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ORIGINAL ARTICLE

Estimation of Soluble Receptor Advanced Glycation End-Products in Diabetic Patients Type 2 Patients in Najaf City, Iraq

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ABSTRACT

Diabetes is a complex metabolic disruption affecting the glucose level of the human body. Intracellular hyperglycemia promotes mitochondrial reactive oxygen species (ROS) production, ROS directly improve the expression of inflammatory, these inflammations are associated with the level of soluble receptors for advanced glycation end-products (sRAGE) in serum. in this work assessed the level of (sRAGE) and study its potential as a biomarker for diabetes mellitus. The research included 108 Iraqis between the ages of (35-65) years of both sexes. The individuals were divided into two groups, (63) with type 2 diabetes mellitus (T2DM) and (45) control group, most of the tests serum have been measurements by colourimetric methods, and sRAGE levels in serum were evaluated by ELISA Technique. The results of the investigation showed that the sRAGE mean was more elevated compared to the mean of the control group ($p < 0.00001$). Statistical study of Pearson's correlation illustrated that the sRAGE level is high positively with FBG, and HBA1C ($r = 0.878$, $p < 0.00001$), ($r = 0.422$, $P=0.05$) respectively. While, negatively correlation with insulin level ($r = -0.204$, $p = 0.010$). Furthermore, most the sRAGE level denoted a positive significant correlation with kidney function parameters inclusive urea, creatinine, and ACR, except eGFR was a negative significant ($r = 0.422$, $p = 0.05$), ($r = 0.501$, $p = 0.01$), ($r = 0.435$, $p = 0.030$), ($r = -0.539$, $p = 0.011$) respectively. These results support a strong relationship between serum sRAGE level and indicators of hyperglycemia, so we can conclude that it is a great biomarker for predicting of diabetes mellitus.

Keywords: ELISA, HOMA, Insulin, sRAGE, Inflamations.

INTRODUCTION

Diabetes Mellitus Type 2 (T2DM) is a systemic metabolic disease that leads the cause of nephropathy, cardiovascular disease, and retinopathy, which outcomes from various etiologies in which its Symptoms hyperglycemia cause result from the pancreas does not make sufficient insulin hormone, or because the cells do not respond to the insulin. The term insulin resistance (IR) describes the inability of cells to respond to insulin activity in the transportation of glucose from the bloodstream to tissues and muscles. Thus, it may have proceeded with obesity and diabetes mellitus. Lipids have long been known as advocates of the etiology of T2DM[1-3], the lack of the transmembrane receptor for the advanced glycation end product (sRAGE) or (soluble RAGE) are hypothesized to counteract the detrimental activity of the full-length receptor (RAGE) via performing as a decoy, and they supply a potential mechanism to treat RAGE related diseases. Multiple investigations have researched the association between sRAGE and obesity, renal function, metabolic syndrome, atherosclerosis, and increased mortality in the public people. Also, sRAGE may be essential in the role of diabetes mellitus pathogenesis and its microvascular as renal disease and cardiovascular disease. In this study, we focus on the possibility of sRAGE as a biomarker. As there is a deficiency of an essential unifying hypothesis about how sRAGE differences according to the disease state or risk characteristic, there is a call to contain all three participants of the AGE-RAGE axis into a new global biomarker/danger marker: (AGE-RAGE)/sRAGE. Nevertheless, the measure of RAGE in humans is not practical as it is a cell-bound receptor for which tissue is in demand for analysis. A high AGE/sRAGE ratio may be an invaluable alternative and practical global biomarker/risk marker for diseases correlated with the AGE-RAGE axis, irrespective of low or high serum sRAGE Concentrations[4-6].

SUBJECTS AND METHODS

Subjects: This research was conducted on 63 (31 female and 32 male) T2DM patients without other diseases such as hypertension and cardiovascular disease and also no history of drinking or smoking as well as 45 (23 female & 21 male) control individuals with old range (35 to 65) years. Controls were selected as non-diabetic, clear from acute diseases, Patients were determined Center of Diabetes and Endocrine Glands, Al-Sadder Teaching Hospital in Najaf, Iraq, every participants should agree about participating in the study, a written consent obtained from them, during the period from November 2019 until May 2020. All essential anthropometric measures that involved weight, height, sex, age, BMI, and WHR will be registered.

Methods: The blood samples were assembled before drug administration in and after overnight fasting of fully 12 hours. BMI has been calculated by the following equation BMI (kg/m^2) = weight (kg)/height (m^2). Routine parameters (glucose, HBA1C, urea and creatinine, Uric acid, and Lipid profile) were assayed on UV-Vis Spectrophotometer using the colorimetric method. Whereas LDL concentration was calculated using the Fried Ewald formula, Fasting human insulin was estimated via Cobas e 411 instruments. By HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) Insulin resistance was calculated [insulin (μIU/mL) x glucose (mg/dL) / 405][7]. Albumin has been estimated using I ChromaII, ACR is calculated via the ratio of the concentration of urine albumin (milligrams) to urine creatinine concentration in grams, by the following equation: [GFR (mL/min/1.73 m2) = 186 × Serum Cr-1.154 × age-0.203 × 1.212 (if the patient is black) × 0.742 (if female)] GFR was estimated[8], while Sandwich ELISA technique was applied to estimate the concentration of sRAGE (enzyme-linked immunosorbent assays).

Statistical Analysis: Statistical Package (SPSS-24) was used to analyze results, data were described as "mean ± standard deviation (SD). The significance of the difference in the mean was assessed through independent t-test. P-value < 0.01, is considered highly significant, statistically significant when $p<0.05$ and non-significant when ($p>0.05$), using Pearson's correlation to estimate the correlation between variables.

RESULTS

Description of the groups of T2DM and healthy control: The characteristics of all volunteers who participated in the current research were given in Table1, the mean of age, duration of disease, Bp systolic, and weight were positively significant ($p>0.05$) for the diabetic patient group compared with the health group. However nonsignificant ($p>0.05$) in a mean of BMI, WHR, and Bp diastolic.

Also, the outcomes of the study illustrated that the body mass index (BMI) was high in (35-44) old group, then (45-55) age group higher than the (56-65) old group in patients.

Table 1: The demographic characteristics of the present study

Parameters		T2DM (m±SD) (n=63)	Control (m±SD) (n=45)	P-value
Age (years)		48.03±8.56	40.02±4.62	< 0.00001
(35-44 years) No. (%)		21 (33.4%)	34 (75.5 %)	a
(45-55 years) No. (%)		27 (42.8%)	11(24.5 %)	
(56-65 years) (No. %)		15 (23.8%)	0 (0 %)	
sex	32 (51%)	21(49%)	22 (49%)	a
	31 (49%)	24 (51%)	23 (51%)	
Duration of Disease (years)		8.063 ±5.51	0.00	< 0.05
BMI (kg/m2)		30.032±5.0	28.15±12.1	N.S
WHR		0.902±0.09	0.895±0.05	N.S
Bp (systolic) mmHg		125.78±19.	116.51±9.3	< 0.05
Bp (diastolic) mm Hg		78.97±10.84	74.91±5.70	N.S
Weight Kg		79.75±14.48	73.05±11.8	< 0.05

NS = the result is non -significant at p-value > 0.05.
The significant variance between proportions by using the Pearson Chi-square test at 0.05 level.

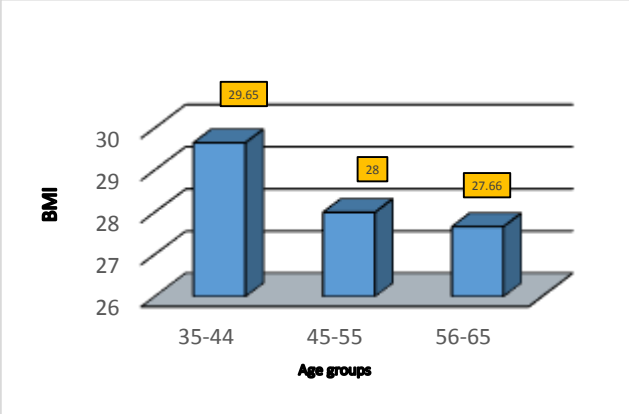

Figure 1: Distribution BMI according to the old groups

Glycemic State of study: It was observed in levels of FBG, HbA1c, insulin, and HOMA a significant raise (p<0.00001) compared to healthy subjects as shown in table 2.

Table 2: Mean ±SD values of FBG, insulin, HOMA, and HbA1c for all the studied groups.

Parameters	T2DM (m±SD) (n=63)	Control (m±SD) (n=45)	P-value
FBG (mg/dl)	196.57±90.37	99.61±13.9	< 0.00001
Insulin (µIU/ml)	14.241±7.075	10.791±4.29	< 0.00001
HOMA-IR	6.117±3.166	2.65±1.395	< 0.00001
HbA1c (%)	8.056±2.204	4.889±0.524	< 0.00001

Insulin relationship with different parameters of the study: Table 3 explained insulin relation with other parameters in the current study, since showing the presence of positive and negative associations by analysis of bivariate statistical.

Table 3: The Pearson correlation and P-value of Insulin with other parameters in the study.

Parameter	Controls		T2DM	
	r	P- value	r	P- value
Age	-0.160	0.293	-0.503	0.05
Duration	a	a	-0.032	0.806
WHR	0.483**	0.001	0.287	0.023
BMI	0.097	0.528	0.048	0.707
SYS	0.031	0.840	0.212	0.096
DIA	0.248	0.100	0.075	0.558
Glucose	0.499	0.002	-0.249	0.049
HOMA	0.947	< 0.00001	0.648	< 0.00001
HbA1c	0.209	0.169	-0.061	0.632
Urea	0.332	0.026	0.184	0.149
Creatinine	0.038	0.802	0.187	0.143
Uric acid	0.254	0.092	0.394	0.001
TG	-0.131	0.390	0.230	0.069
CHOL.	0.004	0.977	-0.066	0.610
HDL	-0.338	0.023	-0.413	0.001
LDL	0.047	0.761	0.003	0.982
VLDL	-0.130	0.393	0.230	0.070
eGFR	0.164	0.283	-0.171	0.179
ACR	0.135	0.378	0.201	0.115
sRAGE	0.425	0.004	-0.204	0.430

Correlation is significant at the 0.05 level (2-tailed).
a. Cannot be computed because at least one of the variables is constant

Lipid profile: All outcomes of the lipid profile are revealed in table 4, there was a high significantly rise in the concentration of HDL, TG, and VLDL (p>0.00001). While it is a non-significant difference in LDL and cholesterol levels.

Table 4: Mean ±SD of lipid profile.

Parameters	T2DM (m±SD) (n=63)	Control (m±SD) (n=45)	P value
TG (mg/dl)	132.21±60.85	83.080±18.72	< 0.005
Chol.(mg/dl)	138.05±41.53	134.82±36.60	NS
HDL (mg/dl)	38.40±13.75	48.719±7.45	< 0.00001
LDL (mg/dl)	72.970±36.47	70.873±36.20	NS
VLDL(mg/dl)	26.440±12.17	16.614±3.748	< 0.005

Renal function: Urea, Creatinine, Uric acid, eGFR, and ACR results have been illustrated a significant difference compared with the health topics in Table (5).

Table 5: Mean and Standard Deviation of Urea, Uric acid, Creatinine, eGFR, and ACR.

Parameters	T2DM (m±SD) (n=63)	Control (m±SD) (n=45)	P-value
Urea (mg/dl)	29.164±8.475	22.827±4.311	< 0.00001
Creatinine (mg/dl)	0.628±0.134	0.598±0.052	< 0.00001
Uric acid (mg/dl)	4.831±1.221	4.803±0.677	< 0.05
eGFR	135.973±32.7	139.782±27.2	< 0.00001
ACR	26.498±5.236	21.040±4.947	< 0.00001

Serum sRAGE level: The results have been shown (mean + standard deviation) of sRAGE (pg/ml) (510.75±120.5) of patients and (275.50±41.22) of normal subject, and p= < 0.00001. As well as, sRAGE correlation with others parameters illustrated in table 6.

Table 6: The correlation of sRAGE and other parameters.

Parameter	sRAGE			
	Controls		T2DM	
	r	P- value	r	P-value
Age	0.086	0.575	0.147	0.249
Duration	a		0.033	0.795
BMI	0.086	0.572	0.033	0.799
WHR	0.330*	0.027	-0.061	0.636
SYS	0.118	0.439	0.056	0.660
DIA	0.209	0.168	-0.061	0.632
Glucose	0.948	<0.00001	0.878	<0.00001
Insulin	0.425	0.004	-0.204	0.010
HOMA	0.575	<0.00001	0.443	<0.00001
HbA1c	0.333	0.027	0.422	0.050
Urea	0.176	0.247	0.422	0.050
Creatinine	0.005	0.972	0.501	0.01
Uric acid	0.012	0.465	-0.059	0.647
T. Protein	0.035	0.818	0.088	0.493
TG	0.352*	0.018	0.150	0.241
CHOL.	0.149	0.329	0.197	0.123
HDL	-0.030	0.844	0.178	0.162
LDL	0.092	0.546	0.111	0.387
VLDL	0.352	0.018	0.151	0.238
eGFR	0.013	0.932	-0.539	0.011
ACR	0.238	0.115	0.435	0.030

Correlation is significant at the 0.05 level (2-tailed). a. Cannot be computed because at least one of the variables is constant.

Roc Area Under The Curve

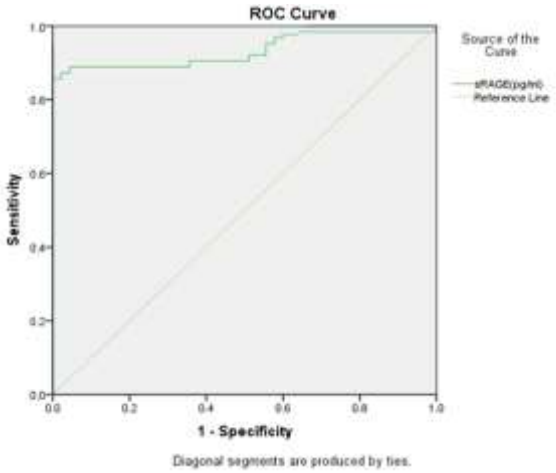

Figure 2: ROC for the different parameter of T2DM and control group.

DISCUISSION

The study found that the anthropometric indices of a diabetic patient are higher than those of normal subjects , These results are compatible with Komatsu et al.[9] The estimated fat precipitation as an outcome of an energy inequality between the energy that is consumed via daily actions and that comes from the diet, obesity is a multifactorial causal relationship of disease in which the adipose tissue, instead of being just a place to store extra energy, acts as an endocrine organ with vasoactive effects that are concerned in the development of metabolic diseases[10], as well as, obesity is a higher risk of the probable incidence of diabetes mellitus. It can be represented by BMI that is a simple index computed from (weight and height), and WHR thus, it is very essential to estimate it[11] Furthermore, Bp systolic has high significance in a patient, this relationship with the level of insulin at a patient, since hyperinsulinemia occurs to cause the sympathetic nervous system may cause water and sodium retention and vasoconstriction that raise blood pressure. In addition, being overweight has a critical play on T2DM patients, Sonmez et.al, (2019) study the preponderance of obesity among patients and search for the influence of obesity on metabolic control.

Also, the results of the investigation showed that BMI was higher in the younger age group because of lifestyle modifications with food and pharmaceuticals that can impact insulin level and insulin resistance as metformin that may cause weight loss. The hormone of leptin plays a vital role in controlling energy balance and body weight. Besides, the fundamental action of glucose homeostasis. Also, Adipokines and Resistin produced from adipose tissues have been demonstrated to be endocrine factors that are even crucial in energy homeostasis and they have an adversarial influence on insulin activity, thus reducing insulin sensitivity.

Our outcomes showed that there was a highly significant variation in the level of HDL of patients compared with a control group (p>0.00001), these outcomes compatible with the investigation of Shukang Wang et.al, who demonstrate that the HDL was statistically significant in type 2 diabetic patients[12]. Also, levels of TG and VLDL have highly positive significance among patients and control subjects (p> 0.00001). Moreover, the previous study has shown that a low mean of HDL may cause a raised risk to conceive T2DM likely because greater β-cell functions decrease over time[13,14]. Obesity is correlated with dyslipidemia interpreted by raised triglycerides and diminished HDL level, and this dyslipidemia is positively associated with a raised risk of T2DM[15-17].

Creatinine is an extremely sensitive marker in comparison to urea utilized in the earlier detection of renal defects. Therefore, blood creatinine can be employed to estimate glomerular filtration, various studies have shown that raised serum levels of creatinine and urea are associated with increased blood glucose[18]. As prior investigations have shown that the levels of serum uric acid have a positive association with insulin secretion[19].Additionally, elevated serum uric acid may affect the availability of nitric oxide endothelial. In turn, nitric oxide tends to be responsible for insulin resistance. Some findings showed that uric acid levels were firmly related to T2DM[20].

The current research reported that the means of sRAGE (510.75±120.5) had a significant rise in T2DM patients when compared to that health control group (275.50±41.22), (p<0.05), Glycation is the essential result of hyperglycemia, which happens from interaction protein with glucose. Glycation is usually observed by an oxidation reaction. AGE product is a complex molecular approach that contains uncomplicated and more complex multistep interactions. RAGE receptor can utilize their action in tissues via interacting with specific ligands as (AGE). As well as, sRAGE is considered to be a parameter of RAGE activity, rather than being concerned in the disease methodology[21,22].

The investigation findings support the theory that RAGE concentration has an actual role in vascular disease. Satisfactory evidence supports this role[23]. RAGE is a more various receptor in the terms of origin and process, in which it has been observed in the macrophages, glomerular, lymphocyte vascular, endothelium, and vascular smooth muscle cells, and RAGE shown to impact the activity of all of these cell kinds, carrying out a proactive role in all steps of inflammation[24]. Additionally, it has been discovered that sRAGE levels are increased significantly in T2DM sufferers than in nondiabetic someone and are positively correlated with the formation of coronary artery disease in diabetes mellitus. These findings indicate that endogenous sRAGE concentration may be introduced in diabetes.

CONCLUSION

From this study it is concluded that sRAGE level is raised with diabetes, hence sRAGE is believed to be useful to denote people at risk of diabetes thus decreasing morbidity and mortality. Furthermore, the ROC analysis of the sensitivity and specificity shows that of biomarkers, sRAGE level can be presented as a potential marker for earlier designation of diabetes Mellitus.

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