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Assessment of Methylglyoxal and Soluble Receptor Advanced Glycation End-Products (sRAGEs) in Pre-Diabetic Patients

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Abstract

Prediabetes is a condition between normal glucose levels and increased levels of type 2 diabetes, and it is connected with a high risk of developing diabetes. Methylglyoxal is a highly reactive α-dicarbonyl compound endogenously generated naturally as a byproduct during the glycolytic pathway and is considered the precursor of an advanced glycation end product. sRAGE acting as decoy receptors help reduce inflammation, oxidative stress, and vascular complications. This study aims to measure methylglyoxal as the precursor of an AGE and its receptor in prediabetic as a biomarker for metabolic dysfunction. This study involved 80 participants, including 40 prediabetic patients and 40 healthy controls diagnosed in Al-Imamin Alkadmeen City Hospital, Baghdad, Iraq. Basic data from clinical examination and laboratory were collected for all participants. The serum methylglyoxal was measured by high-performance liquid chromatography, and soluble receptor, while advanced glycation end-products were measured by using an ELISA technique's kit. Additional parameters were also measured, such as fasting blood glucose, HbA1c, insulin, HOMA-IR, and lipid profile. Subsequently, in prediabetic patients, methylglyoxal and sRAGE levels are significantly elevated compared to healthy controls. Moreover, FBS, HbA1c, insulin, and HOMA-IR are significantly higher in prediabetic patients ($p < 0.001$). Based on the findings of this research, methylglyoxal and sRAGE may serve as potential biomarkers for prediabetic patients.

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1. Introduction

Prediabetes is a condition in which glucose indices are elevated above normal levels but remain below the diagnostic threshold for type 2 diabetes[1] . The diagnostic criteria for prediabetes include a fasting blood glucose (FBG) level between 100 and 125 mg/dL, and a hemoglobin A1c (HbA1c) level ranging from 5.7% to 6.4% [2].An annual conversion rate of 5% to 10% among individuals with prediabetes indicates a significant risk of progression to type 2 diabetes [3]. Furthermore, prediabetes is often associated with other metabolic abnormalities such as central obesity, dyslipidemia, and hypertension [4], which together contribute to increased risk of cardiovascular diseases [5] One of the biochemical consequences of hyperglycemia is the increased production of methylglyoxal (MG), a highly reactive α-dicarbonyl compound that is endogenously generated as a byproduct of the glycolytic pathway [6]. MG is a key precursor in the formation of advanced glycation end-products (AGEs), which accumulates in tissues and contribute to cellular dysfunction. The glyoxalase system, particularly the enzymes glyoxalase I and II, plays a critical role in detoxifying MG using reduced glutathione as a cofactor[7]. Impairment of detoxification pathway leads to MG accumulation, enhanced AGEs formation, and subsequent tissue damage[8] . AGEs are formed through non-enzymatic reactions between reducing sugars, such as glucose, and amino groups in proteins, lipids, and nucleic acids via the Maillard

reaction. This multi-step process includes the formation of Schiff bases and subsequent chemical rearrangements, ultimately resulting in stable AGEs [9] . The accumulation of AGEs in various tissues has been implicated in the pathogenesis and progression of chronic diseases, particularly diabetes and its associated complications[10]. This pathogenic process is primarily mediated by the induction of oxidation induced stress and activation of pro-inflammatory signaling pathways.[11].The Soluble receptor for advanced glycation end-products (sRAGE) acts as a decoy receptor that binds circulating AGEs, preventing their interaction with membrane-bound RAGE receptors[12]. This interaction is known to trigger oxidative stress and inflammation, both of which contribute to vascular complications in diabetes[13]. However, sequestering AGEs, sRAGE plays a protective role, reducing oxidative damage and inflammation [14], also has been proposed as , sRAGE a biomarker and a potential therapeutic target in managing diabetes and its cardiovascular consequences [15].Methylglyoxal is considered one of the most reactive precursors of AGEs. It can rapidly modify proteins and nucleotides leading to structural and functional cellular impairments[16]. These effects have been implicated in the early stages of diabetic complications[17].Elevated levels of MG have been reported in individuals with impaired glucose tolerance and type 2 diabetes, correlating with increased oxidative stress, and endothelial dysfunction [18].The evaluation of MG concentrated in individuals with prediabetes may offer critical insights into early metabolic disruptions that contribute to the onset of diabetes and associated cardiovascular disorders[19]. This research aims to assess the levels of methylglyoxal (MG) and soluble RAGE (sRAGE) in prediabetic patients.

1. Material and methods:

2.1. Materials:

This study's case-control design included 80 Iraqi individuals, of whom 40 had prediabetes and 40 were in the control group and in good health. It was conducted from January 2024 to June 2024, with ages of the participants from 30 to 60 years at Al-Imamin Alkadmeen City Hospital, Baghdad, Iraq. Prediabetic patients were received via a consultant's examination by a specialist and were approved by the institutional ethical review committee (Approval No.:20230901).

2.2. Blood collection and Procedures

All samples were collected from fasting participants during their hospital visit. Prediabetes diagnosis was made according to the American Diabetes Association (ADA) guidelines [1]. Body mass index (BMI) measurements were recorded. A total of 7 ml of whole blood was collected and divided into two tubes, the first EDTA tube for HbA1c measurement, and the second a gel tube allowed to coagulate for 15 minutes. The samples were then centrifuged at room temperature for 15 minutes at 5500 rpm to separate the serum for measuring fasting blood glucose, and lipid profile and store at -20 c to measure serum insulin, methylglyoxal (MG), and soluble receptor advanced glycation end-products (sRAGE).

2.3. Measurement of chemical Parameters

Methylglyoxal (MG) was measured using high-performance liquid chromatography (HPLC) used standard solution from (Mvcklin, China) and soluble receptor for advanced glycation end-products (sRAGE) were quantified using ELISA kit (Sun Long Biotech, China). Serum insulin levels were also determined using ELISA. HbA1c, lipid profile, and fasting blood glucose were measured using the Cobas system using kit from Roche. Germany.

2. Statistical analysis

The results of the current study are evaluated using GraphPad Prism Version 9, Descriptive statistics data as mean and standard deviation (mean ± SD). The comparison of study groups was investigated using an unpaired t-test. (p-value < 0.001) appears to show statistically significant in difference.

3. Results and Discussion

The current study revealed that high level of average serum FBS and HbA1c in prediabetic were significantly higher in the patients' group ($p < 0.001$) (129.93±16.69 mg/dL and 6.10±0.36 %), respectively and when compared with the healthy controls. The levels of insulin and HOMA-IR were significantly higher in the prediabetic patients (9.83±1.24 mUi/mL and 3.06±0.58) compared with the healthy controls ($p < 0.001$). The Methylglyoxal level was significantly higher ($p < 0.001$) in the prediabetic patients (0.66 ± 0.07µg/mL) when compared with healthy controls. The significantly high level of sRAGE ($P < 0.001$) in prediabetics (515.1±117.54 pg/mL) was observed compared to healthy control (414.2±80.57 pg/mL). The total cholesterol levels higher in prediabetic subjects (194.59±34.89 mg/dL) than in the control group (187.48±18.09) and the (p-value 0.91). The level of HDL cholesterol was significantly lower ($P < 0.001$) in prediabetic patients (36.36±5.69 mg/dL) as compared to the controlled group (51.25±8.48 mg/dL). LDL cholesterol was significantly increased ($P < 0.05$) in prediabetic subjects (115.49±16.06 mg/dL)

than in the control group (110.5±11.22 mg/dL). The level of VLDL cholesterol was significantly higher ($p < 0.05$) in prediabetic subjects (28.41±7.40 mg/dL) than in the control group (24.58±3.51 mg/dL). High level of triglycerides in prediabetic patients was significantly observed ($P < 0.05$) (140.97±27.89 mg/dL) as compared to the control group (121.45±16.9 mg/dL), as shown in the Table1 and Figure1 (a, b). Furthermore, according to correlation study, HbA1c showed a significant positive correlation ($p = 0.0005$, $r = 0.5886$) (Table 2). However, there was no correlation between sRAGE and HbA1c was found ($p = 0.875$, $r = 0.02$). Similarly, no correlation was found between sRAGE, MG, and lipid profile ($p > 0.05$). But, no correlation was found between biomarker sRAGE, MG, with insulin, HOMA-IR, and fasting blood glucose ($p > 0.05$) as shown in Table 2. Prediabetes is a condition that may increases the risk of developing type 2 diabetes and is considered a significant risk factor for its progression [20] . This study found that MG levels were significantly higher in the prediabetes group compared to the healthy control group. MG plays an important role in the early stages of metabolic dysfunction, particularly in prediabetic individuals, by causing ß-cell dysfunction and reducing insulin production[21].Moreover, MG showed a statistically significant positive correlation with HbA1c, indicating that higher MG levels are associated with higher HbA1c values, and this result agrees with the study of (Reyaz, A.; et al.) which suggests that MG and HbA1c may act in a complementary manner, with elevated HbA1c reflecting poor glycemic control [22] The current study demonstrated that serum sRAGE level is higher than healthy controls with prediabetic individuals, relatively sRAGE acts as a decoy receptor by binding with AGEs and preventing their interaction with membrane-bound RAGE, thereby reducing the harmful effects of AGEs [23]. However, this finding contrasts with the study that reported no significant difference between prediabetic and control groups[24].This discrepancy may be due to the use of an obese control group in that study, as obesity can influence sRAGE levels and potentially mask the expected differences. Another study by (Huang, Y. et al.) was found showing lower sRAGE levels in prediabetic and newly diagnosed diabetic patients, compared to controls [25].The differences in the results may be attributable to the unstable nature of sRAGE levels during the early stages of diabetes and prediabetes, as well as the influence of various factors such as metabolic syndrome, insulin resistance, and chronic inflammation. Additionally, the current study indicates a significant increase in lipid profile parameters, which include total cholesterol, LDL-C, triglycerides, and VLDL, accompanied by a decrease in HDL levels in prediabetic patients. These findings are consistent with the study by (Mulla et al. 2024) [26]. The pathophysiology of lipid abnormalities is closely linked to insulin resistance, a key feature of T2DM. Insulin resistance promotes excessive free fatty acid release, hepatic triglyceride synthesis, and increased production of very low-density lipoproteins (VLDL), leading to hypertriglyceridemia, which significantly increases the risk of crucial component of diabetic metabolic disturbances [27].

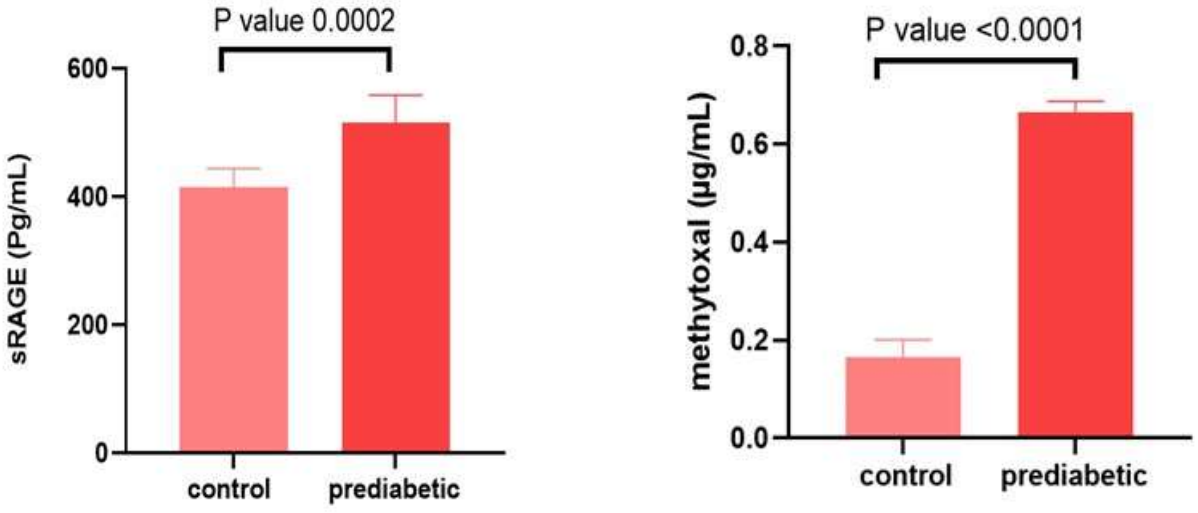
Table 1. Descriptive statistics and comparisons of the main markers between the studied groups

Parameters	Control (n=40)	Prediabetic patients (n=40)	P- value	Significant
	Mean ± SD			
Age (years)	39.77 ± 8.9	40.8 ±1.1	> 0.05	NS
BMI (kg/m²)	25.00 ± 3.9	27.84 ± 6.1	> 0.05	NS
Duration of prediabetes	---------	1–2 year	--------	-----
FBS (mg/dL)	94.26 ± 26	129.93 ±16.6	< 0.001	HS
HbA1c (%)	5.05 ± 0.22	6.10 ± 0.36	< 0.001	HS
Insulin (mU/mL)	4.803 ± 1.1	9.83 ± 1.24	< 0.001	HS
HOMA-IR	1.108 ± 0.2	3.06 ± 0.58	< 0.001	HS
Total cholesterol (mg/dL)	187.48 ± 18.1	194.59 ± 34.9	> 0.05	NS
HDL (mg/dL)	51.25 ± 8.5	36.36 ± 5.7	< 0.001	HS
LDL (mg/dL)	110.5 ± 11.2	115.49 ±16.1	< 0.05	S
VLDL (mg/dL)	24.58 ± 3.5	28.41±7.4	< 0.05	S
TG (mg/dL)	121.45 ± 16.9	140.97 ± 27.9	< 0.05	S
Methylglyoxal (µg/mL)	0.17± 0.1	0.66 ± 0.07	< 0.001	HS
sRAGE (pg/mL)	414.2 ± 80.6	515.1±117.5	< 0.001	HS

S: Significant ($p \leq 0.05$), HS: high significant ($p \leq 0.001$), SD; Standard Deviation.
NS: non-significant

Table 2: Correlation coefficient between MG & sRAGE and other biochemical parameters in prediabetic patients

Parameters	Correlation coefficient-r	P- value
	Control and Prediabetic patients	
Methylglyoxal, sRAGE	0.139	0.454
Methylglyoxal, FBS	0.251	0.171
Methylglyoxal, HbA1c	0.588	0.0005
Methylglyoxal, Insulin	0.0412	0.825
Methylglyoxal, IR	0.189	0.308
Methylglyoxal, Total cholesterol	0.104	0.575
Methylglyoxal, TG	-0.161	0.386
Methylglyoxal, HDL	0.132	0.477
Methylglyoxal, LDL	-0.165	0.375
Methylglyoxal, VLDL	-0.143	0.445
soluble RAGE, FBS	0.0717	0.711
soluble RAGE, HbA1c	0.029	0.875
soluble RAGE, Insulin	-0.196	0.288
soluble RAGE, IR	-0.077	0.678
soluble RAGE, Total cholesterol	0.030	0.869
soluble RAGE, TG	0.264	0.151
soluble RAGE, HDL	0.146	0.434
soluble RAGE, LDL	-0.214	0.248
soluble RAGE, VLDL	0.286	0.118



(a) (b)

Figure 1. (a) Means of sRAGE by groups (95.00% CI) Error Bars (b) Means of Methylglyoxal by groups (95.00% CI) Error Bars.

4. Conclusions

This study discovered the increased serum level of MG and sRAGE among prediabetic individuals compared to healthy controls. Moreover, a positive correlation was observed between MG and HbA1c, suggested a potential link between MG, glycaemia control, and early metabolic dysfunction. Additionally, the elevation of sRAGE levels in prediabetic patients may reflect its role as a decoy receptor that binds to AGEs and limits their

pathological effects. Overall, these results support the potential role of both methylglyoxal and sRAGE as biomarkers for identifying metabolic alterations in prediabetic patients.

Abbreviations

MG: Methylglyoxal
sRAGE: soluble receptor Advanced Glycation End-products
AGE :Advanced glycation end-products
HbA1c: Hemoglobin A1C
FBS: Fasting blood sugar.
HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.
BMI: Body mass index

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