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Investigation of Methylglyoxal, soluble Receptor for Advanced Glycation End-products, and Malondialdehyde in Type 2 Diabetes Mellitus with and Without Cardiovascular Risk Factors

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Abstract

Background: Type 2 diabetes mellitus is a chronic metabolic illness that significantly increases the probability of cardiovascular disorders among individuals with type 2 diabetes. Oxidative stress represents a central pathophysiological connection between type 2 diabetes mellitus and cardiovascular complications. Hyperglycemia in type 2 diabetes mellitus elevates oxidative stress through multiple pathways, including the production of advanced glycation end products and methylglyoxal, which interact with their receptor advanced glycation end product (sRAGE). These processes enhance the generation of reactive oxygen species, which leads to lipid peroxidation with malondialdehyde serving as a biomarker.

Objectives: To investigate the levels of methylglyoxal, sRAGEs, and malondialdehyde in type 2 diabetes patients with and without cardiovascular risk factors.

Patients and Methods: The cross-sectional study involved eighty patients with type 2 diabetes diagnosed with and without cardiovascular risk factors. The study used high-performance liquid chromatography (HPLC) to measure serum methylglyoxal and an ELISA kit (Sun Long Biotech, China) to measure serum sRAGE. Malondialdehyde levels were assessed by spectrophotometry. Moreover, measured parameters included FBS, HbA1c, CRP, and lipid profile by the Cobas system using a kit from Roche, Germany.

Results: Type 2 diabetes patients with cardiovascular risk factors had significantly higher serum methylglyoxal, sRAGE, and malondialdehyde compared to those without CV risk factors. Furthermore, fasting blood glucose, HbA1c, lipid profile, and CRP are higher in diabetes with CV risk factors compared to those without.

Conclusion: The patients with type 2 diabetes and cardiovascular risk factors showed an increase in methylglyoxal, sRAGE, and Malondialdehyde, which are considered useful biomarkers for the indication of T2DM with cardiovascular risk.

Keywords: Methylglyoxal, sRAGE, Cardiovascular risk.

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic disorders worldwide, accounting for approximately 90% of all diabetes cases (1). It developed due to the inability of insulin-sensitive tissues to respond as well as a defect in insulin secretion (2). Therefore, this dysfunction leads to hyperglycemia, which causes microvascular and macrovascular complications (3). Chronic hyperglycemia contributes to endothelial dysfunction and oxidative stress, which is considered a key to cardiovascular risk (4).Common factors include hypertension, hyperlipidemia, and obesity with type 2 diabetes mellitus (5). These factors accelerate the development of cardiovascular complications (6). Early identification and management of cardiovascular risk in T2DM are essential for preventing long-term complications (7). Persistent hyperglycemia promotes highly reactive intermediates such as advanced glycation end products(AGEs)(8). A precursor to these intermediates is a dicarbonyl compound called methylglyoxal (MGO), which is produced mostly during carbohydrate, lipid, and protein metabolism (9). Accumulation of MGO and advanced glycation end products (AGEs) plays a role in the development of type 2 diabetes mellitus (T2DM) and its complications (10,11). Chronic hyperglycemia in diabetes causes the formation of AGEs, which accumulate in tissues and contribute to vascular damage. The receptor for Advanced Glycation End Products (RAGE) is a interacts with a varied range of ligands and a member of the immunoglobulin superfamily that mediates interaction between the advanced glycation end-products (AGEs) and endothelial cells. RAGE is considered a membrane-bound immunoglobulin surface (12,13). Moreover, when AGEs bind to RAGE causes the development of reactive oxygen species (ROS) and the stimulation of transcription factors like nuclear factor-κB (NF-κB) and resulting in the expression involved vascular inflammation and endothelial dysfunction (14). Elevated levels of binding AGEs with RAGE are linked to the development of macrovascular and microvascular complications in diabetes, such as atherosclerosis, nephropathy, and retinopathy (15). The soluble receptor advanced glycation end product (sRAGE) acts as a decoy receptor that binds to AGEs, preventing their interaction with membrane-bound RAGE. This interaction typically triggers oxidative stress and inflammation pathways. By sequestering AGEs, sRAGE reduces these harmful effects (16,17). Moreover, sRAGE plays an essential role in modulating the effects of AGEs in diabetes. It is a valuable biomarker and a potential medicinal target in dealing with diabetes and its associated cardiovascular risks (18). The development and progression of diabetes, alongside its complications, are largely caused by oxidative stress, which is typically associated with increased free radical production or defective antioxidant defenses. Reactive oxygen species ROS attack lipids, and the major consequence of oxidative stress is lipid peroxidation, leading to the generation of malondialdehyde (MDA), a well-established biomarker of oxidative damage (19,20). Therefore, Oxidative stress, as indicated by elevated MDA, and linked to pancreatic beta-cell dysfunction and impaired insulin secretion.

Patients and Methods

Study design: This cross-sectional study design included 80 Iraqi individuals, of whom 40 had DM without CVR Factors and 40 were in the DM with CVR Factors. It was conducted from January 2024 to June 2024. The age of the participants ranged from 40 to 60 years at Al-Imamin Alkadmeen City Hospital, Baghdad, Iraq. Prediabetic patients received a consultant's examination by a specialist and were approved by the institutional ethical review committee.

Inclusion criteria: This study involves two groups: Group 1: 40 patients with Type 2

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diabetes mellitus without cardiovascular risk factors.

Group 2:40 patients with Type 2 diabetes mellitus with cardiovascular risk factors.

Exclusion criteria: This study exclude the following patients:

a. Patients were excluded if they were aged < 40 years or more than 60 years.
b. Type 1 diabetes patients
c. Pregnant females
d. Patients with a history of cardiovascular disease.
e. Patients receiving insulin treatment.
f. Individuals with anemia
g. Patients with kidney, liver, or thyroid disorders
h. Known case of carcinoma anywhere
i. Autoimmune diseases

Blood collection and procedures: All blood samples were collected from fasting participants during their hospital visit. The diagnosis of type 2 diabetes mellitus was based on the American Diabetes Association (ADA) guidelines (21). Body mass index (BMI) measurements were recorded. A total of 7 mL of whole blood was collected and divided into two tubes; the first tube was an EDTA tube for HbA1c measurement, and the second was a gel tube allowed to coagulate for 15 minutes. The samples were centrifuged at 5500 rpm for 15 minutes at room temperature to separate the serum for measuring fasting blood glucose, CRP, and lipid profile. and stored at -20 c to measure serum MDA, methylglyoxal (MG), and soluble receptor advanced glycation end-products (sRAGE).

Measurement of chemical parameters:

Methylglyoxal (MG): Methylglyoxal (MG) levels were determined using high-performance liquid chromatography (HPLC) with a standard solution obtained from Mvcklin (China). The derivatization reagent used was 1,2-diamino-4,5-methylenedioxybenzene (DMP). The mobile phase consisted of acetonitrile, methanol, and distilled water. Separation was performed on a C18 Octadecyl-silica (ODS) column (250 mm × 4.6 mm) with a flow rate of 1 mL/min. Detection was carried out by a fluorescence detector at an excitation wavelength of 355 nm and an emission wavelength of 393 nm.

Sample preparation: Serum samples (100 µl) were centrifuged at 10,000 rpm for 5 minutes to remove cellular components. The supernatant was filtered using a 10 kDa centrifugal ultrafiltration device to eliminate proteins. Subsequently, 50 µL of serum was mixed with 50 µL of DMP (0.7 mM) and incubated at 60°C for 40 minutes to form the MG-DMP derivative. A 10 µL aliquot of the derivatized solution was injected into the HPLC system for analysis. (22).

Soluble receptor for advanced glycation end-products (sRAGE): Soluble receptor for advanced glycation end-products (sRAGE) was quantified with an ELISA kit according to the manufacturer's protocols, according to the manufacturer's protocol NO.:SL0036Ra (Sun Long Biotech, China).

Malondialdehyde: Serum MDA levels were determined using the thiobarbituric acid reactive substances (TBARS) method. In this assay, lipid peroxidation end products, mainly MDA, react with thiobarbituric acid (TBA) under acidic conditions and heating in a boiling water bath (100 °C) to form a pink chromogen. After cooling and centrifugation, the absorbance of the clear supernatant was measured spectrophotometrically at 532 nm against a blank. The concentration of MDA was calculated using the molar extinction coefficient of the MDA–TBA adduct (1.56×10^5 cm^{-1} mol^{-1}), and the results were expressed in µmol/L (23).

Additional tests: HbA1c, fasting blood glucose (FBG), lipid profile, and C-reactive protein (CRP) were measured using the Cobas c111 fully automated analyzer (Roche Diagnostics, Germany), following the manufacturer's

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standard protocols.

Statistical Analysis

To analyze the data, GraphPad Prism (version 10.3.1) and MedCalc software were used to create the ROC curve. date the expression as mean, standard deviation (SD), mean ± SD. Comparison between the two groups used an unpaired t-test with a p-value < 0.05 was considered statistically significant, and very small p-values were reported as p < 0.001.

Results

Demographic and diabetes-associated characteristics of the study cohort eighty patients with type 2 diabetes mellitus with and without cardiovascular risk factors. The study groups were divided into smaller groups based on age, gender, and BMI (Table 1). The study included 25 females (62.5%) and 15 males (37.5%), as shown in Table 1.

Table 1. Descriptive features of the study population (Number = 80).

Parameters	DM without CVR Factors Mean±SD. No.= 40	DM with CVR Factors Mean±SD. No.=40	p–value
Age (years)	**48.87±9.3**	**56.94±4.17**	**<0.001 (S)**
Sex	**M 15 (37.5%) F 25 (62.5%)**	**M 15 (37.5%) F 25 (62.5%)**	**----------**
BMI (kg/m²)	**29.88±5.782**	**30.18±3.209**	**0.775 (NS)**
Duration of type 2 DM	**6.15±5.38**	**9.25±2.38**	**0.0013 (S)**

T-test: significant at p < 0.05, SD: standard deviation; S: significant; NS: non-significant DM: diabetes Mellitus CVR: cardiovascular risk factors

Measurement of glucose profile, methylglyoxal, sRAGE, MDA, and CRP in the patients' groups: The high level of average serum fasting blood glucose (FBS) and HbA1c in diabetes with CV risk factors was (238.0±34.35 mg/dL and 10.03±1.30%), respectively, and when compared with diabetes without CV risk factors (175.4±76.28 mg/dl, 7.86±1.28%) (p < 0.001). The Methylglyoxal level (1.235±0.256 µg/mL) was significantly higher (p < 0.001) in diabetes with CV risk factors patients when compared to those without (0.9139±0.046 µg/mL). The high level of sRAGE in diabetes with CV risk factors (699.8±86.78 pg/mL) compared to without (542.2±72.96 pg/mL) (p < 0.001). The MDA level was higher in diabetes with CV risk factors (5.726±0.82 (µmol/L)) compared to without (p < 0.001). CRP levels were higher in T2DM patients with CV risk (10.81±0.76 mg/l) than without (7.50±0.296 mg/l), with p value < 0.001as shown in Table 2.

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Table 2. The mean difference of biomarkers for patients with type 2 diabetes mellitus with and without cardiovascular risk factors.

Parameters	DM without CVR Factors Mean±SD. N= 40	DM with CVR Factors Mean±SD. N=40	P - value
FBS (mg\dL)	175.4±76.28	238.0±34.35	<0.001 (S)
HbA1c %	7.86±1.28	10.03±1.30	<0.001(S)
MGO (µg/mL)	0.9139±0.046	1.235±0.256	<0.·01 (S)
sRAGEs (pg/mL)	542.2±72.96	699.8±86.78	<0.001 (S)
MDA (µmol/L)	3.509±0.42	5.726±0.82	<0.001 (S)
CRP (mg/l)	7.50±0.296	10.81±0.76	<0.001 (S)
T-test: significant at p < 0.05, SD: standard deviation; S: significant. NS= non-significant DM: diabetes Mellitus CVR: cardiovascular risk factors.			

Measurement of lipid profile and atherogenic index in the patients groups: The total cholesterol level was higher in T2DM with CV risk factors (284.5±34.44 mg/dL) than without CV risk (241.3±77.32 mg/dL), and the p < 0.001. In contrast, the level of HDL cholesterol was lower in T2DM with CV risk factors (27.19±5.686 mg/dL) compared to those without CV risk (36.62±4.89 mg/dL), p < 0.001. While LDL cholesterol was significantly increased in T2DM with CV risk factors (131.7±20.65 mg/dL) as compared to those without CV risk (121.4±14.13mg/dL), the p-value was < 0.05. The level of VLDL cholesterol was significantly higher (p < 0.001) in patients with T2DM and CV risk factors (50.11±5.69 mg/dL) compared to those without CV risk (40.42±11.42 mg/dL).

Triglyceride levels were significantly higher in T2DM with CV risk factors (250.0±26.91mg/dL) as compared to without CV risk (241.3±77.32mg/dL), and the p-value was p < 0.001. Furthermore, the high level of Atherogenic Index of Plasma (AIP) in T2DM with CV risk factors (0.97±0.1) as compared to those without CV risk (0.733±0.12), the p-value was p < 0. 0001, Additionally, the cardiac Risk Index 1 (CRI-1) level was significantly higher in T2DM with CV risk factors (10.91±2.71) as compared to those without CV risk (6.856±3.07), with p < 0.001. The Cardiac Risk Index 2 (CRI-2) level was higher in T2DM with CV risk factors (5.12±1.63) as compared to without CV risk (3.376±0.62) with a p-value < 0.001, as shown in Table 3.

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Table 3. The mean difference in lipid profile for patients with type 2 diabetes mellitus with and without cardiovascular risk factors.

Parameters	DM without CVR Factors Mean±SD. N= 40	DM with CVR Factors Mean±SD. N=40	P - value
Total cholesterol (mg\dL)	241.3±77.32	284.5±34.44	< 0.001 (S)
TG (mg\dL)	202.2±57.02	250.0±26.91	< 0.001 (S)
LDL (mg\dL)	121.4±14.13	131.7±20.65	< 0.05 (S)
VLDL (mg\dL)	40.42±11.42	50.11±5.69	< 0.001 (S)
HDL (mg\dL)	36.62±4.89	27.19±5.686	< 0.001 (S)
AIP Log [TG / HDL-C]	0.733±0.12	0.97±0.1	< 0.001(S)
CRI-1 (TC / HDL-C)	6.856±3.07	10.91±2.71	<0.001 (S)
CRI-2 (LDL-C / HDL-C)	3.376±0.62	5.12±1.63	< 0.001 (S)

T-test significant at $p < 0.05$, SD: Standard Deviation; S: Significant.
NS non-significant DM: Diabetes Mellitus, CVR: Cardiovascular Risk.
AIP= Atherogenic Index of Plasma, CRI-1= Cardiac Risk Index 1, CRI-2= Cardiac Risk Index 2.

Receiver operating characteristic curve (ROC) of MGO, sRAGE, and MDA biomarkers in the patients groups: As shown in Table 4, methylglyoxal (MGO) demonstrated a cutoff value > 0.98 with a 95% confidence interval (CI) of 1.000 to 1.000, indicating a strong diagnostic ability. The sRAGE biomarker exhibited excellent diagnostic performance, with a sensitivity of 100%, specificity of 83.9%, and an area under the curve (AUC) of 0.938 (95% CI: 0.873 to 1.000). The optimal cutoff value for sRAGE was > 597.03. Furthermore, Malondialdehyde (MDA) showed high sensitivity (100%) and specificity (93.5%), with an AUC of 0.982 (95% CI: 0.947 to 1.000) and a cutoff value > 4.1.

Table 4. ROC curve of MGO, sRAGE, and MDA biomarkers between type 2 diabetes mellitus patients without and with cardiovascular risk factors.

Variable	AUC	95 % CI	Cutoffs	Sensitivity	Specificity
MGO(µg/mL)	1.000	1.000 to 1.000	> 0.98	100	100
sRAGE (pg/mL)	0.938	0.873 to 1.000	> 597.03	100	83.9
MDA (µmol/L)	0.982	0.947 to 1.000	> 4.1	100	93.5

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Discussion

Type 2 diabetes mellitus (T2DM) is a chronic metabolic illness strongly associated with increased risk of macrovascular complications (3). Multiple pathways contribute to macrovascular complications, such as oxidative stress, inflammation, and mitochondrial dysfunction (4).Inflammation is commonly indicated by C-reactive protein (CRP). In the present study, CRP levels were significantly elevated in T2DM patients with cardiovascular (CV) risk compared to those without. These results agree with Upreti et al., who reported that CRP is highly correlated with CV risk level in T2DM (24). In the current study, methylglyoxal (MGO) levels were significantly elevated in T2DM with cardiovascular risk compared to those without CV risk. This elevation may be attributed to impaired glyoxalase system activity and increased oxidative stress, which contribute to the accumulation of MGO, leading to the formation of advanced glycation end-products (AGEs) (25).These findings agree with a study by Hanssen et al., (26), who reported elevated levels of MGO in type 2 diabetes mellitus with cardiovascular disease, indicating that MGO contributes to both endothelial dysfunction and inflammation, thereby promoting cardiovascular complications in type 2 diabetes mellitus (26).

Moreover, MGO readily reacts with proteins, DNA, and other macromolecules, leading to the formation of AGEs, which play a crucial role in diabetes-related complications. which supports the role of MGO as a potential biomarker for cardiovascular risk (9). Elevated MGO levels affect metabolic pathways, leading to increased lipid peroxidation, as indicated by elevated levels of MDA in patients with cardiovascular risk factors (27). This relationship shows the role of MGO, oxidative stress, and inflammation in the pathophysiology of diabetic cardiovascular disease. Furthermore, in the present study, the MDA level was higher in T2DM patients with cardiovascular risk factors compared to those without CV risk. This finding agrees with Khan et al., who showed that lipid peroxidation increased in hyperglycemic diabetic patients, leading to diabetic complications (28). Oxidative stress is potentially associated with the development of diabetic complications. The negative correlation between lipid peroxidation and antioxidant cellular activity establishes a pathogenic link between hyperglycemia and complications in type 2 diabetes mellitus patients (29).In the current study, sRAGE levels were significantly elevated in type 2 diabetes mellitus with cardiovascular risk factors than without cardiovascular risk factors. sRAGE levels may reflect a compensatory response to the increased formation of AGEs. This result agrees with Sabbatinelli et al., who suggest that sRAGE plays a crucial protective role in vascular endothelial function. AGE-RAGE interactions impair endothelial integrity, triggering endothelial cell activation and vascular inflammation. However, sRAGE mitigates these effects by neutralizing circulating AGEs, thereby preserving vascular homeostasis and reducing the risk of atherosclerosis (30). This mechanism may explain why the sRAGE levels in type 2 diabetes mellitus patients with cardiovascular risk are higher than those without cardiovascular risk, reflecting an adaptive response to increased vascular stress. Moreover, the current study indicates a significant increase in lipid profile parameters, including total cholesterol, LDL-C, triglycerides, and VLDL, accompanied by a decrease in HDL levels in patients with T2DM who have CV risk factors. These findings are consistent with the study by Mulla et al. (31). The atherogenic index of plasma (AIP) and Cardiac Risk Index 1 and 2 were significantly elevated in T2DM with CV risk compared to those without CV risk. Dyslipidemia and elevated levels of atherogenic lipoproteins are

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markers for cardiovascular risk factors and key contributors to endothelial dysfunction, inhibiting its anti-thrombotic and pro-fibrinolytic functions, thereby impairing endothelial function (32). AIP is recognized as a valuable marker for assessing the risk of atherosclerosis and coronary heart disease. Given the strong association between dyslipidemia and T2DM, these indices serve as essential tools for evaluating cardiovascular risk in diabetic patients (33).

Moreover, the receiver operating characteristic (ROC) analysis (Table 4) supports the diagnostic potential of MGO, sRAGE, and MDA in distinguishing between diabetic patients with and without cardiovascular risk. The ROC analysis curve shows MGO level near perfect diagnostic performance, which is indicated by sensitivity and specificity. Additionally, sRAGEs and MDA demonstrated a good sensitivity and specificity, which is considered a good finding supporting their role as biomarkers of oxidative stress and inflammation in diabetic cardiovascular disease. Overall, MGO, MDA, and sRAGE may serve as a valuable indicator of cardiovascular risk in T2DM patients.

Conclusion

This study shows that T2DM patients with cardiovascular risk have higher levels of Methylglyoxal (MGO), Malondialdehyde (MDA), and sRAGE, indicating increased oxidative stress linked to both diabetes and cardiovascular complications. The elevated MGO and MDA reflect enhanced lipid peroxidation and glycation, while increased sRAGE may represent a protective response as a decoy receptor. These findings highlight the significant role of cardiovascular risk factors in amplifying oxidative stress in T2DM patients and emphasize the importance of monitoring these biomarkers to guide strategies for reducing oxidative stress and preventing complications. It is recommended to increase the sample size in future studies to enhance the accuracy and statistical power of the findings. Additionally, conducting a case-control study is advised to elucidate the relationship between cardiovascular risk factors and biochemical markers in patients with type 2 diabetes mellitus. Furthermore, evaluating the impact of various medications on these biomarkers would provide valuable insights into their potential role in reducing cardiovascular complications.

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Ethical clearance: Official approval has been obtained to use data, and data were analyzed without the names to protect privacy. This study was conducted according to the approval of the College of Medicine/ University of AL-Nahrain and under the ethical guidelines of the Declaration of the ethical committee of the College (No.20230901).

Conflict of interest: None.

Use of Artificial Intelligence (AI): The authors state they did not use any generative AI tools for creating or editing the manuscript's language.

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تقييم ميثيل جليوكسال، sRAGEs، ومالوند ديالديهايد في داء السكري من النوع ٢ مع وبدون عوامل خطر القلب والأوعية الدموية

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الملخص

الخلفية: داء السكري من النوع ٢ هو اضطراب استقلابي مزمن يزيد من خطر الإصابة بأمراض القلب والأوعية الدموية. يُعد الإجهاد التأكسدي حلقة وصل فيزيولوجية مرضية رئيسية بين **T2DM** ومضاعفات القلب والأوعية الدموية. يسهم ارتفاع السكر في الدم في داء السكري من النوع ٢ إلى زيادة الإجهاد التأكسدي من خلال مسارات متعددة ، بما في ذلك تكوين المنتجات النهائية المتقدمة للجليكاسيون وميثيل جليوكسال. تعزز هذه العمليات توليد أنواع الأكسجين التفاعلية ، مما يؤدي إلى بيروكسيد الدهون مع عمل **MDA** كمؤشر حيوي.

الأهداف: تهدف هذه الدراسة إلى التحقيق في مستويات ميثيل جليوكسال ، **MDA،sRAGEs** لدى مرضى السكري من النوع ٢ مع أو بدون عوامل خطر القلب والأوعية الدموية.

المرضى والطرق: أجريت دراسة مقطعية شملت ٨٠ مريضا بمرض السكري من النوع ٢ مع وبدون عوامل خطر القلب والأوعية الدموية تم تشخيصها في مستشفى مدينة الإمامين الكاظمين، بغداد، العراق. تم جمع البيانات السريرية والمخبرية الأساسية لجميع المشاركين. تم قياس ميثيل جليوكسال المصل بواسطة كروماتوغرافيا سوائلة عالية الأداء (HPLC)، وتم قياس المنتجات النهائية للجليكاسيون المتقدمة للمستقبلات القابلة للذوبان باستخدام مجموعة ELISA، وتم تقييم مستويات MDA عن طريق القياس الطيفي. كما تم قياس، نسبة الجلوكوز في الدم الصائم، HbA1c، البروتين التفاعلي C، الملف الدهني.

النتائج: كانت ميثيل جليوكسال، sRAGEs، و MDA أعلى بشكل ملحوظ من مرضى السكري الذين يعانون من عوامل خطر الأمراض القلبية الوعائية، فإن جلوكوز الدم الصائم، HbA1c ، الأنسولين ، HOMA-IR ، ملف الدهون والبروتين التفاعلي C أعلى في مرض السكري مع عوامل خطر الإصابة بأمراض القلب والأوعية الدموية مقارنة بأولئك الذين لا يعانون من أمراض القلب والأوعية الدموية .

الاستنتاج: بناء على نتائج هذا البحث، قد تكون ميثيل جليوكسال وsRAGEs وMDA بمثابة مؤشرات حيوية سريرية محتملة لتحديد مخاطر القلب والأوعية الدموية لدى مرضى T2DM.

الكلمات المفتاحية: ميثيل جليوكسال ، **sRAGEs** ، مخاطر الأمراض القلبية الوعائية.

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