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Insulin Resistance in Pediatric Systemic Lupus Erythematosus and Rheumatoid Arthritis

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Abstract

Background: **Childhood rheumatologic disorders are multisystem diseases characterized by inflammation, damage, and/or pain of the joints, and connective tissues.** ***Aim:*** **This study aimed to detect the presence of insulin resistance (IR) in pediatric patients with systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) which can lead to the development of diabetes mellitus.** ***Subjects and Methods:*** **This case-control study was performed on 60 SLE, 60 RA patients, and 60 healthy subjects as a control group. All subjects were subjected to detailed history taking, physical examination, and laboratory investigations including determination of fasting blood glucose (FBG), total cholesterol, triglyceride (TG), HDL, LDL, and fasting insulin. Homeostatic model assessment of insulin resistance (HOMA IR) was calculated.** ***Results:*** **There was no significant difference in the age, and FBG in the three studied groups but there was a significant difference as regard platelets counts, hemoglobin, ESR, CRP, TG, HDL, fasting insulin levels, and HOMA IR. There is no significant difference between the SLE, and RA in disease duration, ESR, CRP, HDL, LDL, triglyceride, cholesterol, fasting blood glucose, fasting insulin levels, and HOMA IR. There were significant positive correlations between HOMA IR with patients' BMI, ESR, CRP, TG, FBG, and fasting insulin levels in both SLE and RA groups.** ***Conclusions:*** **SLE, and RA patients had a higher insulin resistance than age-matched healthy controls which can lead to the development of type 2 diabetes mellitus. HOMA IR had positive correlations with BMI, TG, FBG, and fasting insulin levels in both SLE and RA groups.**

Keywords: Insulin resistance, cholesterol, triglyceride

Introduction

Rheumatologic disorders comprise more than 100 different medical conditions with a broad array of clinical manifestations but are generally characterized by inflammation, damage and/or pain of the joints and connective tissues. They include common forms such as rheumatoid arthritis (RA), and less common forms such as systemic lupus erythematosus (SLE), dermatomyositis and scleroderma. They have a profound negative impact on almost every aspect of a patient's life as well as on the direct environment and society as a whole. Patients are hampered in their daily activities by pain, physical disability and fatigue[(1)]. Insulin resistance (IR) is defined as

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subnormal biological response to optimal concentration of insulin. It plays a main role in the pathophysiology of type 2 diabetes mellitus; it is also associated with dyslipidemia and cardiovascular risk (subjects with high IR had more than twice the elevated risk for incident cardiovascular events compared with those in the low IR). Moreover, it is the main component of the cluster of metabolic abnormalities that consist of metabolic syndrome[2]. Several mechanisms could contribute to altered insulin sensitivity in patients with RA or SLE including obesity, chronic inflammation and glucocorticoids which are commonly used in SLE and RA therapy[3]. From this point of view, this study aimed to detect the presence of insulin resistance in pediatric patients with rheumatologic disorders which can lead to the development of diabetes mellitus.

Subjects and Methods

This case–control study was performed on 60 cases of systemic lupus erythematosus (SLE) who fulfilled the 1997 revised American College of Rheumatology criteria of SLE[4] and 60 cases of rheumatoid arthritis (RA) who fulfilled the International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis[5]. Those cases were attending the outpatient clinic and inpatient of pediatric and rheumatology departments and recruited consecutively from March 2016 to April 2017 and 60 age, sex and body mass index (BMI) matched healthy children who attend outpatient clinics for routine care or unrelated non-rheumatologic complains represent the control group were included in the study. Informed consents have been obtained from the parents of the patients involved in the study as suggested by our Institutional Ethical Committee and in accordance with the Helsinki declaration after a full clarification of the nature of the study. Patients aged less than one year or older than 16 years, patients with diabetes, hypertension, and patients with concomitant hepatic, cardiac, renal or endocrinal disorders were excluded from this study. All studied patients were subjected to the following: Detailed history taking laying stress on; Age, gender, history of infections or serious illness, history of medications or behavior change and family history of rheumatological diseases. A careful clinical examination was done with stress on, weight, height, hepatosplenomegaly, lymphadenopathy, skin rash and arthritis.

Laboratory investigations

A- Routine investigations including; 1) Complete blood pictures (CBC) were performed on Sysmex-Kx-21 (Sysmex Corporation -Japan), fasting glucose level (FBG) and ESR which was measured manually; 2) Kidney function tests: blood urea nitrogen (BUN, mg/dl), creatinine (mg/dl) on Cobas 8000 C 702, Roche, Germany; 3) C-reactive protein (CRP) was determined using the Tina-Quant C-Reactive protein Gen 3 assays (Roche Diagnostics, Indianapolis, IN) on Roche Modular P800 system; 4) Lipid profile: plasma cholesterol level (by an enzymatic photometric test, cholesterol FS, Diagnostic Systems - Holzheim, Germany), plasma triglyceride (TG) level (assayed by the glucokinase peroxidase-peroxidase method on the BS100), high-density lipoprotein (HDL) was assayed by direct method on the BS100 (Shenzhen Mindory bio-medical electronics), and low-density lipoprotein (LDL) was calculated from three primary measurements with the use of Friedewaldl's equation[6].

B- Special investigations

1) Insulin hormone level by ELISA (Immunospec Corporation, CA, USA); 2) Homeostatic model assessment of insulin resistance (HOMA IR= fasting insulin (µU/mL) x Fasting glucose (mg/dL)/405)[7]; 3) Tests

needed to confirm rheumatologic disorders like antinuclear antibodies (ANA) by immunofluorescence assays using Kallestad® HEp-2 Kit (BIO-RAD, CA, USA); Autoantibodies to native double-stranded DNA (dsDNA) by immunofluorescence assays using Kallestad® Crithidia luciliae IFA Complete Kits (BIO-RAD, CA, USA) and Rheumatoid Factor (RF).

Disease activity

This was assessed by modified SLE Disease Activity Index 2000 (SLEDAI-2K)[8] and Disease Activity Score-28 (DAS28)[9] for SLE and RA patients, respectively. Active SLE has considered if the SLEDAI-2K score was >4, and inactive if it was <4)

Statistical Analysis

The data were processed using the statistical package for social sciences version 23 SPSS (Statistical Package for Social Sciences, Chicago, IL, USA). Data were expressed as a mean± standard deviation for quantitative variables or number and percentage for categorical variables. Student's t test for continuous variables and $\chi 2$ test for categorical variables were used to compare mean values between two independent groups. Data were compared using ANOVA test for more than 2 groups. Correlation coefficient between HOMA IR and fasting insulin, FBG and TG was done by Pearson's coefficient. p value > 0.05 was insignificant, $p < 0.05$ was significant and $p < 0.001$ was highly significant.

Results

Our study included 60 cases of SLE (M/F: 22/38), 60 cases of rheumatoid arthritis (M/F: 20/40) and 60 healthy subjects as a control group (M/F: 24/36), there is a statistically significant difference in both groups regarding the sex. There was no statistically significant difference between SLE and RA in disease duration (41.9±13.4 vs 43.5±11.1 months, respectively) wit p-value=0.7. There was a highly statistically significant difference in ESR, CRP, TG, HDL, fasting insulin level and HOMA IR between SLE, RA and controls but there was no statistically significant difference in age and BMI, FBG, LDL and cholesterol between the three groups as shown in (Table 1). In the present study, there is no significant difference between cases with RA and SLE in HDL, LDL, TG, total cholesterol, FBG and fasting insulin levels. There was a statistically significant positive correlation between HOMA IR with patients' BMI, ESR, CRP, TG, FBG and fasting insulin level in both SLE and RA groups; otherwise, there was no statistically significant correlation between HOMA IR and other patients' characteristics as shown in (Table 2 and figure1). HOMA IR was positively correlated with SLEDAI-2K and DAS28 in SLE and RA patients, respectively as shown in (Table 2).

Discussion

Childhood rheumatologic disorders are multisystem, inflammatory, autoimmune diseases with a broad array of clinical manifestations but are generally characterized by inflammation, damage and/or pain of the joints and connective tissues. In the present study, there is no significant difference in BMI between SLE, RA and controls. This agreed with the results of other investigators[10,11]. Our study reported a higher prevalence of rheumatologic disorders in females than males of the same age group. This was the same finding of Lisnevskaia et al study[12], which can be explained as rheumatologic disorders are a part of autoimmune diseases that are common in females. In the current study, there was a significant difference in hemoglobin levels and platelets between SLE, RA and controls. This attributed to the hematological abnormalities of the inflammatory

rheumatic diseases as proved previously[13]. Our results revealed that both SLE, RA patients have higher plasma TG and lower HDL levels than the control.

Table 1: Demographic, metabolic and disease related features of the population

Variables	SLE (60) mean ± SD (Range)	R.A (60) mean ± SD (Range)	Controls (60) mean ± SD (Range)	F	p-value	p-value
Age (years)	13.3±2.4 (5-16)	12.9±2.4 (5-16)	12.6±2.8 (5-16)	1.6	0.1	
BMI (kg/m2)	28.6±7.7 (15-45)	27.6±6.7 (15-44)	26.6±4.6 (18-45)	1.3	0.1	
Hemoglobin (%)	9.6±2.2 (5.5-14)	9.9±2.4 (5.5-14)	11.3±1.3 (7.2-14)	2.7	**0.02***	0.92[1] 0.01*[2] 0.02*[3]
ESR (mm/h)	41.1±11.2 (1-109)	37.1±8.6 (4-75)	5.2±1.5 (2-12)	4.9	**0.001****	0.1[1] <0.001**[2] <0.001**[3]
CRP (ug/ml)	12.4±1.6 (1-51.6)	7.7±0.4 (1-16)	2.3±0.6 (0.1-7)	2.9	**0.02***	0.01*[1] 0.03*[2] 0.02*[3]
Cholesterol (mg/dl)	165.5±25.5 (105-200)	152.5±39.3 (105.2-210)	146.4±33 (92-200)	1.16	0.47	
HDL (mg/dl)	52.6±10.1 (33.2-82.8)	54.5±11.8 (30.3-72)	65.6±10.9 (41-91)	2.2	**0.03***	0.65[1] 0.01*[2] 0.02*[3]
LDL (mg/dl)	105.2±22.2 (67.5-139)	101.2±24.2 (59.8-138)	97.9±19.8 (50-134)	0.15	0.86	
TG (mg/dl)	158.1±50.3 (47-461)	119.2±20.9 (47-202)	80.3±22 (46.7-188)	3.5	**0.01***	0.031*[1] 0.014*[2] 0.02*[3]
FBG (mg/dl)	92.8±3.8 (74-119)	84.2±4 (70-101)	86.6±14.7 (68-107)	1.4	0.25	
Fasting insulin (µIU/ml)	11.4±1.6 (2.2-19.0)	10.7±1.5 (3.6-17)	3.9±1.7 (0.9-9.1)	2.7	**0.015***	0.09[1] <0.001**[2] <0.001**[3]
HOMA IR	3.2±1.0 (0.9-5)	3.0±1.1 (1.2-4.8)	0.9±0.2 (0.2-1.9)	2.4	**0.02***	0.8[1] <0.001**[2] <0.001**[3]

F: ANOVA analysis of variance; **: $p<0.001$ (highly significant); *: $p<0.05$ (significant).
$p>0.05$: Non-significant; *p1*: SLE *vs* RA; *p2*: SLE *v.s* control; *p3*: RA *vs.* control

This finding was explained by the effects of cytokines which increase free fatty acids release from adipose tissue and increase hepatic synthesis of free fatty acids and TG. Moreover, the activity of lipoprotein lipase activity at the vascular endothelium, which is the principal catabolic enzyme for TG-rich lipids, is reduced. High TG levels reduce

HDL by virtue of neutral lipid exchange [14]. Chung et al.[15] and Dessein et al.[16] supported our results as regard plasma TG level in cases of rheumatoid arthritis and Sabio et al.[17] and Lozovoy et al.[11] found the same results in cases of SLE. In contrast to our study, Tso and Huang[18] found no significant difference in TG and HDL in SLE cases and controls. Also, Dessein et al.[16] found no significant difference between RA patients and controls in HDL level. In the present study, there is no significant difference in the levels of total cholesterol and LDL between all groups.

Table 2: Correlation between HOMA IR with demographic and laboratory criteria of the systemic lupus erythematosus and rheumatoid arthritis groups

HOMA IR	Systemic Lupus Erythematosus (n=60)		Rheumatoid Arthritis (n=60)	
	r	*p*	r	*p*
– Age (years)	-0.006	>0.05	-0.009	>0.05
– Disease duration (mos)	-0.06	>0.05	-0.08	>0.05
– BMI(kg/m^2)	0.3	0.04*	0.4	0.03*
– Hb%	-0.2	>0.05	-0.3	>0.05
– ESR (mm/h)	0.69	<0.001**	0.72	<0.001**
– CRP (ug/ml)	0.4	0.01*	0.45	0.01*
– Cholesterol (mg/dl)	0.3	>0.05	0.4	>0.05
– HDL (mg/dl)	-0.1	>0.05	-0.16	>0.05
– LDL (mg/dl)	0.3	>0.05	0.35	>0.05
– TG (mg/dl)	0.4	0.04*	0.5	0.03*
– FBG (mg/dl)	0.5	0.004*	0.6	0.002*
– Fasting insulin (µIU/ml)	0.4	0.04*	0.54	0.032*
– Disease Activity				
SLEDAI-2K	0.72	<0.001**	-	-
DAS28	-	-	0.75	<0.001**

r: Pearson correlation coefficient; **: *p*<0.001 (highly significant); *: *p* <0.05 (significant); *p*>0.05: Non-significant

Our results are concordant with those of La Montagna.[19] on the RA cases and Tso and Huang[18] on the SLE cases who found no significant differences in total cholesterol and LDL between case and control groups. In contrast, and Ormseth et al.[20] found that RA patients had higher LDL cholesterol and Wierzbicki[21] found that lipid and lipoprotein profiles in SLE are often abnormal compared with those of the general population. In our study, there is no statistically significant difference in FBG between SLE, RA and control groups. This was in agreement with Gazareen et al.[22] regarding SLE cases and in contrast to their study regarding RA cases which may conclude different degrees of IR between different types of rheumatologic disorders. In the present study, RA patients had significantly higher fasting insulin and HOMA IR than controls. This is in agreement with Chung et al.[23] who reported higher levels of IR among RA patients compared with non-RA controls and founded that the major determinant of IR is fat mass, in particular visceral fat, with increasing visceral fat mass, adipose and skeletal muscle uptake and utilization of glucose while the free fatty acid uptake and utilization are impaired. Also, hepatic glycogen storage is reduced, and synthesis of TG-rich lipoproteins is increased concomitant with

a reduction in their clearance; common features of the metabolic syndrome that accompanies insulin resistance. Also, we found that SLE patients had significantly higher fasting insulin and HOMA IR than controls. This is similar to what is reported by previous studies[18,22]. This can be explained by type B insulin resistance syndrome which an autoimmune phenomenon is caused by polyclonal immune-globulin G antibodies with antagonist activity directed against the insulin receptor[24]. Other mechanisms that could contribute to altered insulin sensitivity in patients with SLE are obesity, glucocorticoids, which are commonly used in SLE therapy. In contrast, Ormseth et al. found no statistically significant difference in HOMA IR between SLE patients and controls[25].

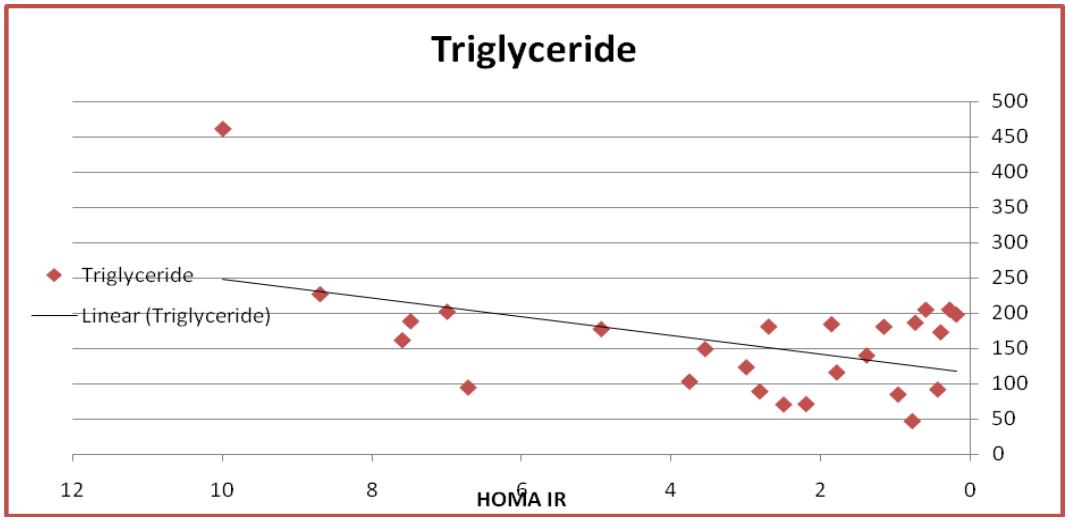

Figure 1: Scatter plot with line show a positive correlation between HOMA IR and TG in systemic lupus erythematosus patients

There was statistically significant higher ESR and CRP in SLE and RA patients than in controls. Our observations are best explained by that rheumatologic disorders are a group of inflammatory diseases in which there is a release of pro-inflammatory mediators that play a role in the mechanism of IR. Cytokines, particularly TNFα, can directly impede insulin-mediated glucose uptake in skeletal muscles and reducing glucose transport by inhibition of the transcription of insulin receptor substrate 1 (IRS-1) and glucose transporter (GLUT)-4 genes. Moreover, TNFα and IL6 can stimulate adipocyte lipolysis, leading to increased release of free fatty acids from peripheral tissues and the enhanced cycle of fatty acids between liver and adipose tissue. An increase in fatty acid fluxes has a significant role in the pathophysiology of IR[26]. Our study revealed no statistically significant difference between the RA and SLE groups in FBG, fasting insulin level and HOMA IR levels. This might be due to the performance of this study on children and the absence of significant differences in age and disease duration. On the other hand, Chung et al.[15] and Gazareen et al.[22] performed a study on adult cases of RA and SLE, observed higher FBG, fasting insulin and HOMA IR in RA than SLE patients. They explained that by some factors such as older age in RA patients than SLE and longer duration of disease in RA patients reflecting the burden of such disease. In the present study, there was a positive

correlation between HOMA IR and TG in both SLE and RA groups. This is in agreement with the study by Chung et al.[27] who found that SLE patients with IR (HOMA IR >2.11) had higher TG levels than SLE patients without IR and other studied which revealed that RA patients with IR (HOMA IR >2.11) have significantly higher TG[26,28]. There are three sources of higher TG observed in individuals with IR as explained by Chung et al.[27]. First, the lipolysis of TG from the adipose tissue leads to increased serum fatty acid levels. Second, decreased lipoprotein lipase levels causes inhibition of lipolysis of chylomicrons, VLDL and TG, which leads to elevations in TG-rich remnants that ultimately are delivered to the liver. Third, IR cause increased hepatic de-novo TG synthesis. The current study revealed a statistically significant positive correlation between HOMA IR on one hand and ESR, CRP, FBG and fasting insulin level on the other hand in both SLE and RA groups as stated by Negron et al.[29] and Dessein et al.[16] on cases of SLE and RA respectively. This is attributed to the elevated level of IL6 as an inflammatory mediator in rheumatologic disorders which is incriminated in both the condition of IR and elevation of acute-phase reactant levels. However, this does not agree with the study by Stagakis et al.[26] and Karimi et al.[30] who did not find a statistically significant difference in ESR and CRP between RA patients with and without IR. Our study revealed a positive correlation between IR and SLEDAI-2K in SLE patients that agree with Sabio et al.[17] and Gazareen et al.[22] who concluded an association of metabolic syndrome with higher disease activity but did not agree with Chung et al.[27] who did not find any association of metabolic syndrome with lupus disease activity. Also, there were significant correlations of IR with DAS28 which support the role of systemic inflammation in the pathogenesis of IR in RA. This was also supported by Sattar et al.[31] who reported that RA is a disease characterized by an increased level of circulating pro-inflammatory cytokines that induce IR through direct interfering with insulin signaling and by Escárcega et al.[32] who found that IR promotes further inflammation by an increase in free fatty acid fluxes and interference with the anti-inflammatory effects of insulin. Our study has other limitations. *First,* the sample size was relatively small and did not have enough statistical power to generalize these results. *Second,* the patients were recruited only from our university hospitals, and not from other areas in Egypt. *Third,* ethnic differences may be an important factor.

Conclusion

SLE and RA patients had a higher insulin resistance than age-matched healthy controls which can lead to the development of type 2 diabetes mellitus. HOMA IR had a positive correlation with BMI, TG, FBG, and fasting insulin level in both groups.

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Abbreviations
Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Insulin resistance (IR), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), Homeostatic

model assessment of insulin resistance (HOMA IR), fasting blood sugar (FBG).

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