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The role of diabetic drugs on levels of Glucose Regulated Protein- 78 in Type 2 Diabetes Mellitus

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Abstract

The combined effects of glycemic dysregulation, dyslipidemia, and cellular stress responses lead to increased expression of glucose-regulated protein-78 (GRP-78), a key mediator in type 2 diabetes mellitus (T2DM) development. Due to its involvement in glucose and lipid metabolism, GRP-78 is considered a potential therapeutic biomarker. This study aimed to assess the impact of various antidiabetic medications on GRP-78 levels in individuals with T2DM. A cross-sectional study comprised 134 participants: 96 T2DM patients who were divided into patients under treatment with glucovance 500 (n=38), or insulin injection (n=42), and newly diagnosed diabetic patients (n=16). A control group of 38 healthy subjects were enrolled. Serum levels GRP-78 were measured using the ELISA method and lipid profiles were measured by standard biochemical tests. HbA1c levels in blood were determined using the Roche Cobas c111 analyzer. Statistical analyses were performed using ANOVA and Pearson correlation. In patient groups, GRP-78 levels were significantly higher than healthy controls ($p<0.05$). Patients with insulin treatment had the highest GRP-78, followed by patients with glucovance 500 and newly diagnosed. Both patient groups under treatment demonstrated a strong positive link between HbA1c and GRP-78, whereas newly diagnosed groups showed a medium correlation. The insulin group had reduced triglycerides and increased HDL levels. Higher GRP-78 levels in T2DM patients support glycemic control and endoplasmic reticulum stress. GRP-78 may be a glycemic biomarker due to its significant connection with HbA1c. Different lipid profiles show how therapy affects metabolic parameters. The research focused on the GRP-78's role in T2DM management and treatment.

Keywords: Glucose Regulated Protein-78, Glucovance 500, Insulin, Lipid Profile, Type 2 Diabetes Mellitus

دور أدوية السكري على مستويات البروتين المنظم للجلوكوز 78 في مرض السكري من النوع الثاني

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التأثيرات المشتركة لخلل تنظيم سكر الدم، والدهون في الدم، واستجابات الإجهاد الخلوي تؤدي إلى زيادة تعبير بروتين منظم الجلوكوز−78 (GRP−78)، وهو وسيط رئيسي في تطور مرض السكري من النوع الثاني (T2DM). نظرًا لاشتراكه في أيض الجلوكوز والدهون، يُعتبر GRP−78 علامة حيوية علاجية محتملة. هدفت هذه الدراسة إلى تقييم تأثير الأدوية المضادة للسكري المختلفة على مستويات GRP−78 لدى الأفراد المصابين بالنوع الثاني من داء السكري. شملت الدراسة المقطعية 134 مشاركًا: 96 مريضًا بداء السكري من النوع الثاني تم تقسيمهم إلى مرضى يتلقون علاجًا باستخدام جلوكوفانس 500 (عددهم=38)، أو حقن الأنسولين (عددهم=42)، ومرضى السكري الذين تم تشخيصهم حديثًا (عددهم=16). تم تسجيل 38 شخصًا أصحاء كمجموعة ضابطة. تم قياس مستوى GRP−78 في المصل باستخدام طريقة ELISA وتم قياس ملف الدهون بواسطة الاختبارات الكيميائية الحيوية القياسية. تم اختبار مستوى HbA1c في الدم باستخدام جهاز Rosh Cobas c111. تم إجراء التحليلات الإحصائية باستخدام ANOVA و Pearson correlation. في مجموعات المرضى، كانت مستويات GRP−78 أعلى بشكل ملحوظ من مستويات الأصحاء ($p<0.05$). كان لدى المرضى الذين يتلقون علاج الأنسولين مستويات أعلى من GRP−78، تلاهم المرضى الذين يتناولون جلوكوفانس 500 والمرضى الذين تم تشخيصهم حديثًا. أظهر المرضى الخاضعين للعلاج من كلا المجموعتين ارتباطًا إيجابيًا قويًا بين HbA1c وGRP−78، في حين أظهرت المجموعات التي تم تشخيصها حديثًا ارتباطًا متوسطًا. مجموعة الأنسولين كانت لديها مستويات منخفضة من الدهون الثلاثية ومستويات مرتفعة من HDL. المستويات المرتفعة من GRP−78 في مرضى السكري من النوع الثاني تدعم التحكم في نسبة السكر في الدم وإجهاد الشبكة الإندوبلازمية. قد يكون GRP−78 علامة حيوية جلايسيمية بسبب ارتباطه الكبير مع HbA1c. تُظهر ملفات الدهون المختلفة كيف تؤثر العلاجات على المعايير الأيضية. البحث ركز على دور GRP−78 في إدارة وعلاج مرض السكري من النوع الثاني.

1. Introduction

Diabetes mellitus (T2DM) causes a decrease in functional β-cell mass, which adjusts for insulin resistance and maintains normoglycemia. T2DM is characterized by a progressive decline in β-cell insulin production resulting from insulin resistance [1, 2]. A persistent hyperglycemic disorder, Unhealthy diets, physical inactivity, and obesity—among other lifestyle choices—have greatly contributed to the worldwide increase in diabetes prevalence [3]. Many countries, including Iraq, have recently documented many cases of diabetes [4]. Iraq has 13.9% diabetic adults, according to the International Diabetes Federation (IDF). In 2021, 2.5 million Iraqis have diabetes, and this figure rises annually. These numbers demonstrate the need for public health actions to combat Iraq's diabetes pandemic [5, 6].
T2DM leads to long-term complications that significantly impact quality of life and healthcare systems worldwide [1, 3].

The use of certain nutritional supplements and advised diabetes treatments is necessary to lower these risks and complications [7]. Key components of the regulation of T2DM include new medications aiming at β-cells, the incretin axis, hepatic glucose metabolism, and insulin sensitivity via direct and indirect channels [8]. Supported by almost all recommendations globally, metformin, the gold standard glucose-lowering medication causes weight reduction by increasing hunger and reducing calorie intake [9]. While effective in lowering glucose levels, insulin therapy is associated with limitations such as delayed absorption, nocturnal hypoglycemia, and variable absorption rates, resulting in less-than-optimal glucose control [10].

A growing body of evidence indicates that cellular stress responses, particularly endoplasmic reticulum (ER) stress, play a crucial role in the pathogenesis of T2DM. One of the key mediators of ER stress is Glucose-Regulated Protein 78 (GRP-78), also known as

Binding Immunoglobulin Protein a chaperone protein of the heat shock protein 70 family. GRP-78 maintains ER homeostasis by assisting in protein folding and regulating the unfolded protein response (UPR). Under conditions of metabolic stress, such as prolonged hyperglycemia and insulin resistance, GRP-78 becomes upregulated to counteract the accumulation of misfolded proteins in the ER [11].

In T2DM, elevated GRP-78 expression has been linked to impaired insulin signaling, particularly in insulin-sensitive tissues such as skeletal muscle. Persistent ER stress can contribute to β-cell dysfunction and exacerbate insulin resistance, thereby playing a significant role in disease progression [11]. When ER stress is prolonged, the unfolded protein response (UPR) is activated, contributing to the pathogenesis of T2DM by disrupting insulin secretion and impairing β-cell function. MicroRNAs (miRNAs) regulate the expression of glucose-regulated protein 78 (GRP-78), a key chaperone involved in the endoplasmic reticulum stress response. Aberrant miRNA activity can suppress GRP-78 expression, impairing ER stress resolution and promoting insulin resistance and β-cell dysfunction, thereby contributing to the pathogenesis of T2DM, including those related to insulin resistance and insufficient secretion. Investigating GRP-78's function and its correlation with miRNAs might point to potential T2DM treatment targets [11]. This study aimed to evaluate the effect of different antidiabetic medications on the levels of Glucose-Regulated Protein-78 (GRP-78) in individuals with T2DM.

Methods

Subjects

In this cross-sectional study, the total sample number 134 was collected from healthy individuals and participants at AL-Kindy Educational Hospital, Baghdad, Iraq, between February 2024 and June 2024. They were divided into four groups: 38 healthy controls (G1; age range 28- 78 years), 16 newly diagnosed patients with no medication (G2; 39-65years), 38 patients who use Glucovance 500 treatment (G3; 35±69 years), and 42 patients on insulin treatment (G4; 27-75years). The total age range of the participants was 27 and 78 years.
The duration of T2DM in the patient's groups was less than 6 months for the newly diagnosed group, between 1–5 years for the Glucovance group, and over 5 years for those receiving insulin treatment. All participants had a diagnosis of T2DM in the age range specified and were free from other systemic diseases such as cardiovascular diseases or other diabetes complications. Chronic diseases that could interfere with glucose or lipid metabolism, iron deficiency anemia were also excluded.

Sample Size

The sample size was calculated using the online tool EPITOOLS (https://epitools.ausvet.com.au/casecontrols) at an alpha level of 0.05 for a 95% confidence interval. Based on expected differences in GRP-78 levels between treated and untreated T2DM patients and healthy controls, the minimum required total sample size was estimated to be 120 participants, assuming a 2:1 case-to-control ratio. Accordingly, the study enrolled 96 patients with T2DM—divided into three subgroups (Glucovance 500, Insulin, and Newly Diagnosed)—and 38 healthy controls, resulting in a total of 134 participants. This sample size was considered adequate to detect statistically significant differences across groups and ensure sufficient statistical power.

Ethical statement

The study was approved by the Ethics Committee of the University of Baghdad, College of Science, Department of Chemistry, project No. (CSEC/0124/0006) in 24/11/2023. All

participants were informed about the study objectives and procedures, and written informed consent was obtained from each participant before enrollment, following the Declaration of Helsinki guidelines.

Sample Collection:

Venous blood samples (5 mL) were obtained from each participant in the morning between 8:00 AM and 10:00 AM after an overnight fast of at least 10 hours, using sterile syringes. The samples were processed as follows: 3mL was used for serum analysis to quantify GRP-78 by sandwich ELISA method using a kit from Elabscience Biotechnology Inc. (USA). The assay is based on utilizing a biotinylated detection antibody specific to GRP-78 and Avidin-HRP conjugate for amplification. The assay was performed under the manufacturer's protocol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and total cholesterol were assessed using the BIOLABO kit and spectrophotometric methods, which facilitated the calculation of very low-density lipoprotein cholesterol (VLDL-C), and low-density lipoprotein cholesterol (LDL-C) levels, while 2 mL was collected in EDTA tubes for HbA1c analysis using the Roche Cobas c111 analyzer.

Determination of VLDL and LDL was by the following equations:[12]

VLDL = TG/5

LDL= cholesterol –(HDL+ VLDL)

Calculation of Atherogenic Index and Ratios [13]

The atherogenic index of plasma (AIP) was calculated using the following equation: $AIP=Log\ (TGs\ (mg/dL))/(HDL\ (mg/dL))$

The atherogenic ratio 1 (AR1) and atherogenic ratio 2 (AR2) were calculated according to the following equations:

$$\boldsymbol{AR1=(Chol\ (mg/dL))/(HDL\ (mg/dL))}\quad \boldsymbol{AR2=(LDL\ (mg/dL))/(HDL\ (mg/dL))}$$

Statistical Analysis

Data were analyzed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as means ± standard deviations (SD). Group comparisons were performed using one-way analysis of variance (ANOVA), and when significant, LSD (Least Significant Difference) post hoc tests were used to evaluate pairwise differences among the groups. Pearson correlation analysis was conducted to assess the relationship between HbA1c and GRP-78 levels. To evaluate the diagnostic performance of GRP-78 in distinguishing between diabetic subgroups and healthy controls, receiver operating characteristic (ROC) curve analysis was carried out. Area under the curve (AUC), sensitivity, specificity, and optimal cutoff values were calculated. A p-value of less than 0.05 was considered statistically significant throughout the analysis.

Results

Table 1 summarizes the demographic characteristics (age and BMI), lipid profile parameters, and atherogenic indices across all study groups. There were no statistically significant differences in age among the groups, as indicated by the overall p-values exceeding 0.05. Similarly, BMI levels did not differ significantly between groups based on ANOVA analysis.

Table 1: Demographic and clinical characteristics among the studied groups.

Parameters	G1 N= 38	G2 N = 16	G3 N = 38	G4 N = 42	P- Value
Age (years)	50.74 ±12.73	50.18 ± 7.59 c,e,f	51.95 ± 7.82 a	53.48±11.53 b,d	0.124[a] 0.161[b] 0.174 [c] 0.285 [d] 0.377 [e] 0.295 [f]
BMI (kg/m^2)	29.158 ± 4.13	28.377 ± 2.362 c,e,f	31.085 ± 2.944a	28.177 ± 3.479 b,d	0.072a 0.078b 0.182c 0.076d 0.097e 0.182f
HbA1c	4.91 ± 0.26	8.31 ± 3.04 c,e,f	7.45 ± 1.65a	8.57 ± 2.02 b,d	**0.033a** **0.027b** **0.019c** 0.094d 0.193e 0.639f
Cholesterol (mg/dL)	181.14 ± 36.38	172.42 ±34.65 c,e,f	166.55 ± 37.73 a	176.49 ± 39.85 b,d	**0.008a** **0.027b** **0.038c** **0.042d** **0.041e** 0.635f
Triglycerides (mg/dL)	185.45 ± 96.18	195.63 ± 122.04 c,e,f	232.458 ± 114.23 a	138.67 ± 55.66 b,d	**0.028a** **0.018b** **0.024c** **0.024d** **0.017e** **0.034f**
HDL (mg/dL)	28.36 ± 9.69	28.71 ± 7.80 c,e,f	28.20 ± 8.90 a	30.44 ± 10.92 b,d	0.173a **0.028b** 0.087c 0.028d 0.733e **0.026f**
LDL (mg/dL)	122.11 ± 37.69	125.34 ± 36.71c,e,f	129.16 ± 34.66 a	116.46 ± 27.45 b,d	**0.024a** **0.037b** **0.026c** **0.041d** 0.837e **0.035f**
VLDL (mg/dL)	37.09 ± 19.24	39.13 ± 24.41 c,e,f	47.23 ± 22.49 a	27.55 ± 11.28 b,d	**0.032a** **0.013b** 0.087c **0.028d** **0.038e** **0.024f**
AR1	6.96 ± 2.47	6.19 ± 1.77 c,e,f	6.06 ± 1.67 a	5.92 ± 1.96 b,d	0.139a 0.095b 0.746c 0.178d 0.237e 0.206f

AR2	4.66 ± 1.66	4.44 ± 1.29 c,e,f	4.55 ± 1.31 a	4.31 ± 1.98 b,d	0.182a 0.305b 0.176c 0.088d 0.094e 0.184f
AIP	0.09 ± 0.03	0.08 ± 0.02 c,e,f	0.09 ± 0.04 a	0.08 ± 0.07 b,d	0.172a 0.294b 0.134c 0.098d 0.134e 0.157f

The results are presented as (mean ± SD) - p-value < 0.05 is considered as significant between a (G1 and G3), b (G1 and G4), c (G1 and G2), d (G3 and G4), e (G3 and G2), f (G4 and G2). AR1= Atherogenic ratio-1, AR2= Atherogenic ratio-2, AIP= Atherogenic index of plasma.

As shown in Table 1, HbA1c levels were significantly elevated in all patient groups (Glucovance 500, insulin-treated, and newly diagnosed) relative to controls, indicating worse glycemic control. However, no significant differences were found among the treatment groups themselves, indicating comparable glycemic states across these subgroups.

Significant differences in lipid profiles were also observed across the study groups. Cholesterol levels were significantly lower in the Glucovance 500, insulin, and newly diagnosed groups compared to the control group, with no notable difference between the insulin and newly diagnosed groups. Triglyceride levels were highest in the glucovance 500 group and lowest in the insulin group, indicating differing impacts of therapeutic interventions. In the newly diagnosed group, triglyceride levels were also significantly elevated compared to controls. HDL levels were significantly higher in the insulin group compared to all other groups, suggesting a positive treatment effect on HDL. LDL levels were highest in the glucovance 500 group and lowest in the insulin group, while VLDL levels followed a similar pattern, being elevated in the glucovance 500 group and lower in the insulin group. These findings reflect the varying influences of treatments on lipid metabolism.

Additionally, AR1, AR2, and AIP levels did not show any significant differences among the groups, suggesting that these indices were not markedly affected by the treatment modalities under investigation.

Figure 1 shows the comparison of GRP-78 levels among the studied groups. A significant difference ($p<0.01$) by using the ANOVA test highlights elevated GRP-78 levels in treated groups compared to control.

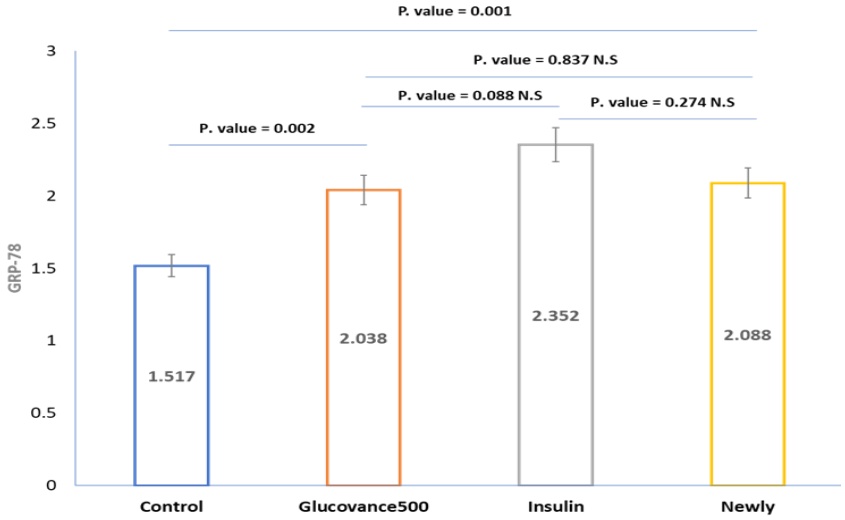

Figure 1: The comparison of Glucose GRP-78 level among the studied groups.

The correlation analysis findings between HbA1c and GRP-78 in the examined groups, as shown in Figure 2, demonstrate strong positive correlations. The control group has a medium positive connection (r = 0.517, p = 0.045), indicating that elevated HbA1c levels correlate with heightened GRP-78 levels. The glucovance 500 group exhibits a robust positive association (r = 0.782, p = 0.028), while the insulin group reveals a very high connection (r = 0.839, p = 0.028), indicating a significant link between HbA1c and GRP-78. The newly diagnosed group has a medium positive connection (r = 0.727, p = 0.029). These findings consistently highlight that as HbA1c levels increase; GRP-78 levels also tend to rise, underscoring the potential link between glycemic control and GRP-78 among different treatment modalities.

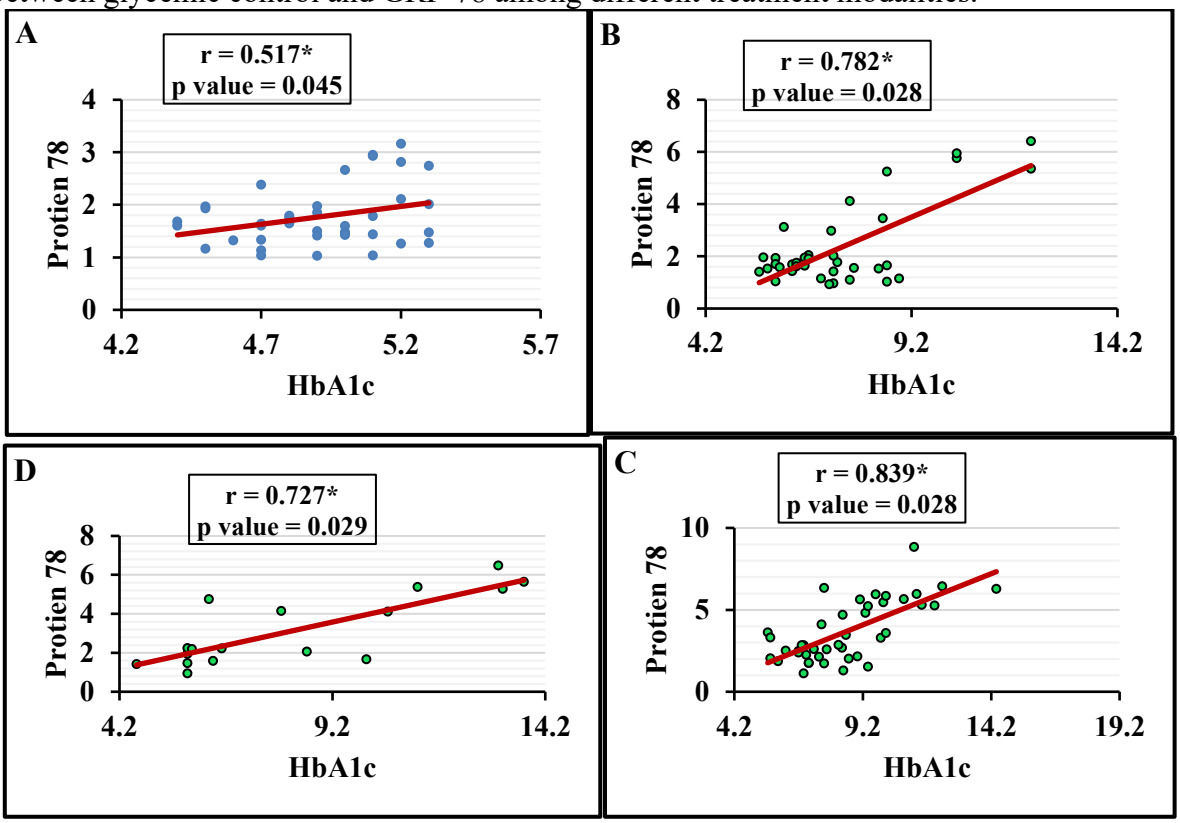

Figure 2: Pearson's Correlation analysis between HbA1c and GRP-78 in (A) control, (B) Glucovance 500, (C) Insulin, and (D) Newly diagnosed groups**.**

Figure 3 and Table 2 summarize the diagnostic performance of GRP-78 levels in distinguishing the treatment groups from control (glucovance 500, insulin, and newly diagnosed). The AUC values show fair to strong discrimination: 0.724 for glucovance 500 (p=0.001), 0.793 for insulin (p<0.001), and 0.717 for newly diagnosed (p=0.012). Sensitivity and specificity are highest for the Insulin group (69.0% and 73.7%), suggesting GRP-78 as an effective diagnostic marker, with the strongest performance in the Insulin group. These findings support the potential clinical utility of GRP-78 in evaluating treatment responses.

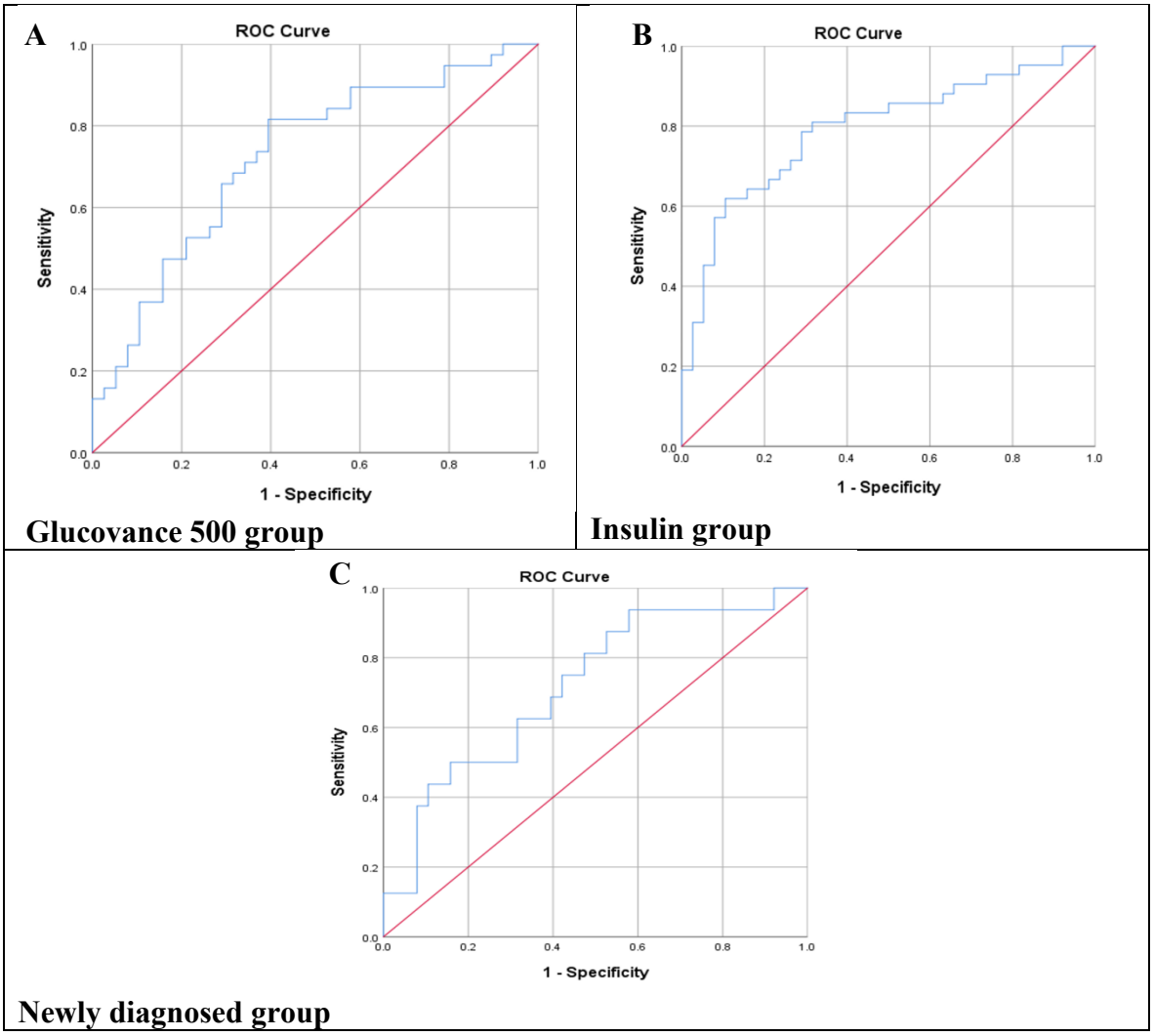

Figure 3: Receiver Operating Characteristic (ROC) curve of GRP-78 level between (A) Glucovance 500 treated group., (B) Insulin treated group, and (C) newly diagnosed group.

Table 2: Diagnostic performance metrics of GRP-78 levels: Area Under the Curve (AUC), Sensitivity, and Specificity in all study groups.

Groups	AUC	SE	p-value	Cut-off	Sensitivity	Specificity
Glucovance 500 treated group	0.724	0.058	0.001*	1.684	65.8%	71.1%
Insulin treated group	0.793	0.051	<0.001*	1.77	69.0%	73.7%
Newly diagnosed group	0.717	0.076	0.012*	1.64	62.5%	68.4%

* Significant (p value < 0.05)

Discussion

The age-matched among the studied groups is necessary for minimizing age-related confounding factors in the study. Age is a critical factor in diabetes research, influencing disease progression and treatment outcomes. Studies have shown that the incidence of T2DM increases with age, and age at diagnosis can impact morbidity and mortality rates [11-13].
A study by Cigolle *et al*. (2022) indicates that older adults diagnosed with diabetes at a younger age have a higher risk of complications and mortality [14]. Similarly, Seo *et al*. (2024) in their

study show that people diagnosed with T2DM before the age of 40 are more likely than those without diabetes to have heightened mortality rates and cardiovascular complications [15]. According to Nanayakkara *et al*. (2021), a diagnosis of T2DM at a younger age is associated with an increased risk of death and cardiovascular problems [16].
Al-Saeed *et al.* (2016) found an inverse association between the age of diabetes starting and death rates, suggesting that earlier onset is associated with higher standardized mortality ratios [17]. Age greatly affects physiological systems like insulin sensitivity, β-cell activity, and comorbidities, thereby influencing the course of diabetes development and treatment efficacy. Age-related declines in pancreatic islet activity and insulin production might help elderly individuals have less severe diabetes [18].
Regarding lipid profiles, the study confirms the known effects of antidiabetic therapies. Insulin treatment was associated with improved triglyceride and HDL levels, while Glucovance therapy, likely due to its glyburide component showed elevated triglyceride and VLDL levels. Studies by Després (2003) and Lin *et al.* (2018) confirm this as metformin treatment dramatically lowers total and LDL cholesterol levels, hence improving lipid profiles in individuals with T2DM [19, 20].
Rigato *et al.* (2020) that insulin glargine and standard care groups had similar total cholesterol and LDL cholesterol levels, implying that continuous insulin treatment may slow down cholesterol and LDL levels but improve triglycerides [21].

A sulfonylurea, glyburide boosts insulin production, which may cause weight gain and raised triglyceride levels from more lipogenesis. On the other hand, the other ingredient in glucovance, metformin, is usually linked with either a small or negligible drop in triglyceride levels [22]. In agreement with Haffner, (2004) who concluded that using sulfonylurea is associated with weight gain and potential adverse effects on lipid profile [23].
Insulin plays a role in lipid metabolism, and its administration can influence lipoprotein levels [24]. The present study is in agreement with the previous study by Rask-Madsen *et al*. (2001) which stated that insulin therapy improved lipid profiles, including increases in HDL levels, in patients with T2DM [25]. In contrast, the glucovance 500 group, which combines metformin and glyburide, did not show significant differences in HDL levels compared to the control group. Metformin is generally considered to have a neutral or modestly beneficial effect on HDL, while sulfonylureas like glyburide have minimal impact on HDL levels. A meta-analysis by Zhang *et al*. (2013) in endocrine found that combination therapy with sulfonylureas and metformin did not significantly affect HDL cholesterol levels [26]. Sauriasari *et al*. (2022) found that patients on metformin monotherapy had higher HDL levels compared to those on combination therapy with sulfonylureas, though the differences were not statistically significant [27].
Metformin exerts its lipid-lowering effects primarily through two interrelated mechanisms: by suppressing hepatic glucose production and enhancing insulin sensitivity. These actions collectively lead to reduced hepatic lipogenesis and decreased secretion of very low-density lipoprotein (VLDL). Additionally, metformin may enhance fatty acid oxidation and decrease intestinal absorption of glucose, contributing to improved lipid profiles [28].

In the current study, elevated GRP-78 levels were seen in the glucovance 500, insulin, and newly diagnosed groups compared to the control group. No significant changes occurred in any of the treatment groups. This discovery corroborates the findings of Nourbakhsh *et al.* (2022), who noted a substantial elevation in GRP-78 serum levels in T2DM patients compared to healthy controls, suggesting that endoplasmic reticulum stress may play a role in the aetiology of diabetes [29]. Increased levels of GRP-78 have been associated with metabolic changes, particularly those seen in T2DM [30]. Moreover, metformin, an ingredient in

glucovance 500, has shown the ability to regulate ER stress responses, possibly resulting in elevated GRP-78 expression as a strategy to enhance insulin sensitivity [22]. In a similar vein, insulin treatment may affect cellular stress pathways, therefore influencing GRP-78 levels [31, 32]. Protein folding and the ER unfolded protein response (UPR) rely critically on GRP-78. From a clinical standpoint, GRP-78 could be integrated into routine diabetic assessments to identify patients at higher risk of complications due to unresolved metabolic stress. Serial monitoring of GRP-78 levels may offer insight into treatment effectiveness and help guide adjustments in therapeutic strategies. However, its utility in practice will depend on the establishment of standardized reference ranges and validation in larger prospective cohorts. According to Shiraj Sen *et al.* (2013) and Meshkani *et al.* (2020), find that metformin's stimulation of AMP-activated protein kinase (AMPK) and effects on lowering hepatic glucose production may indirectly alter ER stress pathways, hence generating enhanced GRP-78 expression. By enhancing glycemic management, insulin treatment may also change cellular stress responses, thereby influencing perhaps GRP-78 levels [33, 34, 35]. The current findings suggest that rising GRP-78 levels in T2DM patients might point to their possible use as a biomarker for metabolic dysregulation and ER.

In every group in this study, HbA1c and GRP-78 levels showed a clear significant positive connection. Chronic hyperglycemia causes ER stress, according to research by Nourbakhsh *et al.,* (2022) which suggested that the rise of GRP-78 levels is a compensatory method to preserve cellular homeostasis [29]. The data analysis of the ROC curve shows that GRP-78 has a good sensitivity and specificity to distinguish between all the investigated groups and hence introduce GRP-78 as a promised biomarker for diabetes progression as well as for monitoring the effect of glucovance 500 and insulin treatment on diabetes progression.

Limitations

This study has several limitations. First, its cross-sectional design prevents conclusions about causality or the directionality of observed associations. Longitudinal studies are needed to establish whether GRP-78 levels predict worsening glycemic control or treatment response over time. Second, although the sample size was statistically powered, the newly diagnosed group was relatively small, which may limit subgroup analyses. Additionally, unmeasured confounding factors—such as detailed dietary intake, physical activity, or medication adherence—may have influenced the results despite exclusion criteria to minimize variability.

Conclusion

Elevated GRP-78 levels in patients with T2DM highlight its role as an indicator of ER stress and metabolic dysregulation. The strong correlation between GRP-78 and HbA1c across all diabetic subgroups indicates its potential as a supplementary biomarker for evaluating glycemic control and treatment response. Clinically, GRP-78 could be incorporated alongside established markers such as HbA1c, lipid profile, and fasting glucose to provide a more comprehensive picture of disease status and cellular stress in T2DM patients. Its use may help identify individuals at higher risk of treatment failure or complications and support more personalized therapeutic interventions. Further research is warranted to establish reference ranges, assess its predictive value in longitudinal settings, and explore its integration into routine diabetes care protocols.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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