors for insulin resistance. Previous studies showed that the presence of inflammatory phenotype in SLE patients as lupus nephritis, increased lupus activity [48], low C3 [49], and elevated CRP [50] were significantly associated to insulin resistancerather than traditional risk factors. In the longitudinal study by Parker et al., the presence of lupus nephritis, SLICC and SLEDAI were independently related to metabolic syndrome [51]. Interestingly, this longitudinal study showed no significant association between steroid use and metabolic syndrome after 2 years of follow-up. Moreover, in a lupus mouse model the researchers supposed that insulin resistance could develop before the onset of the clinical disease manifestations [52]. Hence, insulin resistance has been related to the inflammatory process and damage that occur early in SLE. Thus, early introduction of therapies to ameliorate insulin resistance in SLE is promising. Adding metformin to conventional treatment was found to decrease disease activity index, the dose of steroid exposure and BMI in SLE patients compared to conventional treatment [53].

There were limitations in our study: Firstly, we did not exclude the effect of steroid use on insulin resistance in our studied subjects asour studied patients were receiving steroids in different doses and durations which could affect the calculated value of HOMA-IR. Thus, it was better to select newly diagnosed naïve patients or patients not on steroids use. Also, we did not exclude the presence of diabetes and obesity that would contribute in the development of insulin resistance in our included patients. Lastly, our study was relatively small sample size.

We concluded that patients with lupus nephritiswere at increased risk of insulin resistance than non-nephritis SLE patients that was associated with traditional CVD risk factors, subclinical atherosclerosis, lupus activity and damage index. Increase in serum creatinine and damage index were significant associated factors for insulin resistance in lupus nephritis patients that could increase the risk for early CVD besides other traditional risk factors. Thus, identification of these disease related factors could help in early introduction for the suitable treatment modality that could ameliorate cardiovascular disease progression in lupus nephritis patients. Future studies is needed for introducing novel treatment modalities targeting insulin resistance in SLE patients.

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مقاومة الأنسولين فى مرضى التهاب الكلية الذئبى ارتباطها بعوامل الخطر القلبية الوعائية ونشاط المرض وتصلب الشرايين تحت الإكلينيكى

\الملخص : مقاومة الأنسولين هى من أحد عوامل الخطر لأمراض القلب والأوعية الدموية فى مرضى الذئبة الحمامية الجهازية. يعتبر إلتهاب الكلية الذئبى أحد أخطر المضاعفات فى مرضى الذئبة الحمامية الجهازية وترتفع فيه مخاطر الإصابة بأمراض القلب والأوعية الدموية ولم تقيم أى دراسات سابقة لمقاومة الأنسولين فى مرضى التهاب الكلية الذئبى ولذلك أجريت الدراسة لتقييم مقاومة الأنسولين لدى مرضى الالتهاب الكلية الذئبى وتقييم علاقته بعوامل الخطر القلبية الوعائية ونشاط المرض وتصلب الشرايين تحت الإكلينيكى

لقد أجريت الدراسة على ٩٠ شخص من مرضى الذئبة الحمامية الجهازية وقد قسموا إلى مجموعتين، ٤٥ مريض لديهم التهاب الكلية الذئبى و ٤٥ مريض ليس لديهم التهاب الكلية الذئبى و ١٠٠ شخص من الأصحاء كمجموعة ضابطة. وتم قياس مستوى الأنسولين والسكر الصائم والدهون الثلاثية، والكوليسترول ووظائف الكلى فى الدم وحساب نسبة مقاومة الأنسولين وتم فحص المرضى بالموجات الصوتية للشرايين السباتية كعلامة مبكرة لتصلب الشرايين.

وبعد الدراسة وجدنا ارتفاع فى نسبة مقاومة الأنسولين ذو دلالة إحصائية فى مرضى إلتهاب الكلية الذئبية مقارنة بمرضى الذئبة غير مصابين بالتهاب الكلى وقد ارتبطت مقاومة الأنسولين بشكل طردى ذو دلالة إحصائية بعوامل الخطر القلبية مثل (مستوى مؤشر كتلة الجسم والدهون الثلاثية والكوليسترول فى الدم) ووظائف الكلى وأيضاً ارتبطت بنشاط المرض ومؤشر الضرر المرضى وتصلب الشرايين تحت الإكلينيكى. وقد أظهر تقرير الانحدار اللوجستى علاقة ذو دلالة إحصائية بين ارتفاع كرياتين الدم ومؤشر الضرر المرضى ومقاومة الأنسولين.

\الاستنتاجات : مرضى التهاب الكلية الذئبى أكثر عرضة لمقاومة الأنسولين عن مرضى الذئبة غير المصابين بالتهاب الكلى وذلك يجعلهم أكثر عرضة لأمراض القلب والأوعية الدموية. ارتفاع كرياتنين الدم ومؤشر الضرر المرضى من الأسباب الهامة لإرتفاع نسبة مقاومة الأنسولين فى مرضى الكلية الذئبى. لذلك التدخل المبكر بالعلاج المناسب قد يؤدى إلى منع تطور أمراض القلب والأوعية الدموية فى مرضى التهاب الكلية الذئبى.