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ORIGINAL ARTICLE

Fasting Triglycerides and Glucose (TyG index) and Systemic Lupus Erythematosus Disease Activity Score (SLEDAS)

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Abstract

Background: Dyslipidemia is a common drawback in systemic lupus erythematosus (SLE) patients; it is also related to disease activity. Fasting triglycerides and glucose (TyG index) was originally employed as a substitute for measuring insulin resistance (IR), we hypothesized that the TyG index may be an indicator of disease activity. **Method:** In this study, 87 SLE patients participated. Their demographic, clinical, and laboratory data were assessed. Patients were split into two groups based on the Low Lupus Disease Activity State (LLDAS). Factors correlated with activity were entered in regression analysis with the TyG index.

Results: A statistically significant relation was detected between the TyG index and disease activity. There was a significant positive correlation between SLE-DAS & all of the TyG index (r=0.267, p=0.012), ESR (r=0.338, p=0.001), Fasting blood glucose (r=0.268, p=0.012), TGs (r=0.232, p=0.031) and LDL cholesterol (r=0.213, p=0.048). TyG index (unstandardized β=20.425, p=0.028) was significantly and independently associated with disease activity. However, the TyG index revealed a sensitivity of 71.8% but a specificity of 47.2% for identifying high disease activity among SLE patients.

Conclusion: A statistically significant correlation is detected between SLEDAS and TyG index. Although the TyG index is sensitive but not specific for the detection of high disease activity in SLE patients, it is still not valid and needs further research.

Keywords: SLE, TyG index, disease activity, SLEDAS.

Key points:

A positive correlation was found between the TyG index & high disease activity in SLE patients.

The TyG index is still not a valid test to detect disease activity among SLE patients.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune illness marked by the formation of autoantibodies and the deposition of immune complexes [1]. The main reasons for death include infections, lupus nephritis (LN), and cardiovascular disorders with high morbidity and mortality rates associated with them. [2].

Dyslipidemia is characterized by increased total cholesterol (TC), triglycerides (TGs), low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL). Patients with lupus frequently have dyslipoproteinemia, which is defined by a rise in TGs and a reduction of HDL, it is also associated with disease activity, especially LN[3],[4].

The fasting triglyceride and glucose index, or TyG index, is a parameter that is measured using the fasting blood glucose (FG) and triglyceride levels and is computed as ln [TG (mg/dL) × FG (mg/dL)/2] [5]. TyG index was originally employed as a substitute evaluation of insulin resistance (IR), the TyG index has been approved as a screening instrument for IR in non-rheumatic conditions, since it is a workable, inexpensive

screening technique for high-risk individuals, such as those suffering from long-term autoimmune diseases like SLE and rheumatoid arthritis (RA) [6]. Dyslipoproteinemia affects 30%-73% of adult lupus patients and is linked to elevated TG and HDL levels [7]. Therefore, this research aimed to assess the role of TyG index in monitoring disease activity in patients with SLE.

METHODS

Type of study and sampling:

This cross-sectional study was done on 87 SLE patients collected between March 2023 and June 2023 from the outpatient clinics and inpatient wards at the Rheumatology and Rehabilitation Department, Zagazig University Hospitals.

SLE patients were involved based on Systemic Lupus International Collaborating Clinics (SLICC) modification of the ACR classification criteria [7]. Patients were excluded if they had diabetes mellitus, uncontrolled hypertension, autoimmune thyroiditis, and metabolic syndrome. Official approval had been received from the Institutional Review Board (IRB) (ZU-IRB#10523/7-3-2023) at the Faculty of Medicine, Zagazig University Hospitals as well as the Rheumatology& Rehabilitation Department at this University. Written informed consent was gained from every participant. This research was done based on The Code of Ethics of the World Medical Association for research including individuals, which is the 1964 Helsinki Declaration.

Basic Information:

Data were gathered from clinical history, and general and musculoskeletal examination, including patient age, sex, body mass index (BMI), duration of disease, smoking, & medications.

Clinical and Laboratory Assessments:

venous blood samples collected in the early morning on an empty stomach and tested for FG, TG, TC, LDL, HDL, C-reactive protein (CRP), erythrocyte-sedimentation rate (ESR), C3& C4 complement, & 24-hour urinary protein. The TyG index is based on the formula, TyG index = **ln** [TGs (mg/dL) ×FG (mg/dL)/2].

Assessment of SLE activity:

The activity of the disease in lupus patients was detected by The SLE Disease Activity Score (SLEDAS) which is a certified continuous disease activity score and has a greater accuracy in measuring SLE activity and more sensitivity to change compared to the SLE Disease Activity Index (SLEDAI) [8]. We used the definition of Abdelhady et al for LLDAS at 6.62 as a cut-off and according to it, low disease activity (LDA) and high disease activity (HDA) groups were defined [9].

Statistical analysis:

The data was analyzed by a statistical package for the social sciences (SPSS) software version 26. Categorical variables were created using their absolute frequencies, and they were compared by the chi-square test and the Fisher's exact test. The assumptions utilized in parametric testing were verified using the Shapiro-Wilk test. Depending on the type of data, the means, and standard deviations or the median and interquartile range were used to characterize quantitative variables.

The Mann-Whitney test and the independent sample t-test were used to compare quantitative data between the two groups. The Spearman rank correlation coefficient was used to evaluate the direction and strength of correlation between two constant variables. To diagnose a certain condition, the receiver operating characteristic curve (ROC) curve was utilized to establish the best cutoff of a particular quantitative parameter. To determine related independent factors for the dependent factor, linear regression analysis was used. The level of statistical significance was set at $P<0.05$. If $P\leq0.001$, there was a highly significant difference.

RESULTS:

This study included 87 SLE patients with a mean age of 33.82 years, 13.8% of them were males, and 9.2% were smokers with a duration of disease ranging from 1 to 20 years with a median of 6 years. Total SLEDAS ranged from 4.77 to 28.8 with a median of 17.7. About 61% of patients were in a high disease activity. All patients received steroids with doses ranging from 10 to 60 mg/day with a median of 30 mg. The fasting blood glucose of the patients ranged from 75 to 97 mg/dl. Also, we recorded triglycerides level mg/dl median (IQR) 177(130 – 250) and total cholesterol median 213 mg/dl. Cyclophosphamide was used by 24.1% while Azathioprine was used by 32.2% of patients. Mycophenolate mofetil was used by 43%. TyG index ranged from 4.09 – 4.68 with a mean of 4.46 **Table (1).**

As shown in figure (1), we found that 60.9% were in a high disease activity whereas 39.1% were in a low disease activity according to Abdelhady et al for LLDAS at 6.62 as a cut-off point.

A statistically significant relation was detected between the TyG index & SLE activity. The mean TyG index in patients with high disease activity was 4.5 versus 4.4 in those with low disease activity (p=0.02) **Table (2)**.

To assess the validity of TyG index for detecting disease activity in SLE, ROC curve was used

against the SLEDAS as a gold standard test. The ROC curve in **Figure (2)** detected that the area under the curve was 0.645 at a 95% confidence interval (CI) with a cut-off value of ≥4.4248 **Table (3).**

As regards correlations between SLE disease activity and the studied variables, we found that there were significant correlations between SLE-DAS and all of TyG index (r=0.267, p=0.012), ESR (r=0.338, p=0.001), Fasting blood glucose (r=0.268, p=0.012), TGs (r=0.232, p=0.031) and LDL cholesterol (r=0.213, p=0.048). There was a statistically insignificant negative correlation between SLE-DAS and other variables **Table (4).**

Regarding linear stepwise regression analysis, among factors significantly correlated with SLEDAS, TyG index (unstandardized β=20.425, p=0.028) was significantly independently associated with disease activity **Table (5).**

Table (1): Demographic data, clinical and laboratory characteristics of patients.

CHARACTERISTIC		**N=87**
Age (year)	mean ± SD range	33.82 ± 9.03 18 – 50
Male gender	No (%)	12 (13.8%)
Smokers	No (%)	8 (9.2%)
BMI (kg/m^2)	mean ± SD range	24.63 ± 4.54 17 – 33
Disease duration (year)	median(IQR)	6(3 – 10)
Total DAS LDA HDA	median(IQR) No (%) No (%)	17.7(4.77 – 28.8) 34 (39.1%) 53 (60.9%)
Dose of steroid (mg)	median(IQR)	30 (10 – 60)
ESR (mm/hr)	median(IQR)	40(22 – 61)
CRP (mg/L)	median(IQR)	5.4(3.5 – 10.9)
Fasting blood glucose (mg/dl)	median(IQR)	86(75 – 97)
TC (mg/dl)	median(IQR)	213(176 – 276)
TGs (mg/dl)	median(IQR)	177(130 – 250)
HDL (mg/dl)	median(IQR)	45(35 – 54)
LDL (mg/dl)	median(IQR)	153(110 – 201.7)
TyG index	mean ± SD range	4.46 ± 0.2 4.09 – 4.68
24-hour protein (g/24h)	median(IQR)	1800(418 – 3000)
C3 (mg/dl)	median(IQR)	0.7(0.32 – 1.3)
C4 (mg/dl)	median(IQR)	11.1(0.34 – 14)
Treatment Cyclophosphamide Rituximab Mycophenolate mofetil Azathioprine	No (%)	 21(24.1%) 1(1.1%) 37(42.5%) 28(32.2%)

SD: standard deviation, **IQR:** interquartile range, **NO:** number, **LDA:** low disease activity, **HDA:** high disease activity, **BMI:** body mass index, **ESR:** erythrocyte sedimentation rate, **CRP:** C-reactive protein, **TC:** total cholesterol, **TGs:**Triglycerides, **LDL:** low density lipoprotein, **HDL:** high density lipoprotein, **C3:** complement, **C4:** complement, **TyG index:** Fasting triglycerides and glucose index.

Table (2): Relation between TyG index and disease activity:

ACTIVITY	**MEAN ± SD**	TEST	P VALUE
LDA (N=34) **HDA (N=53)**	4.4 ± 0.15 4.5 ± 0.22	-2.578 (t)	0.012*

t :independent sample t test, **LDA:** low disease activity, **HDA:** high disease activity, *p<0.05 is statistically significant

Table (3): Performance of TyG index in diagnosis of high activity among studied patients:

Cutoff	AUC	Sensitivity	Specificity	Accuracy	p
≥4.4248	0.645	71.8%	47.2%	60.9%	0.023*

AUC: area under curve, ***p**<0.05 is statistically significant.

Table (4): Correlation between SLE DAS and the studied parameters:

Parameter	r	P
Age (year)	0.091	0.402
BMI (kg/m^2)	0.107	0.326
Disease duration (year)	-0.06	0.581
Tyg index	**0.267**	**0.012***
ESR (mm/hr)	**0.338**	**0.001****
CRP (mg/L)	0.057	0.602
Fasting blood glucose (mg/dl)	**0.268**	**0.012***
TC (mg/dl)	0.2	0.063
TGs (mg/dl)	**0.232**	**0.031***
HDL (mg/dl)	-0.108	0.318
LDL (mg/dl)	**0.213**	**0.048***
C3 (mg/dl)	-0.2	0.36
C4 (mg/dl)	0.149	0.541

BMI: body mass index, **ESR:** erythrocyte sedimentation rate, **CRP:** C-reactive protein, **TC:** total cholesterol, **TGs:** Triglycerides, **LDL:** low density lipoprotein, **HDL:** high density lipoprotein, **C3:** complement, **C4:** complement, **TyG index:** Fasting triglycerides and glucose index, **r:** Pearson correlation coefficient, ***p**<0.05 is statistically significant, ****p**≤0.001 is statistically highly significant.

Table (5): Linear stepwise regression analysis of factors significantly associated with SLE-DAS.

	Unstandardized Coefficients		T	P	Standardized Coefficients	95% CI
	B	Std. Error			β	
(Constant)	-70.31	38.5	-1.826	0.072		-14.008, 6.396
TyG index	20.425	9.12	2.239	**0.028***	0.306	2.25, 36.6
Fasting blood glucose (mg/dl)	0.009	0.004	1.861	0.067	0.338	0.007, 0.159
TGs (mg/dl)	0.032	0.01	2.960	0.07	0.280	0.001, 0.005
LDL (mg/dl)	-0.017	0.03	-0.589	0.558	-0.08	-0.076, 0.042

LDL: low density lipoprotein, **TyG index:** Fasting triglycerides and glucose index, **TGs:** Triglycerides, ***p**<0.05 is statistically significant, ****p**≤0.001 is statistically highly significant.

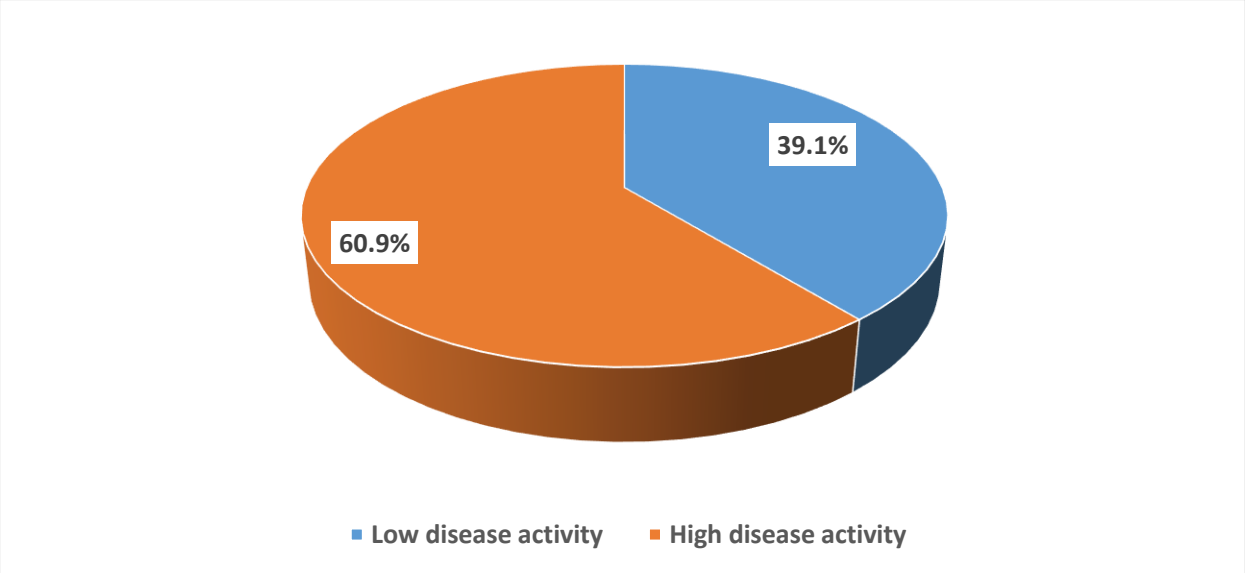

Figure (1): Pie chart showing distribution of patients according to disease activity.

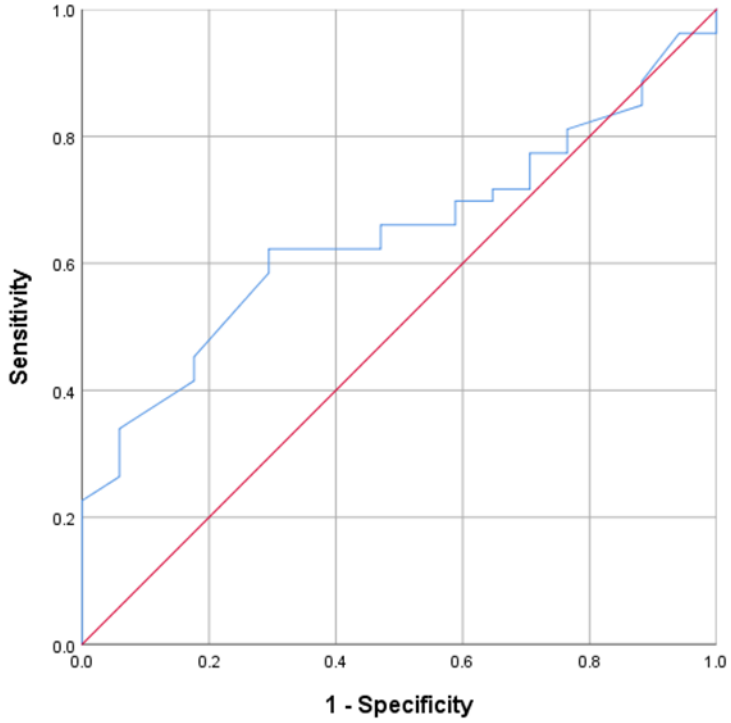

Figure (2): ROC curve showing performance of TyG index in detection of high activity among studied patients.

DISCUSSION:

SLE is a complicated and diverse autoimmune systemic disease linked to innate and adaptive immunological dysfunction. Despite advancements in treatment options, SLE patients typically endure times of elevated disease activity and flare, which can cause increased morbidity, early death, and long-term organ damage. Thus, the management of clinical diseases urgently requires novel, proactive approaches [10].

Dyslipoproteinemia in SLE patients is multifaceted. Inflammatory and autoimmune responses trigger the recruitment and activation of lymphocytes, monocytes, and adipocytes, which increases lipid deposition [11]. The TyG index is a unique indicator for the measurement of glucolipid metabolism levels. This research was carried out to demonstrate the relationship between the TyG index & disease activity in SLE. About the serologic features of the patients that were part of this study, lupus patients with high

disease activity were reported in 60.9% while patients with low disease activity patients were detected in 39.1% with a significant correlation between TyG index and disease activity. TC level, LDL, and fasting blood glucose level were higher among the HDA group than the LDA group. These results were in agreement with the studies of Formiga et al. who reported that dyslipoproteinemia which is defined by an elevation in TC and TGs as well as an abnormal distribution of HDL, is a prevalent characteristic in active SLE patients [12]. On the other hand, our results were not matched with Chung et al. and Lozovoy et al. who noted that patients with lupus had significantly decreased levels of TC and LDL [13,17].

These findings can be explained by the recruitment and activation of monocytes and lymphocytes, which are the results of systemic inflammatory and autoimmune responses. Moreover, increased inflammation and increased lipid deposition in vascular intima are the main contributors to hyperlipidemia in autoimmune rheumatic disorders [14]. Increased fatty acid flow to the liver and a decrease in lipoprotein lipase (LPL) levels are the results of the lipolysis of TGs from adipose tissue, which also results in the inhibition of the lipolysis of LDL, which results in an increase in TGs level [15].

A significant correlation was detected between the SLEDAS score and TyG index. These results did not agree with the study of Contreras-Haro et al. who reported that no correlation was found between the TyG index & SLE activity with SLEDAI [6]. Our finding can be explained by the metabolic condition associated with SLE which causes abnormalities in glycogen synthesis and glucose uptake and also results in oxidative damage, and hyperglycemia [16]. Gazareen et al. were matched with our results as they found a relation between the activity of disease using the systemic lupus activity measure (SLAM) index and IR [15]. Also using SLEDAS as an activity tool allows quantitative assessment of proteinuria, platelet, and WBCs count, also neuropsychiatric lupus, gastrointestinal, cardiopulmonary involvement, and hemolytic anemia, when compared to SLEDAI [9], so it is designed to more precisely measurement for disease activity of SLE & to better assess its changes over time.

A statistically significant correlation was observed between disease activity (SLEDAS) with ESR and LDH. However, there was no significant correlation with HDL. This was in agreement with the studies of Lozovoy et al. and Gazerren et al. who detected that patients of SLE with activity had significantly higher ESR and CRP [13],[15]. Furthermore, the SLEDAS score revealed significant correlations with TG and fasting blood sugar. This was in agreement with Negrón and colleagues who concluded that there was an association of metabolic syndrome, hypertriglyceridemia, and increased fasting blood sugar with higher disease activity [17]. However, other studies revealed that there was no association between metabolic syndrome and hyperinsulinemia with lupus disease activity[18],[19].

Studies in the literature have linked the dyslipidemia that has been observed in SLE patients to disease activity on several occasions. [11],20]. This result can be explained by tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), two inflammatory cytokines, that promote lipolysis and raise free fatty acids (FFAs) levels and induce hyperlipidemia. On the other hand, an abrupt increase in FFAs causes alterations in inflammation and oxidative stress so FFAs and hyperlipidemia are raised by inflammation as well as promoted by it [21].

Furthermore, validity testing was done and revealed that the TyG index was not valid for the detection of high disease activity in SLE patients despite the TyG index having a significant correlation with SLEDAS.

When performing the linear step-wise regression analysis for previously correlated parameters for disease activity in SLE, the TyG index was significantly independently associated with disease activity. Sustained inflammatory activity leads to an imbalance in glycolipid metabolism which is reflected here by the TyG index.

To the best of our knowledge, this is the first study to use the TyG index to screen for disease activity among lupus patients. There was a significant positive correlation between SLE-DAS and the TyG index. However, the TyG index was not valid for the detection of high SLE disease activity.

It is necessary to show some limitations of the current study. With participants of the same ethnicity, the current investigation was carried out in a single facility. We strongly recommend conducting more studies using multi-centric and multi-ethnic cohorts. Moreover, other factors considered to be linked with dyslipidemia, specifically pro-inflammatory cytokines such as IL-6, TNF-α, and LPL were not evaluated. Additionally, further studies comparing the TyG index with parameters of activity are needed to evaluate its potential use as a routine parameter for assessing activity among lupus patients.

CONCLUSION:

There is a significant correlation between the TyG index and high disease activity in SLE patients and linear regression analysis shows that increasing TyG index values has an independent relationship with the high SLEDAS. However, the TyG index is still not a valid test for the detection of high disease activity in SLE patients. So, further researches are required to test the validity of the TyG index among SLE patients.

Disclosure of potential conflicts of interest:

The authors confirm that they have no conflict of interest between them.

Conflict of interest:

The authors declare that they have no competing interests.

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Authors' contributions:

DM was responsible for the research conceptualization and proposal design; AH and MS contributed to the data collection. MS and NA contributed to formal analysis and interpretation. MR, NA and DM were responsible for writing and editing the original manuscript. MR was responsible for the final editing and revision. Lastly, all authors have collectively approved the final manuscript.

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