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Original Article

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The Link Between Cardio-Metabolic Risk Factors, Serum sIL-2R and Echocardiography Data in Type 2 Diabetes

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ABSTRACT

This study aimed to demonstrate the link between the inflammatory process, cardio-metabolic risk factors and echocardiography data in type 2 diabetic (T2D) patients. A total number of fifty-two patients (12 male and 40 females) with a median age of 57 year were enrolled in this study. Anthropometric measurements that related to the cardio-metabolic risk factors and blood pressure were measured. Fasting serum glucose, lipid profiles and soluble interleukin -2 receptor (sIL-2R) using the technique of enzyme linked immunnosorbent assay (ELISA) were determined. The patients categorized according to the presence of metabolic syndrome components using the National Cholesterol Education program (NCEP) definition. Echocardiography data that related to systolic and diastolic left ventricular dysfunction were recorded using B-mode ultrasound with a frequency of 2-4MHz. There was non-significant difference in echocardiography data that related to systolic and/or diastolic dysfunction and the cardio-metabolic risk factors. The mean serum sIL-2R level was 3.469±3.062 pg/ml (range: 1.316-12.5); it inversely and non-significantly correlated with ejection fraction (r = - 0.12) and atherogenic index (r=-0.148). There is a link between the left ventricular systolic function and the circulating sIL-2R in asymptomatic T2D, which does not relate to the components of metabolic syndrome

Key words: *Cardio-metabolic risk factors, Type 2 diabetes, sIL-2R, Echocardiography*

Tip 2 Diyabetde Serum sIL-2R ve Ekokardiyografi Veri ile Kardiyo-Metabolik Risk Faktörleri Arasındaki İlişki

ÖZET

Bu çalışma, tip 2 diyabetli (T2D) hastalarda inflamatuar süreç, kardiyo-metabolik risk faktörleri ve ekokardiyografi verileri arasındaki bağlantıyı göstermek için amaçlanmıştır. Bu çalışmaya ortalama 57 yaşında olan elli iki hasta (12 erkek ve 40 kadın) alındı. Kardiyo-metabolik risk faktörleri ve kan basıncı ile ilgili antropometrik ölçümler ölçüldü. Enzim bağlantılı immunnosorbent ölçüm (ELISA) tekniği kullanılarak açlık kan şekeri, lipid profili ve çözünür interlökin -2 reseptörü (sIL-2R) ölçülmüştür. Hastalar Ulusal Kolesterol Eğitim Programı (NCEP) tanımı kullanarak metabolik sendrom bileşenlerinin varlığına göre kategorize edilmiştir. Sistolik ve diyastolik sol ventrikül disfonksiyonu ile ilgili Ekokardiyografi verileri 2-4MHz bir frekans ile B-mod ultrason kullanılarak kaydedildi. Sistolik ve / veya diyastolik disfonksiyon ve kardiyo-metabolik risk faktörleri ile ilgili ekokardiyografi verileri nde belirgin farklılık yoktu. Ortalama serum sIL-2R düzeyi 3.469±3.062 pg/ml (1.316-12.5) idi. Aterojenik indeks (r = -0,148) ve ejeksiyon fraksiyonu (r = 0.12) ile ters bir korelasyon vardı. Asemptomatik T2D de metabolik sendromun bileşenleri ile ilgili olmayan sol ventrikül sistolik fonksiyonu ile dolaşan sIL-2R arasında bir bağlantı vardı.

Anahtar kelimeler: *Kardiyometabolik risk faktörleri, tip 2 diyabet, sIL-2R, ekokardiyografi*

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INTRODUCTION

Interleukin-2 (IL-2) is a growth factor played a role in activation, and maturation of T lymphocytes. Functional IL-2 receptors (IL-2R) were expressed on activated B cells, dendritic cells, natural killer cells, and eosinophils. The functional importance of IL-2R was identified in tumorigenesis (1). Soluble IL-2R-alpha (sIL-2Rα) released directly from the surface of neoplastic cells thus reflecting the tumor bulk, turnover and activity (2). High concentrations of soluble (sIL-2R) detected in sera from healthy subjects and are increased in subjects with autoimmune disease including type 1 diabetes (3), inflammation and infection (4). In type 2 diabetes (T2D) complicated with atherosclerosis, high circulating sIL-2R is detected even in the absence of obesity and marked hyperglycemia (5). In experimental animal model of myocardial infarction, it was observed that single injection of recombinant human interleukin-2 improved angiogenesis and preserved heart function via activation the natural killer cells and thereby contributed in vascular remodeling (6). In heart failure of whatever cause, serum sIL-2R level is high before treatment, and then reduced after using therapeutic agents with pleiotropic effects like statins (7). Recent study shows that sIL-2R level is high in patients with acute coronary syndrome in presence of systolic dysfunction or acute heart failure, and the levels of sIL-2R were proportional to left ventricle end-diastolic diameter and end-systolic diameter (8). Cardiometabolic risk factors as well as abnormal ventricular function often exited in diabetic patients. Therefore, the rational of this study is to prove that inflammatory process plays a role in cardiac complications in diabetic patients presented with metabolic syndrome features. This study aimed to demonstrate that sIL-2R level (as a marker of inflammatory process) could be used to explain the association between the cardiometabolic risk factors (using the criteria of metabolic syndrome) and changes in ventricular function assessed by echocardiography in T2D.

MATERIALS AND METHODS

This study conducted in Departments of Pharmacology and Physiology, College of Medicine, Al-Mustansiriya University in cooperation with Laboratories of Al-Yarmouk Teaching hospital in Baghdad, Iraq. The study approved by an institutional review committee and informed consent obtained from each patient prior to admit in the study. This study was designed as a cross sectional in cohort of patients with type 2 diabetes (T2D). The criteria of inclusion were patients with T2D of both genders using oral glucose-lowering medication(s) alone and/or with once- or twice-daily insulin. The criteria of exclusion were patients with a history of hematological, neoplastic, renal, hepatic or thyroid diseases, or patients receiving treatment with anti-inflammatory drugs. Patients with acute or chronic infections and autoimmune disease also excluded from the study. A total number of fifty- two patients (12 male and 40 females) with a median age of 57 year admitted in this study. Anthropometric measurements that related to the cardio-metabolic risk factors were measured. They included height (m), weight (kg), waist circumference (cm) and hip circumference (cm). The body mass index (BMI) and waist/hip ratio (W/H) were calculated. According to the BMI values the patients were categorized: normal (BMI < 25 kg/m2), over weight (BMI: 25-29 kg/m2), and obese (BMI: ≥ 30 kg/m2). A value of W/H ratio > 0.9 (male) and 0.8 (female) indicated central obesity.

The blood pressure was measured on sitting position and the mean of three readings recorded. Pulse and mean arterial pressures calculated using the following formula: Pulse pressure (mm Hg) = Systolic blood pressure – diastolic blood pressure Mean arterial blood pressure = Diastolic blood pressure + 1/3 (Pulse pressure)Participants enrolled in the study subjected to echocardiography (B mode) investigation. The echocardiography investigation performed from the patient left side so that the transducer (with a frequency of 2-4MHz) is at the long axis of the heart. Echocardiography data that related to systolic and diastolic left ventricular dysfunction were recorded and these included: shortening fraction (%), stroke vol-

Table 1*. The anthropometric measurements*

Gender (M:F)	*12:40*
Age (year)	*57.0±8.3*
Anthropometric measurements	
Weight (kg)	*83.8±22.2*
Height (m)	*1.621±0.087*
Body mass index (kg/m2)	*31.7±6.9*
< 25 kg/m2	*8(15.4)*
25 -29 kg/m2	*13(25)*
≥ 30 kg/m2	*31(59.6)*
Waist circumference (cm)	*102.1±18.4*
Hip circumference (cm)	*109.6±16.2*
Waist/Hip ratio	*0.933±0.123*
Male (≥0.9)	*9(75)*
Female (≥0.8)	*36(90)*

The results expressed as number (%), mean ±SD.

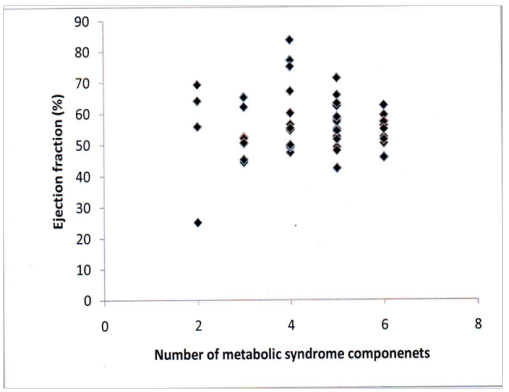

***Figure 1**. Ejection fraction (%) of patients categorized according to the cluster of metabolic syndrome components.*

ume (ml), ejection fraction (%), end systolic volume (ml), end diastolic volume (ml), left ventricular posterior wall (systole). Fractional shortening of the left ventricle is determined using the following equation: (End diastolic dimension-End systolic dimension)/(End diastolic dimension) x 100

Peripheral venous blood samples were obtained, then the samples were centrifuged at 2500 rpm for 10 min., and the sera were separated for determination of fasting serum glucose, lipid profile (total cholesterol, triglycerides, high density lipoprotein-cholesterol and calculated atherogenic index which is equal to the ratio Triglycerides/ (High density lipoprotein)) and sIL-2R using the technique of enzyme linked immunnosorbent assay (ELISA).

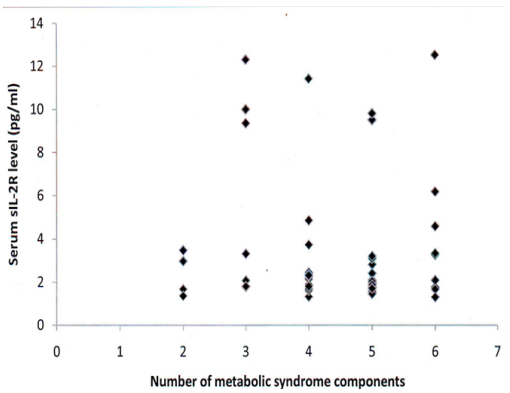

***Figure 2**. Serum IL-2R levels of patients categorized according to the cluster of metabolic syndrome components.*

***Table 2**. Blood pressure measurements*

Systolic blood pressure (mmHg)	*140.5±22.4*
Diastolic blood pressure (mmHg)	*91.3±14.2*
Mean arterial blood pressure (mmHg)	*107.7±14.5*
Pulse pressure (mmHg)	*49.1±20.4*

The results expressed as mean ±SD.

The patients categorized according to the presence of metabolic syndrome components. According to the National Cholesterol Education program (NCEP) definition, metabolic syndrome is present if a subject has three or more of the following (9): High waist circumference values (>102 cm) High triglyceride levels (≥150 mg/dl)

Reduced high density lipoprotein HDL cholesterol levels (< 40 mg/dl in male and (< 50 mg/dl in female), Elevated systolic blood pressure (≥130) and/or diastolic blood pressure (≥85 mmHg) elevated glucose values (≥110 mg/dl)

Statistical analysis

Data expressed as means ± SD. Unpaired Student's t-test and multi-variant correlation test used to evaluate differences between the two groups. For all tests, a two-tailed $p \leq 0.05$ considered statistically significant. All calculations were made using Excel 2003 program for Windows.

RESULTS

Fifty-two patients (12 male and 40 female) with a mean age of 57 years enrolled in this study. Table 1 showed that approximately 60% of patients were obese and most of them presented with central obesity by the evidence of waist circumference and waist/hip ratio. Table 2 showed that the mean systolic and diastolic blood pressures were at the hypertensive levels (Table 2). The fasting lipid profile of patients showed high mean serum level of triglycerides and atherogenic index (Table 3). No significant differences in echocardiography data that related to systolic dysfunction or to the gathered components of metabolic

***Table 3**. Fasting serum lipid profile*

Triglycerides (mg/dl)	*194.4±81.7*
Cholesterol (mg/dl)	*204.2±37.9*
High density lipoprotein(mg/dl)	*45.1±6.9*
Low density lipoprotein (mg/dl)	*120.3±38.7*
Very low density lipoprotein (mg/dl)	*38.9±16.3*
Atherogenic index	*4.43±2.11*

The results expressed as mean ±SD.

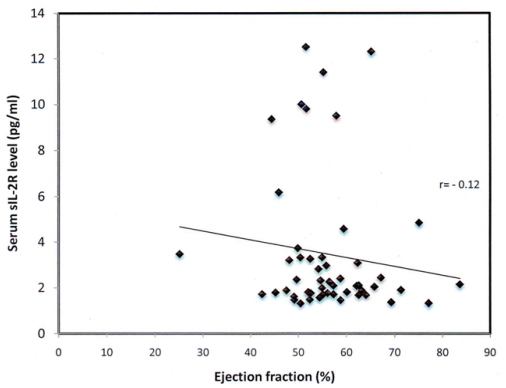

***Figure 3**. Correlation between serum sIL-2R and ejection fraction in type 2 diabetes*

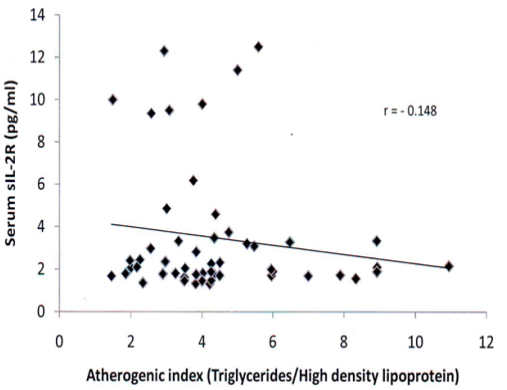

***Figure 4**. Correlation between serum sIL-2R and atherogenic index in type 2 diabetes*

syndrome observed. The mean value of ejection fraction was 56.3%, which is below the cut-off value of healthy subjects. Figure 1 shows that twelve out of fifty two patients (23.1%) have ejection fraction below 50% and these values do not relate to the clustering components of metabolic syndrome. The mean value of serum sIL-2R was 3.469±3.062 pg/ml (range: 1.316-12.5). Ten out of fifty-two patients have serum level of sIL-2R > 4 pg/ml and these values do not relate to the clustering components of metabolic syndrome (Figure 2). Serum IL-2R inversely and non-significantly correlated with ejection fraction (r = - 0.12) and atherogenic index (r = - 0.148) (Figures 3 and 4).

DISCUSSION

The results of this study demonstrate that T2D patients presented with metabolic syndrome have left ventricular dysfunction that does not relate to components of metabolic syndrome. The left ventricular dysfunction assessed by ejection fraction does non-significantly correlate with serum sIL-2R level. Most studies investigated the serum level of sIL-2R in type 1 diabetes with or without complications. The results of this study are in agreement with that reported by Pereira et al who demonstrated that the significant high level of sIL-2R in T2D did not relate to the components of metabolic syndrome including obesity and hyperglycemia (5). Therefore, the obtained results indicated the presence of organ dysfunction resulted from systemic inflammatory response in T2D patients by the evidence that high serum sIL-2R is previously reported as a predictor marker of organ dysfunction (10). Further study reported that the elevated plasma sIL2r is associated with progressed calcification of coronary artery which independent to the traditional coronary artery disease risk factors in type 1 diabetic and non-diabetic young adults (11). Type 2 diabetic patients with metabolic syndrome have a greater incidence and absolute progression of coronary artery calcification (12). On the other hand, one meta analysis study reviewed twelve studies and the authors concluded that sIL-2R is not a useful inflammatory marker of coronary artery calcification (13). In

***Table 4**. Ehocardiographic data in respect to the number of metabolic syndrome component*

Echocardiograph determinants	*Number of component of metabolic syndrome*					
	2 (n:4)	*3 (n:8)*	*4 (n:13)*	*5 (n:18)*	*6 (n:9)*	*Total (n:52)*
Shortening fraction (%)	*29.0±12.2*	*27.3±5.0*	*33.2±8.9*	*30.0±4.8*	*28.5±3.4*	*30.0±6.7*
Stroke volume (ml)	*85.0±31.2*	*65.7±26.3*	*69.1±23.6*	*73.9±29.3*	*73.2±3.4*	*70.8±27.2*
Ejection fraction (%)	*53.6±19.8*	*52.9±7.4*	*60.1±11.9*	*56.6±7.0*	*54.6±5.0*	*56.3±9.5*
End systolic volume (ml)	*75.9±38.6*	*50.0±24.6*	*46.8±24.8*	*57.0±25.4*	*61.3±26.7*	*55.5±26.6*
End diastolic volume (ml)	*160.9±19.8*	*106.6±48.6*	*115.3±42.1*	*130.9±49.6*	*134.6±52.0*	*126.2±47.1*
Left ventricular posterior wall (systole)	*0.977±0.185*	*1.217±0.216*	*1.159±0.278*	*1.112±0.261*	*1.103±0.226*	*1.128±0.247*
Left ventricular posterior wall (diastole)	*0.92±0.04*	*1.1380.217*	*0.902±0.215*	*0.969±0.198*	*0.998±0.221*	*0.98±0.210*

this study, coronary CT scan did not carry on to look for coronary artery calcification and to link the changes in serum sIL2R with coronary calcification. This study demonstrates that there is an association between low ejection fraction (that indicated left ventricular dysfunction) and serum sIL-2R in T2D with metabolic syndrome in corresponding cases. The non- significant association is related to small sample number of patients. Therefore, this study adds new information about the link between the left ventricular function and sIL-2R. De Gennarol et al. demonstrated that the circulating sIL-2R level was high and a significant correlation with left ventricular ejection fraction observed in patients with acute coronary syndrome (14). This study demonstrates such findings but in asymptomatic patients and in absence of acute myocardial infarction. The clinical significance of determination the serum sIL2R is still under investigation and conflicting data were reported in this concern. Cesari et al (15) found that serum sIL-2R is not an important cytokine in clinical as well as subclinical cardiovascular diseases whereas Limas et al (16) demonstrates significant higher sIL-2R levels in dilated cardiomyopathy compared with the ischemic heart disease in which significantly correlated with the left ventricular end-diastolic diameter but not with the LV ejection fraction.

The clinical implications of the results of this study are to utilize serum sIL-2R level as a marker in assessment left ventricular function in diabetes and to consider it in the criteria of metabolic syndrome. Immune therapy that targeted sIL-2R could be useful in management of ventricular dysfunction in diabetic patients. Limitations of the study included small sample size, variations in duration of diabetes and glycemic control. Therefore, it concludes that there is a link between the left ventricular systolic function and the circulating sIL-2R in asymptomatic T2D which does not relate to the associated components of metabolic syndrome.

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