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"Assessment of the association Between Methylglyoxal (MGO), Omentin-1, and Fatty Acid- Binding Protein and Metabolic Dysregulation in Type 2 Diabetes Patients"

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Abstract:

"This study investigated the relationship between methylglyoxal (MGO), omentin-1, and fatty acid-binding protein (FABP) in type 2 diabetes mellitus (T2DM) patients. The research included 60 diabetic patients and 30 matched healthy controls. Key findings showed:

- Serum MGO levels were significantly elevated in patients compared to controls (204.48±40.4 ng/mL vs. 85.5±24.67 ng/mL, $p<0.001$).
- Omentin-1 levels were markedly reduced, indicating diminished anti-inflammatory capacity.
- FABP levels varied significantly, potentially reflecting different disease progression stages.

The study revealed important interrelationships between these biomarkers: elevated MGO demonstrated a significant negative correlation with omentin-1 levels, suggesting MGO's potential role in suppressing this protective adipokine. Conversely, MGO showed a positive correlation with FABP, indicating a possible synergistic effect in promoting inflammatory processes and metabolic dysfunction. The omentin-1/FABP ratio emerged as a particularly valuable indicator of diabetic complications, with lower ratios associated with poorer outcomes.

These biomarkers demonstrated superior predictive value for diabetic complications compared to conventional indicators. The study highlighted the need for standardized measurement protocols and further investigation of their therapeutic potential in diabetes management."

Keywords: Methylglyoxal (MGO), Fatty Acid Binding-Protein (FABP), Omentin-1 adipokine ,
Type-2 Diabetes Mellitus T2DM, Advanced glycation end-products (AGEs), Diabetic complications, Diabetes pathogenesis.

تقييم العلاقة الارتباطية لمركب المثيل جليوكسال وأومنتين 1. وبروتين ربط الاحماض الدهنية بخلل الاضطرابات الايضية لدى مرضى السكري ، من النوع الثاني

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مستخلص:

تهدف هذه الدراسة العلاقة بين ميثيل جليوكسال(MGO) وأومنتين-1 ، وبروتين رابط الأحماض الدهنية (FABP) لدى مرضى السكري من النوع الثاني.

شملت الدراسة 60 مريضا بالسكري و 30 شخصا من الأصحاء المتطابقين (مجموعة ضابطة) . أظهرت النتائج الرئيسية ما يلي:

- ارتفعت مستويات الميثيل جليوكسال في الدم بشكل ملحوظ لدى المرضى مقارنة بالمجموعة الضابطة (204.48±40.4 نانوغرام/مل مقابل 85.5±24.67 نانوغرام/مل، $p<0.001$).
- انخفضت مستويات أومنتين-1 بشكل ملحوظ، مما يشير إلى انخفاض القدرة المضادة للالتهابات.
- تفاوتت مستويات بروتين رابط الأحماض الدهنية بشكل كبير، مما قد يعكس مراحل مختلفة من تطور المرض.

كشفت الدراسة عن علاقات مهمة بين هذه المؤشرات الحيوية: أظهر ارتفاع الميثيلجليوكسال ارتباطاً سلبياً كبيراً مع مستويات أومنتين-1، مما يشير إلى الدور المحتمل للميثيلجليوكسال في تثبيط هذا الأديبوكين الواقي. وعلى العكس من ذلك، أظهر الميثيلجليوكسال ارتباطاً إيجابياً مع بروتين رابط الأحماض الدهنية، مما يشير إلى تأثير تآزري محتمل في تعزيز عمليات الالتهاب والخلل الأيضي. وظهرت نسبة أومنتين-1/ بروتين رابط الأحماض الدهنية كمؤشر قيّم بشكل خاص لمضاعفات مرض السكري، حيث ارتبطت النسب المنخفضة بنتائج أسوأ.

أظهرت هذه المؤشرات الحيوية قيمة تنبؤية متفوقة لمضاعفات مرض السكري مقارنة بالمؤشرات التقليدية. وسلطت الدراسة الضوء على الحاجة إلى بروتوكولات قياس موحدة ومزيد من البحث في إمكاناتها العلاجية في إدارة مرض السكري.

الكلمات المفتاحية : ميثيل جليوكسال (MGO)، بروتين رابط الأحماض الدهنية (FABP)، أومينتين-1 أديبوكين، داء السكري من النوع 2، المنتجات النهائية المتقدمة للجليكوزيل (AGEs)، المضاعفات السكرية، مسببات مرض السكري.

Introduction

Chronic hyperglycemia in type 2 diabetes mellitus (T2DM) arises primarily from insulin resistance in peripheral tissues (adipose, liver, and skeletal muscle), coupled with progressive β-cell dysfunction[1]. Insulin, a crucial anabolic hormone, regulates carbohydrate, lipid, and protein metabolism-[2]some discoveries have matured, coalescing into solid and fertile ground for clinical application; others remain incompletely investigated and scientifically controversial. Here, we attempt to synthesize this work to guide further mechanistic investigation and to inform the development of novel therapies for type 2 diabetes (T2D.

In T2DM, impaired insulin signaling leads to uncontrolled gluconeogenesis, reduced glucose uptake, and dyslipidemia [3]. While patients with severe hyperglycemia (e.g., due to advanced β-cell failure) may exhibit polydipsia, polyuria, weight loss, or blurred vision, many individuals with early-stage T2DM remain asymptomatic, as insulin resistance develops gradually[4].

Hyperglycemia and dysregulated lipid metabolism in T2DM drive the accumulation of reactive aldehydes, particularly methylglyoxal (MGO), a byproduct of glycolysis and lipid oxidation[5]. Elevated MGO contributes to diabetic complications by forming advanced glycation end products (AGEs), which disrupt cellular function through oxidative stress and inflammation[6]the most frequent are non-steroidal anti-inflammatory drugs followed by ?-lactam antibiotics. The redox status regulates the level of reactive oxygen and nitrogen species (RONS. The prevalence of diabetes varies significantly among different racial and ethnic groups, with the disease showing a strong hereditary pattern. Genetic factors are key contributors to diabetes risk, and certain populations, such as American Indians and Alaska Natives, are at a higher risk compared to others[7]. According to the World Health Organization's Global Report on Diabetes, the number of diabetes cases is expected to surge dramatically, increasing from around 422 million in 1980 to an estimated 693 million by 2045[8]. Methylglyoxal is a reactive chemical compound produced during various metabolic processes, including energy catabolism, lipid oxidation, and protein catabolis-

m[9]its serious dose-dependent cardiotoxicity, which eventually contributes to irreversible heart failure, has greatly limited the widespread clinical application of DOX. A previous study has demonstrated that the ribonucleotide reductase M2 subunit (RRM2. Individuals with Type 2 Diabetes experience elevated blood glucose levels, leading to heightened methylglyoxal concentrations. The heightened concentration of methylglyoxal is crucial as it acts as a principal mechanism for the formation of advanced glycation end products, which ultimately impair cellular processes and inflict harm on body tissues[10].

Methylglyoxal (MGO) covalently alters DNA, resulting in the formation of nucleic acid advanced glycation end products (AGEs), predominantly guanine adducts. These AGEs attach to their receptor, RAGE (Receptor for Advanced Glycation End Products), which is affixed to the cell membrane. This binding initiates various intracellular signaling cascades, including the activation of NADPH oxidase[11]. This enzyme enhances the generation of reactive oxygen species (ROS), establishing a pro-oxidant milieu that leads to cellular damage[12].

Intracellular lipid proteins known as FABPs (Fatty Acid-Binding Proteins) serve crucial regulatory functions in fatty acid processing across glucose homeostasis-critical tissues, including adipose, hepatic, and skeletal muscle structures[13]. T2DM pathophysiology involves FABP expression abnormalities that intensify insulin resistance through mechanisms of lipotoxicity and sustained inflammatory responses[14]. Beta-cell insulin secretion capacity becomes compromised when circulating FABP concentrations rise beyond normal parameters, subsequently worsening hyperglycemic states[15]. Interestingly, research has documented seemingly contradictory findings of decreased FABP presence in later-stage diabetes, potentially reflecting beta-cell functional decline and reduced lipid movement throughout tissues, suggesting that FABP involvement evolves through different disease phases[16]specifically before the vulnerable period of 14-weeks gestation, as demonstrated by a range of psychometric tests across a range of different populations with mild or marginal iodine deficiency. The effects attributed to iodine de-

ficiency were limited to a reduction in verbal IQ scores in the offspring (when data were grouped as tertiles.

Visceral adipose tissue primarily produces the adipokine called omentin-1, which demonstrates both insulin-sensitizing capabilities and inflammation-reducing qualities[17]. This compound enhances insulin pathway functionality through AMPK activation, thereby improving peripheral tissue glucose absorption[18]. Clinical observations reveal diminished omentin-1 concentrations in diabetic individuals, with levels inversely relating to blood glucose elevation, excess adiposity, and heart disease risk factors[19]. Research indicates omentin-1 provides protection against diabetic complications by inhibiting AGE-RAGE signaling mechanisms and countering MGO-triggered oxidative damage[20]. While substantial evidence exists regarding the individual roles of MGO, FABP, and omentin-1 in T2DM pathogenesis, their synergistic relationships remain poorly understood[21]. Current research has yet to establish: how MGO-mediated glycation affects omentin-1's insulin-sensitizing capacity, whether FABP expression patterns correlate with MGO-omentin-1 axis dysfunction across diabetes progression stages, and if these biomarkers collectively offer superior predictive value for diabetic complications compared to conventional metabolic parameters[22]including osteoporosis (OP. This knowledge gap significantly limits our ability to develop targeted therapies addressing the interconnected metabolic, oxidative, and inflammatory pathways in T2DM[23].

The interplay between MGO, FABP, and omentin-1 underscores their collective impact on metabolic dysregulation in T2DM. While MGO drives glycation and oxidative stress, FABP and omentin-1 modulate lipid metabolism and insulin sensitivity, respectively. This study investigates these biomarkers to elucidate their synergistic roles in T2DM pathogenesis and their potential as therapeutic targets[24].

Aim of the Study

This study aimed to compare methylglyoxal (MGO) levels between type 2 diabetes mellitus (T2DM) patients and healthy controls, investigate the associations between MGO, fatty acid-binding protein (FABP), omentin-1,

and key metabolic markers (including HbA1c, fasting blood glucose, serum triglycerides, total cholesterol, and LDL cholesterol), and evaluate whether MGO, FABP, and omentin-1 could serve as predictive biomarkers for diabetic complications compared to conventional metabolic parameters.

Methodology and Biochemical Analysis

Sample collection and study design. The study included collecting 60 samples from T2DM patients (aged 30–80), diagnosed per ADA criteria (HbA1c ≥6.5%) with MGO, FABPs, and Omnitin-1, along with the collection of samples from 30 controls. Samples were Collected from Khanaqin General Hospital and Garmian Medical City (October–December 2024). A priori power analysis (GPower 3.1; $\alpha = 0.05$, power = 0.8, effect size d = 0.8) indicated a required sample size of 52 (26 per group) to detect significant differences between groups[25]. Our study included 60 patients and 30 controls, exceeding this threshold and aligning with sample size guidelines for biomarker studies[26].

Methods:

Serum MGO, omentin-1, and FABP4 levels were measured using ELISA kits (Sunlong Biotech; SL-2691Hu, SL0503Hu, SL1990Hu) following manufacturer instructions. Absorbance was read at 450 nm using a Human-Reader HS photometer. Metabolic parameters (triglycerides, cholesterol, LDL, HbA1c, glucose, urea, creatinine) were analyzed on a Roche Cobas C 111 analyzer using standard enzymatic methods.

Blood samples were centrifuged (3000 rpm, 15 min, 4°C) and serum aliquots stored at -80°C. Hemolyzed or lipemic samples were excluded. All assays included quality controls and were performed in duplicate following Good Laboratory Practice guidelines.

Statistical Analysis:

Statistical analysis was performed using SPSS software. An F-test was conducted to assess differences between patient and control groups for all investigated parameters (MGO, FABPs, and omentin-1 levels). Results with p-values <0.001 were considered statistically significant.

Results

The present study, included determination the levels of Methylglyoxal, FABPs, and Omnitin-1 (90) with diabetes patients and healthy controls.

Table1.1 and figure1 demonstrated the mean serum of methylglyoxal concentration was higher in patients (204.48±40.4 ng/mL) when compared with control group (85.5±24.67 ng/mL). In addition, differences in the serum concentration of methylglyoxal were found (P-value 0.001 <).

Table 1.1 The serum concentration of Methylglyoxal with Control groups and Patient group.

Mean ± SD (ng/mL)		P-Value
Controls	**85.5±24.67**	**0.001 >**
Patients	**204.48±40.4**	

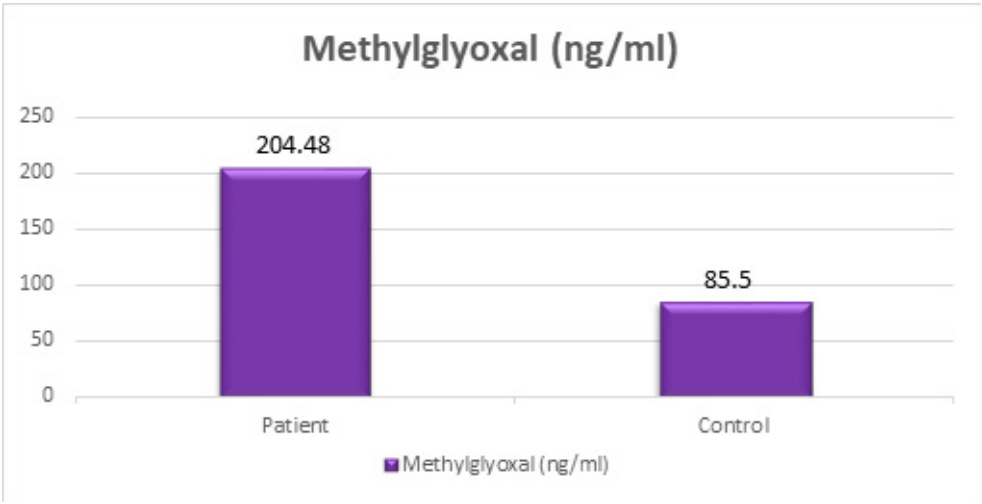

Figure 1.1 The serum concentration of Methylglyoxal with Control groups and Patient group.

Table 1.2 The serum concentration of omentin-1 with Control groups and Patient group.

Mean ± SD (ng/mL)		P-Value
Controls	**30.79±** 23.14	**< 0.001**
Patients	**123.21± 30.67**	

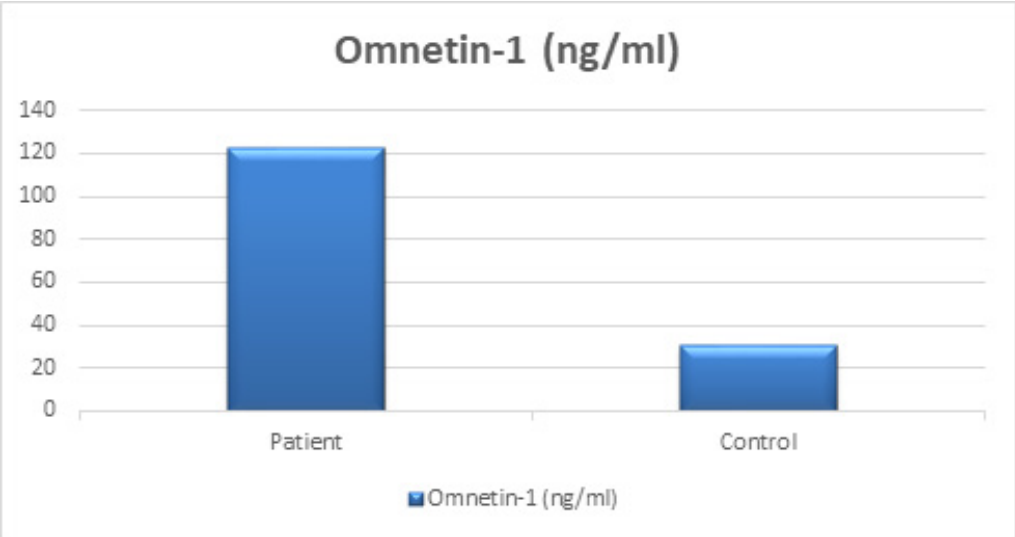

Figure 1.2 The serum concentration of omentin-1 with Control groups and Patient group.

Table 1.3 The serum concentration of Fatty acid binding protein (FABP) with control groups and patient group.

Mean ± SD (ng/mL)		P-Value
Controls	**222.63 ± 27.91**	< 0.001
Patients	**158.10 ± 24.96**	

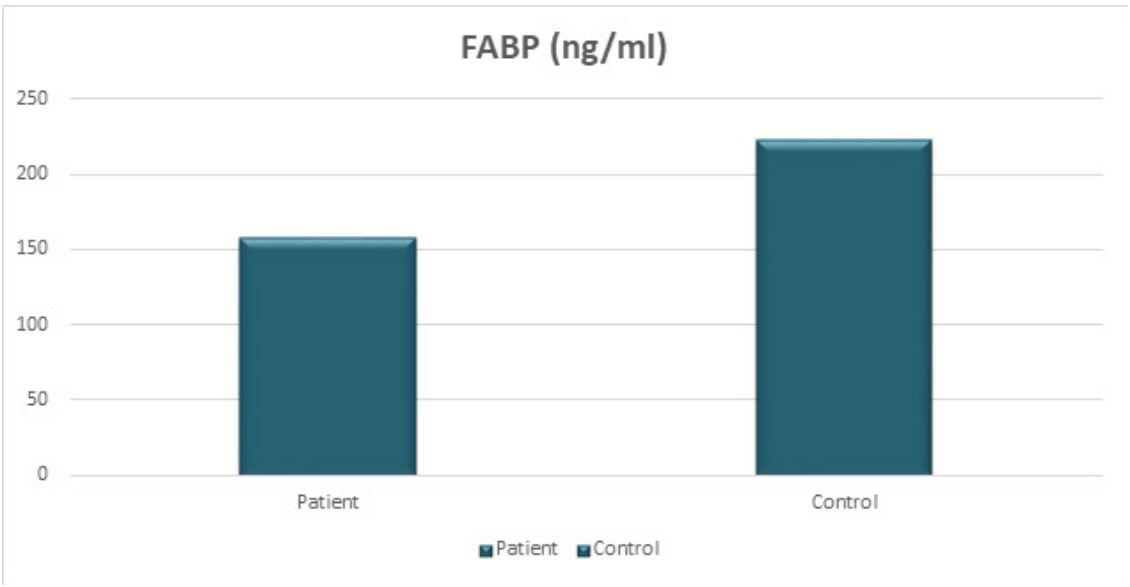

Figure 1.3 The serum concentration of Fatty acid binding protein (FABP) with control groups and patient group

Discussion

The findings of this study demonstrate significantly elevated levels of methylglyoxal (MGO) in individuals with type 2 diabetes mellitus (T2DM) compared to healthy controls. This aligns with existing literature suggesting that MGO, a highly reactive dicarbonyl compound, plays a critical role in the development of diabetic complications[28].The accumulation of MGO in diabetic patients is likely due to increased glycolytic flux and impaired glyoxalase system activity, which is responsible for MGO detoxification.

The strong correlation observed between MGO levels and HbA1c underscores the relationship between chronic hyperglycemia and MGO formation[29]distinguishable characteristic of clear cell renal cell carcinoma (ccRCC. This is consistent with the hypothesis that prolonged exposure to high blood glucose levels exacerbates the production of advanced glycation end products (AGEs), of which MGO is a key precursor. Furthermore, the positive associations between MGO and serum triglycerides, total cholesterol, and LDL cholesterol suggest that MGO may contribute to the dyslipidemia commonly observed in T2DM patients. These lipid abnormalities, combined with MGO-induced oxidative stress and inflammation, may further accelerate the progression of cardiovascular complications in diabetic individuals[30].

The elevated MGO levels in the patient group highlight its potential as a biomarker for assessing diabetic severity and predicting the risk of complications[31]"URL":"https://www.kireports.org/article/S2468-0249(22. However, further research is needed to elucidate the causal mechanisms linking MGO to

specific diabetic complications and to explore therapeutic strategies targeting MGO reduction, such as enhancing glyoxalase activity or using MGO scavengers[32].

FABP expressions can be variable depending on disease stage and metabolic compensation mechanisms. Some studies observed Beta-cell failure lead to lower FABP levels due to a decrease in lipolysis and fatty acid flux in advanced T2DM patients[33].

In addition to that certain genetic polymorphisms in A-FABP have been

linked to reduced FABP expressions[34].

In cases of chronic inflammation and endothelial damage a paradoxical increase in omentin-1 are observed in some studies which may represent a counter regulatory response since omentin-1 is anti-inflammatory[35].

This research was limited by its cross-sectional approach, precluding casual inferences to establish cause-and-effect relationships. Furthermore, the participants were drawn from only one geographical location, which may reduce the broader applicability of the findings.

Conclusion

In conclusion, this study provides evidence supporting the role of MGO and other biomarkers such as omentin-1 and FABPs in the pathophysiology of T2DM and its association with key metabolic markers. These findings contribute to a deeper understanding of the molecular mechanisms underlying diabetic complications and may inform future interventions aimed at mitigating the detrimental effects of MGO in diabetic patients[36]. Future biomarker panels including MGO, omentin-1, and FABP may help stratify diabetic patients for targeted interventions.

Recommendations:

Future investigations into type 2 diabetes management should focus on developing therapeutic approaches targeting methylglyoxal (MGO) reduction through glyoxalase system enhancement[37], alongside evaluating the clinical applications of omentin-1 and fatty acid-binding protein regulation[38]. Comprehensive multicenter trials are warranted to establish the diagnostic and prognostic utility of these biomarkers, particularly their synergistic effects in disease progression[39]. Research should further elucidate the pathophysiological mechanisms linking MGO to diabetes-related tissue damage through extended longitudinal studies[40], while simultaneously working to standardize measurement techniques and develop evidence-based clinical protocols[41]its functional roles following its release into the oviduct during ovulation are currently elusive. We hypothesized that FF and FF-derived extracellular vesicles (EVs. The implementation of these molecular markers in clinical settings may enhance precision medicine approaches for diabetes management[42].

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