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The Correlation between Estimated Glucose Disposal Rate (eGDR) and the Severity of Nonalcoholic Fatty Liver Disease (NAFLD) in Type 2 Diabetes

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Abstract

Purpose: To correlate between the degree of insulin sensitivity and degree of nonalcoholic fatty liver disease (NAFLD) in type 2 Diabetes.

Methods: Our study included a total of 211 patients. For each participant, we calculated the Fibrosis-4 Index (FIB-4), an indicator for assessing the presence of advanced liver fibrosis, and the NAFLD score, which assesses the extent of liver fibrosis. These scores were then correlated with the estimated Glucose Disposal Rate (eGDR), a measure used to evaluate insulin sensitivity.

Results: The mean FIB-4 score was 1.22 ± 1.54, and the mean NAFLD score was -0.75 ± 1.46. Moderate to severe fibrosis was present in 2.8% of patients according to the FIB-4 score and in 10.9% according to the NAFLD score. The mean eGDR score was 4.58 ± 2.41. Spearman correlation coefficients demonstrated that eGDR was weakly but significantly correlated with the FIB-4 score ($r = -0.143$, $p = 0.042$). Additionally, eGDR showed a significant correlation with NAFLD scores ($r = -0.344$, $p < 0.001$). The FIB-4 score was also significantly correlated with NAFLD scores ($r = 0.821$, $p < 0.001$). ROC curves demonstrated that eGDR significantly predicted moderate-severe fibrosis indicated by FIB-4 (71.1%; 95% CI: 58.3%-83.8%) or NAFLD scores (73.4%; 95% CI: 63.0%-83.8%). The optimal cut-off point for eGDR to predict moderate-severe fibrosis indicated by FIB-4 was 4.07, achieving a sensitivity of 65.2% and specificity of 73.8%. For predicting moderate-severe fibrosis indicated by NAFLD scores, the optimal eGDR cut-off point was 5.34, with a sensitivity of 83.3% and specificity of 65.5%.

Conclusion: Our study demonstrated a significant correlation between eGDR scores and the severity of NAFLD. Based on our findings, we suggest considering a lower cut-off point for eGDR, specifically between 4.07 to 5.34, to enhance the prediction of NAFLD in the context of insulin resistance.

Keywords: Diabetes; estimated glucose disposal rate (eGDR); insulin sensitivity; Nonalcoholic Fatty Liver Disease (NAFLD); screening

1. INTRODUCTION

Insulin resistance has been implicated in both the pathogenesis and progression of nonalcoholic fatty liver disease (NAFLD) [1, 2]. The global prevalence of NAFLD in type 2 diabetes is around 65% [3]. Recent American Diabetes Association (ADA) practice guidelines recommend systematic screening of all people with type 2 diabetes for NAFLD using the Fibrosis-4 (FIB-4) index [4].

The estimated Glucose Disposal Rate (eGDR) is a relatively new biomarker for measuring insulin sensitivity. Initially developed for type 1 diabetes, it has also been validated in patients with type 2 diabetes using the euglycemic-hyperinsulinemic clamp method [5]. A higher eGDR indicates higher insulin sensitivity. An eGDR level below 8.77 mg/kg/min suggests insulin resistance and metabolic syndrome [5].

The prevalence of type 2 diabetes (T2DM) in Jordan has been steadily increasing. A study published in 2019 found that diabetes prevalence among men aged ≥25 years rose from 14.2% in 1994 to 32.4% in 2017 [6]. Unfortunately, this T2DM epidemic in Jordan is projected to continue growing over the next three decades, driven by an aging population and rising obesity rates [7].

With the rising rates of type 2 diabetes and obesity in Jordan, an increase in the prevalence of NAFLD was anticipated. A 2010 study found that elevated liver enzymes were present in approximately 10.4% of patients with type 2 diabetes [8]. However, a recent (2021) study reported an NAFLD prevalence of 80.4% among patients with diabetes [9].

The aim of our study was to correlate the degree of insulin sensitivity, assessed using the eGDR score, with the severity of NAFLD in type 2 diabetes, utilizing FIB-4 and NAFLD scores [5,10,11].

2. MATERIALS AND METHODS

2.1. Subjects

This single-center study was conducted at the Endocrinology Clinic of Jordan University Hospital (JUH), a tertiary medical center in Amman, Jordan, from December 2023 to June 2024. The study protocol received approval from the Institutional Review Board (IRB) at Jordan University Hospital (JUH) (IRB approval number: 10 2023/30524).

Subjects diagnosed with prediabetes and type 2 diabetes, based on the latest ADA guidelines in 2023 [4], were recruited from patients attending the Endocrinology Clinic at Jordan University Hospital (JUH) during the study period. Inclusion criteria included males or females aged 16 to 65 years. We excluded known cases of NAFLD or liver disease from the study.

2.2 Assessments

Data on age, gender, Body Mass Index (BMI = Weight in kilograms / Height in meters^2), waist circumference (WC) in centimeters, and duration of diabetes were recorded for each participant. Serum AST, ALT, and γ-glutamyltransferase (GGT) levels were measured using the Roche cobas c system. The normal reference ranges for these enzymes were AST 8-33 units per liter (U/L), ALT 7-56 U/L, and GGT 5-40 U/L (Roche Diagnostics GmbH, 2020). Serum triglyceride levels, with normal values defined as below 150 mg/dL, and serum albumin levels, with a normal range of 3.4-5.4 grams per deciliter (g/dL), were also quantified using the Roche cobas c system (Roche Diagnostics GmbH, 2020).

Hemoglobin A1C (HbA1c) levels were determined using turbidimetric inhibition immunoassay (TINIA) on the Roche cobas system, with a normal reference range of 4.0%-5.6% (Roche Diagnostics, 2023).

The Fibrosis-4 Index (FIB-4) is used to assess the presence of advanced liver fibrosis. It is calculated using age, AST, ALT, and platelet count. The formula for FIB-4 is: "FIB-4=Age ([yr] x AST [U/L]) / ((PLT [10(9)/L]) x (ALT [U/L])(1/2)" [10]. Interpretation of the FIB-4 score in relation to advanced liver fibrosis risk is as follows: a score of < 1.30 indicates low risk, scores between 1.30 and 2.67 indicate intermediate risk, and a score of > 2.67 indicates high risk for advanced fibrosis [10].

The NAFLD score is used to assess the extent of liver fibrosis in patients with NAFLD and is calculated using age, BMI, AST, ALT, albumin, and platelets. The formula for the NAFLD score is: −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m²) + 1.13 × impaired glucose tolerance or diabetes mellitus (yes = 1, no = 0) + 0.99 × AST to ALT ratio − 0.013 × platelet count (× 10^9/L) − 0.66 × albumin (g/dL) [7]. Interpretation of the NAFLD score is as follows: a score of -1.455 or lower (F0-F2) indicates no significant fibrosis, a score higher than 0.676 (F3-F4) indicates significant fibrosis, and a score between -1.455 and 0.676 is considered undetermined, suggesting consideration of a liver biopsy [11].

The estimated Glucose Disposal Rate (eGDR) is used to determine the degree of insulin sensitivity and is calculated using waist circumference (WC), HbA1c%, and the presence or absence of hypertension [5, 16]. The formula for eGDR (mg/kg/min) is: 21.158 - (0.09 × WC in cm) - (3.407 × hypertension [1 = yes, 0 = no]) - (0.551 × HbA1c%) [5]. A higher eGDR indicates higher insulin sensitivity; an eGDR level below 8.77 mg/kg/min suggests insulin resistance and metabolic syndrome [5].

2.3 Statistical Analysis

Data analysis was conducted using IBM SPSS v.25. Categorical data were presented using counts and percentages, while continuous data were reported as mean and standard deviation. The correlations between eGDR, FIB-4, and NAFLD scores were assessed using Spearman correlation coefficients, with rho (r) and p-values representing the results. ROC curves were employed to evaluate the accuracy, sensitivity, and specificity of eGDR scores in predicting moderate to severe fibrosis.

3. RESULTS

3.1 Patients' Characteristics.

Our study included a total of 211 patients, with a mean age of 58.87 years (± 9.96) and a mean BMI of 33.58 kg/m² (± 6.34). The majority of participants were female (62.1%). Additionally, 86.3% of the sample had diabetes, and 73.9% had hypertension. Table 1 presents the characteristics of the included patients.

Table 1. The characteristics of the study participants

		Mean±SD	Count	%
Age		58.87±9.96		
BMI		33.58±6.34		
Gender	Male		80	37.9%
	Female		131	62.1%
DM	No		29	13.7%
	Yes		182	86.3%
Pre-DM	No		182	86.3%
	Yes		29	13.7%
Duration		10.81±9.00		
Hypertension	No		55	26.1%
	Yes		156	73.9%

BMI=Body Mass Index; DM=Diabetes Mellitus; SD=Standard Deviation

3.2 Characteristics of liver fibrosis among the included patients

The mean FIB-4 score was 1.22 (± 1.54), and the mean NAFLD score was -0.75 (± 1.46). Approximately 2.8% and 10.9% of the included patients exhibited moderate to severe fibrosis based on the FIB-4 and NAFLD scores, respectively. The mean eGDR score was 4.58 (± 2.41) (see Table 2).

Table 2. The degree of liver fibrosis among the participants

		Mean±SD	Count	%
FIB-4 Score		1.22±1.54		
FIB-4 Score Interpretation	None-mild fibrosis		205	96.6%
	Moderate-severe fibrosis		6	2.8%
NAFLD Score		-0.75±1.46		
NAFLD Score Interpretation	No		188	89.1%
	Yes		23	10.9%
eGDR (mg/kg/min)		4.58±2.41		

eGDR=estimated glucose disposal rate; FIB-4=Fibrosis 4; NAFLD=non-alcoholic fatty liver disease; SD=standard deviation

3.3 The correlation between eGDR and fibrosis scores

Spearman correlation coefficients indicated that eGDR showed a weak but significant association with the FIB-4 score ($r = -0.143$, $p = 0.042$). Additionally, eGDR was correlated with NAFLD scores ($r = -0.344$, $p < 0.001$). Furthermore, the FIB-4 score demonstrated a strong positive correlation with NAFLD scores ($r = 0.821$, $p < 0.001$) (see Figure 1).

3.4 The association between eGDR and fibrosis scores interpretation

ROC curves demonstrated that eGDR significantly predicted moderate-severe fibrosis as indicated by FIB-4 (AUC = 71.1%, 95% CI: 58.3%-83.8%) or NAFLD scores (AUC = 73.4%, 95% CI: 63.0%-

83.8%) (see Figure 2). The optimal eGDR cut-off point for predicting moderate-severe fibrosis indicated by FIB-4 was 4.07, achieving a sensitivity of 65.2% and specificity of 73.8%. For NAFLD scores, the optimal eGDR cut-off point was 5.34, with a sensitivity of 83.3% and specificity of 65.5%. Table 3 summarizes the ROC curve results.

Table 3. ROC curve results of eGDR and fibrosis scores interpretations

Variable	eGDR Cut-off point	Sensitivity	Specificity	Accuracy (95%CI)
FIB-4 Interpretation	4.07	65.2%	73.8%	71.1% (58.3%-83.8%)
NAFLD Score Interpretation	5.34	83.3%	65.5%	73.4% (63.0%-83.8%)

eGDR=estimated glucose disposal rate; FIB-4=Fibrosis 4; NAFLD= Nonalcoholic fatty liver disease; SD=standard deviation; 95%CI=95% confidence intervals.

4. DISCUSSION

As the prevalence of obesity and type 2 diabetes mellitus continues to increase globally, the prevalence of NAFLD is also rising proportionately [12]. Therefore, ongoing efforts are needed to identify accurate non-invasive screening tests for the early diagnosis of insulin resistance and NAFLD to aid in early prevention and management [12,13]. Lifestyle modification through a healthy diet and regular exercise, with a primary goal of weight loss, is the mainstay of treatment for insulin resistance and NAFLD, which often coexist. Weight loss leads to significant improvements in insulin sensitivity and histologic changes in NAFLD, including improvements in liver fibrosis [13,14]. Intensive lifestyle intervention can also lead to improvements in cardiovascular risk factors in overweight or obese adults with metabolic syndrome [14].

Although the gold standard test for measuring insulin resistance is the euglycemic hyperinsulinemic clamp, its complexity has led researchers to develop other valid surrogate markers based on serum insulin and glucose concentrations, either fasting or postprandial after an oral glucose or meal tolerance test [15,16]. One such marker is the HOMA-IR index, which has been extensively used as a screening test for insulin resistance [16,17]. However, it is not yet recommended for routine screening due to its lack of reproducibility [17]. This limitation is because it depends on changes in beta-cell function over time and requires standardized and universal insulin assays [16,17].

The estimated Glucose Disposal Rate (eGDR) is a biomarker based on waist circumference, hypertension, and HbA1c. Initially developed as a measure of insulin sensitivity in type 1 diabetes, it has also been used to predict the risk of chronic complications and mortality in this population [18-20]. Additionally, eGDR has been validated in patients with type 2 diabetes using the euglycemic-hyperinsulinemic clamp method and is considered suitable and straightforward for clinical practice [5,21,22]. A higher eGDR indicates greater insulin sensitivity, while an eGDR level below 8.77 mg/kg/min suggests insulin resistance and metabolic syndrome [5].

Regarding NAFLD, several screening systems are available that are considered cost-effective and non-invasive tests for

screening liver fibrosis in high-risk patients who may benefit from early detection and intervention [23,24]. Among these systems are the FIB-4 and NAFLD scoring systems, which not only detect NAFLD but also assess the degree of liver fibrosis [25-27].

Since insulin resistance and fatty liver disease are interconnected [1], we explored the correlation between the insulin resistance score (eGDR) and NAFLD scores (FIB-4 and NAFLD score). As expected, our results revealed a significant correlation between eGDR and NAFLD scores, along with a weak but significant association between eGDR and FIB-4 scores. Moreover, the FIB-4 score showed a strong positive correlation with NAFLD scores. Regarding severity and cutoff points, eGDR significantly predicted moderate to severe fibrosis, as indicated by FIB-4 and NAFLD scores. The optimal eGDR cutoff points for predicting moderate to severe fibrosis were 4.07 and 5.34, respectively, suggesting a lower eGDR cutoff point to enhance NAFLD prediction in the context of insulin resistance.

One of the limitations of our study is its single-center design; however, Jordan University Hospital is a tertiary center that treats cases from across Jordan. We also anticipate variations in eGDR scores due to fluctuations in HbA1c control over months or even years, suggesting that serial eGDR testing may yield more accurate results.

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العلاقة بين معدل التخلص من الجلوكوز المقدر (eGDR) وشدة مرض الكبد الدهني غير الكحولي (NAFLD) في مرض السكري من النوع الثاني

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الملخص

خلفية الدراسة والاهداف: الربط بين درجة حساسية الأنسولين (eGDR) ودرجة مرض الكبد الدهني غير الكحولي (NAFLD) في مرضى السكري من النوع الثاني.

منهجية الدراسة : شملت دراستنا 211 مريضًا. تم حساب مؤشر تليف الكبد (FIB-4) لكل مشارك، وهو مؤشر يستخدم لتقييم وجود تليف الكبد المتقدم، وكذلك درجة الكبد الدهني (NAFLD) التي تُستخدم لتقييم مدى تليف الكبد. ثم تم ربط هذه الدرجات بمعدل التخلص من الجلوكوز المقدّر(eGDR) ، وهو مقياس يُستخدم لتقييم حساسية الأنسولين.

النتائج : كان متوسط درجة FIB-4 هو 1.22 ± 1.54، ومتوسط درجة NAFLD هو −0.75 ± 1.46. كان هناك تليف معتدل إلى شديد لدى 2.8% من المرضى وفقاً لمؤشر FIB-4 ، و10.9% وفقاً لدرجة NAFLD. كان متوسط درجة eGDR هو 4.58 ± 2.41. أظهرت معاملات الارتباط سبيرمان أن eGDR كان مرتبطًا بشكل ضعيف ولكنه ذو دلالة إحصائية مع درجة FIB-4 (r = −0.143, p = 0.042). بالإضافة إلى ذلك، أظهر eGDR ارتباطاً ذا دلالة إحصائية مع درجات NAFLD (r = −0.344, p < 0.001). كما كان لمؤشر FIB-4 ارتباط كبير مع درجات NAFLD (r = 0.821, p < 0.001). أظهرت منحنيات ROC أن eGDR يمكنه بشكل كبير التنبؤ بالتليف المعتدل إلى الشديد كما هو موضح في FIB-4 (71.1%; 95% CI: 58.3%–83.8%)؛ أو درجات NAFLD (73.4%; 95% CI: 63.0%–83.8%) كانت نقطة القطع المثلى لـ eGDR للتنبؤ بالتليف المعتدل إلى الشديد وفقاً لـ FIB-4 هي 4.07، حيث حققت حساسية بنسبة 65.2% ونوعية بنسبة 73.8%. وللتنبؤ بالتليف المعتدل إلى الشديد وفقاً لدرجات NAFLD، كانت نقطة القطع المثلى لـ eGDR هي 5.34، بحساسية بلغت 83.3% ونوعية بلغت 65.5%.

الاستنتاجات: أظهرت دراستنا وجود ارتباط كبير بين درجات eGDR وشدة مرض الكبد الدهني غير الكحولي (NAFLD) بناءً على نتائجنا، نقترح النظر في نقطة قطع أقل لـ eGDR، تتراوح بين 4.07 و5.34، لتعزيز دقة التنبؤ بـ NAFLD في سياق مقاومة الأنسولين.

الكلمات الدالة: السكري؛ معدل التخلص من الجلوكوز المقدّر (eGDR)؛ حساسية الأنسولين؛ مرض الكبد الدهني غير الكحولي (NAFLD)؛ الفحص الوقائي