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ORIGINAL ARTICLE

Correlation between Glycated Albumin/Glycosylated Hemoglobin Ratio and C-PEP and Liver Injury in Patients with T2DM

Yajie Zhao [1], Zhaoyu Zhu [1], Wentan Hu [2], Ju Li [1]

[1] *School of Medical Laboratory Technology, Xinyang Vocational and Technical College，Xinyang City Henan Province, China*
[2] *Department of Clinical Laboratory, Xinyang Central Hospital, Xinyang City Henan Province, China*

ABSTRACT

Background: **Diabetes mellitus (DM) is a disorder of the endocrine-metabolic system, identified by ongoing hyperglycemia and exacerbated by liver function problems. The association of the glycated albumin/hemoglobin A1c (GA/HbA1C) ratio and C-peptide (C-PEP) with liver injury in diabetes mellitus type 2 (T2DM) patients remains a topic of controversy.**
Methods: **530 T2DM patients were divided into two groups: non-liver injury and liver injury group. All patients' clinical information and lab indices were gathered. In the univariate analysis, variables having a $p < 0.05$ were evaluated to determine the correlation between liver injury severity and variable levels, based on the patients' Child-Pugh classification. In the multivariate logistic regression analysis, GA, GA/HbA1c, and C-PEP were incorporated as separate variables to identify independent factors. The effectiveness in prediction was assessed through the receiver operating curve method. The Pearson's correlation method was employed to examine the link between liver injury and the levels of GA/HbA1c and C-PEP in patients with T2DM.**
Results: **GA and GA/HbA1c were higher in the liver injury group than in the non-liver injury group, while C-PEP levels were lower. Increased levels of GA/HbA1c independently increased the risk of liver injury, showing a positive association with injury severity, while C-PEP independently acted as a protective factor, inversely related to the severity of the liver injury. Both GA/HbA1c and C-PEP had moderate predictive efficacy for liver injury in patients in the T2DM group.**
Conclusions: **Patients with T2DM have a high incidence of liver injury. Both GA/HbA1c and C-PEP are independent influences on liver injury in patients with T2DM, and correlate with the severity of liver injury.**
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Correspondence:
Ju Li
School of Medical Laboratory Technology
Xinyang Vocational and Technical College
No. 48, 24th Street
Yangshan New District, Xinyang City
Henan Province, 464000
China
Email: dr.liju1917li@outlook.com

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KEYWORDS

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INTRODUCTION

Disorders of glucose metabolism cause accumulation of glycogen in the liver and hepatic microangiopathy, which impairs liver function. Patients with diabetes mellitus type 2 (T2DM) often exhibit insulin resistance or inadequate secretion, along with hyperlipolysis in peripheral tissues. The influx of free fatty acids into the liver surpasses its ability to clear them [1]. The accumu-

lation of lipids in the liver results in fatty liver, which disrupts liver function. This disruption heightens insulin resistance, further advancing diabetes mellitus (DM) and creating a negative feedback loop [2]. Liver injury complicates DM treatment and directly impacts its efficacy and prognosis. Early detection and effective prevention and treatment of diabetic liver injury is crucial for improving the quality of life in patients.

Glycated hemoglobin A1c (HbA1c) is a specific compound formed when hemoglobin A undergoes a binding reaction with glucose in living organisms and is found mainly inside red blood cells [3]. Albumin (ALB) is glycosylated 10 times faster than HbA1c, which makes glycated albumin (GA) more sensitive than HbA1c to changes in blood glucose, and better reflecting changes in blood glucose over a short period of time [4]. The GA/HbA1c ratio is positively correlated with the stage of liver fibrosis, and the GA/HbA1c ratio in patients with T2DM has a significant correlation [5,6].

Serum C-peptide (C-PEP) is a peptide primarily produced when protein hydrolases cleave insulinogen, and it is not easily degraded by the liver [7]. Serum C-PEP concentration usually reflects insulin secretion, and the ratio of insulin to C-PEP is usually relatively stable in healthy populations. In patients with T2DM, C-PEP levels may be reduced, which may be due to insulin resistance or insufficient secretion [8,9]. Therefore, C-PEP measurements are commonly used clinically to assess islet function in DM patients. It has been found that metabolic alterations caused by abnormal C-PEP secretion may contribute to T2DM complications [10], and serum C-PEP levels in T2DM patients are negatively correlated with cardiovascular autonomic neuropathy [11]. There are fewer studies on the relationship between C-PEP and diabetic liver injury in patients with T2DM, and the preliminary findings obtained are not yet fully conclusive.

Based on this, this study collected and analyzed the clinical characteristics of 530 patients with T2DM, and discussed in depth the influencing factors of liver injury in patients with T2DM.

MATERIALS AND METHODS

Study population

530 cases of T2DM patients admitted to Xinyang Central Hospital from January 2021 to January 2024 were selected, of which 336 cases were male and 260 cases were female and all of them met the diagnostic criteria of DM. They were divided into non-liver injury group and liver injury group. There were 378 cases in the non-impairment group, 192 cases were male, the average age was 41.28 ± 8.25 years, and the duration of DM was 5.08 ± 2.04 years. In the liver injury group, there were 152 cases including 78 males, with an average age of 42.72 ± 10.37 years and the duration of DM of 5.46 ± 3.16 years.

Inclusion criteria: 1) T2DM had been diagnosed before liver injury and met the diagnostic criteria in the Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition); 2) diabetic liver injury was clinically diagnosed; 3) there was no malignant tumors or psychiatric disorders; 4) normal cognitive performance and high compliance were observed.

Exclusion criteria: 1) patients with diabetes mellitus type 1 (T1DM), pregnancy, and special types of DM; 2) patients with previous acute and chronic pancreatitis disease; 3) patients with a history of chronic alcohol consumption; 4) patients with acute infectious diseases; 5) patients with non-fatty liver diseases including autoimmune liver disease, hepatitis A/B/C/E, and hereditary liver disease; 6) patients with missing clinical data.

Diagnostic criteria

Diagnostic criteria for liver injury: 1) liver function abnormalities meet one or more of the following criteria: 1) alanine aminotransferase (ALT) > 40 U/L^{-1}; 2) aspartate aminotransferase (AST) > 40 U/L^{-1}; 3) gamma-glutamyl transferase > 40 U/L^{-1}; 4) alkaline phosphatase > 135 U/L^{-1}; 5) serum bilirubin > 17.3 $\mu mol/L^{-1}$; 2) ultrasonographic imaging reveals abnormalities in liver function indices on laboratory tests or liver disease such as liver enlargement or fatty liver, ruling out that they are due to other causes.

The Child-Pugh scale, consisting of five components - hepatic encephalopathy, ascites, bilirubin, serum ALB, and prothrombin time - was employed for assessment. Each component was rated from 1 to 3 points, resulting in a total score range of 5 to 15, where a higher score indicates a more severe condition. Scores of 5 - 8 indicate a low risk (grade A), 9 - 11 indicate a medium risk (grade B), and 12 - 15 indicate a high risk (grade C).

General information

General information was collected from all study participants, including gender, age, medical history, past history, alcohol use, family history, and history of DM. A general physical examination was performed, height and weight were measured, and body mass index (BMI) = weight/height^2 (kg/m^2) was calculated.

Laboratory indicators

Fasting venous blood samples were taken from all patients on the next day after 8 hours of fasting, and blood biochemical parameters were measured by a fully automated biochemical analyzer, including fasting blood glucose (FBG), total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Liver function indices such as ALT, GA, ALB, and creatinine (Cr) were measured by using AU5821 Automatic Biochemistry Analyzer (Beckman Coulter). Blood for HbA1c testing was placed in ethylenediaminetetraacetic acid (EDTA)-K2 anticoagulation tubes and measured by a HbA1c analyzer. Detecting C-PEP concentrations involved gathering blood in EDTA-K2 anticoagulated tubes and spinning it at 4,000 rpm for five minutes, followed by measuring C-PEP levels us-

ing a Roche E601 automated immunoassay analyzer (Roche Diagnostics, Germany).

Statistical analysis

Statistical analysis was conducted using SPSS 26.0. The data from measurements underwent normality testing, with those adhering to the normal distribution represented as mean ± standard deviation (SD), and the student's *t*-test facilitated the comparison between the two groups. Information that deviated from a normal distribution was presented as the median and the interquartile range M (Q25 - Q75), with group comparisons conducted via the Wilcoxon rank-sum test. Count data underwent a chi-squared analysis. No correction for multiple comparisons was performed (e.g., different Child-Pugh classification groups) and multiple indicators (e.g., GA, GA/HbA1c, C-PEP, etc.). Multivariate logistic regression analysis incorporated independent variables showing statistically significant variances ($p < 0.05$) in univariate analysis to identify independent factors ($p < 0.05$). Predictive efficacy was analyzed using receiver operating curve (ROC) analysis. Pearson's correlation was used to analyze the relationship between liver injury and GA/HbA1c and C-PEP levels in T2DM patients. $p < 0.05$ suggested significant difference.

RESULTS

General clinical characteristics between the two groups of patients

All enrolled patients were categorized into non-liver injury group (n = 378) and liver injury group (n = 152), and the probability of T2DM patients in developing liver injury was 28.68%. The clinicopathologic characteristics of all subjects are shown in Table 1. There was no significant difference in age, gender, and disease duration between the two groups ($p > 0.05$). No significant differences in BMI, past medical history, and routine blood tests (AST, ALT, FBG, etc.) were found between the two groups ($p > 0.05$). However, GA and GA/HbA1c were higher in the liver injury group than in non-liver injury group, while C-PEP levels were lower than in non-liver injury group ($p < 0.05$).

Classification of liver injury in patients with T2DM

All patients with liver injury were categorized into 77 cases of Child A, 44 cases of Child B and 31 cases of Child C according to Child-Pugh scale. GA and GA/HbA1c were higher in Child B and C liver injury patients than in Child A liver injury patients, and C-PEP levels were lower in Child C liver injury patients than in Child A liver injury patients ($p < 0.05$). Patients with Child C liver injury had higher GA/HbA1c than Child B, and lower C-PEP levels than Child B ($p < 0.05$) (Figure 1).

Multivariate logistic regression analysis of liver injury in T2DM patients

A multivariate logistic regression model was established using the factors with significant differences ($p < 0.05$) analyzed in Table 1 as independent variables: GA, GA/HbA1c and C-PEP. The test results showed that GA [OR (95% CI) = 0.99 (0.95 - 1.08), $p = 0.67$] was not an independent factor influencing liver injury in patients with T2DM. Elevated GA/HbA1c [OR (95% CI) = 361.89 (81.77 - 1,601.66), $p < 0.05$] was an independent risk factor, while C-PEP [OR (95% CI) = 1.61(1.35 - 1.93), $p < 0.01$] was an independent protective factor affecting liver injury in patients with T2DM (Table 2).

ROC results of GA/HbA1c and C-PEP in predicting liver injury in patients with T2DM

ROC curves were plotted with the liver injury group as positive samples and non-liver injury group as negative samples. GA/HbA1c showed moderate predictive efficacy. The area under curve (AUC) of GA/HbA1c was 0.72 (95% CI = 0.65 - 0.78, $p < 0.05$). The AUC for GA/HbA1c was 0.72 (95% CI = 0.65 - 0.78, $p < 0.05$), and when the cutoff value was GA/HbA1c > 2.17, the sensitivity of predicting liver injury was 66.45%, and the specificity was 89.15%. The predictive efficacy of C-PEP was relatively low, with an AUC of 0.65 (95% CI = 0.60 - 0.70, $p < 0.05$), and when the cutoff value was C-PEP < 1.98 ng/mL, the sensitivity of predicting liver injury was 44.74% and the specificity was 77.78% (Table 3, Figure 2).

Correlation analysis of liver injury with GA/HbA1c and C-PEP in patients with T2DM

Pearson's correlation analysis revealed a direct link between liver injury and GA/HbA1c ($r = 0.28$, $p < 0.05$), and an inverse relationship with C-PEP ($r = 0.20$, $p < 0.05$) in individuals with T2DM. Additionally, a negative relationship was observed between GA/HbA1c and C-PEP ($r = 0.19$, $p < 0.05$) (Figure 3).

DISCUSSION

T2DM is a globally prevalent chronic metabolic disease, with the main clinical treatment focusing on blood glucose control. As T2DM progresses, the risk of complications gradually increases. Therefore, controlling the occurrence of complications means prolonging the survival time of T2DM patients, and exploring indicators that can quickly and accurately assess the occurrence of complications in T2DM can help achieve better management of T2DM patients [12]. This study showed that elevated GA/HbA1c was an independent risk factor for the occurrence of liver injury, and C-PEP was an independent protective factor. GA/HbA1c and C-PEP had moderate predictive efficacy in predicting liver injury in patients with T2DM and correlated with liver injury grading.

GA, indicative of brief glycemic regulation spanning 2

Table 1. Comparison of the general clinical characteristics of the two groups of patients.

Characteristics	Non-liver injury group (n = 378)	Liver injury group (n = 152)	p-value
Age (year)	41.28 ± 8.25	42.72 ± 10.37	0.13
Gender (male)	192 (50.79%)	78 (51.32%)	0.91
BMI (kg/m^2)	23.76 ± 2.75	24.28 ± 6.05	0.31
Course of T2DM (year)	5.06 (3.59, 6.44)	5.21 (3.32, 7.37)	0.37
Hypertension	77 (20.37%)	35 (23.03%)	0.50
Coronary heart disease	172 (45.50%)	61 (40.13%)	0.26
Smoking history	98 (25.93%)	43 (28.29%)	0.58
TG (mmol/L)	1.25 ± 0.51	1.20 ± 0.42	0.26
TC (mg/dL)	175.32 ± 42.24	182.61 ± 51.41	0.12
HDL-C (mg/dL)	48.16 ± 10.43	50.47 ± 13.09	0.07
LDL-C (mg/dL)	102.01 ± 30.44	108.88 ± 47.73	0.10
WBC (x 10^9/L)	13.51 ± 2.94	13.79 ± 3.66	0.40
UA (mmol/L)	318.52 ± 86.05	331 ± 92.85	0.14
FBG (mmol/L)	6.13 (5.20, 6.99)	6.45 (3.93, 8.95)	0.27
ALB (g/L)	36.08 ± 5.33	35.21 ± 4.82	0.08
AST (U/L)	42.97 ± 5.04	43.97 ± 6.11	0.08
ALT (U/L)	46.33 ± 5.04	46.18 ± 6.12	0.79
Cr (mmol/L)	56.88 ± 7.13	57.11 ± 8.82	0.78
HbA1c (%)	9.36 (8.20, 10.21)	9.14 (8.04, 10.63)	0.79
GA (%)	19.61 (17.53, 21.37)	21.71 (18.55, 24.59)	< 0.01
GA/HbA1c	2.08 (1.89, 2.37)	2.38 (2.08, 2.52)	< 0.01
C-PEP (ng/mL)	2.79 (2.02, 3.51)	2.24 (1.59, 2.93)	< 0.01

Data were expressed as mean ± standard deviation (SD) or number of cases (%). Continuous variables were tested using the Student's *t*-test. Non-normally distributed data were expressed as median and interquartile spacing M (Q25 to Q75), and comparisons between groups were made using the Wilcoxon signed rank-sum test. Qualitative information was expressed as the number of cases (n) and the percentage (%), and the chi-squared test was used. p < 0.05 was statistically different.
BMI: body mass index, T2DM: diabetes mellitus type 2, TG: triglyceride, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, WBC: white blood cell, UA: uric acid, FBG: fasting blood glucose, ALB: serum albumin, AST: aspartate transaminase, AL: alanine aminotransferase, Cr: creatinine, HbA1c: hemoglobin A1c, G: glycated albumin, C-PEP: C-peptide.

Table 2. Multivariate logistic regression modeling to analyze risk factors affecting liver injury in patients with T2DM.

Indices	OR	95% CI	p-value
GA	1.01	0.95 - 1.08	0.67
GA/HbA1c	375.97	84.89 - 1,665.22	< 0.01
C-PEP	0.57	0.45 - 0.72	< 0.01

HbA1c: hemoglobin A1c, GA: glycated albumin, C-PEP: C-peptide, OR: odds ratio, CI: confidence interval, p < 0.05.

Table 3. Predictive value of GA/HbA1c and C-PEP for liver injury in patients with T2DM.

Indices	Cutoff	Youden index	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
GA/HbA1c	2.17	0.56	66.45	89.15	71.12	86.86
C-PEP (ng/mL)	1.98	0.23	44.74	77.78	44.72	77.78

T2DM: diabetes mellitus type 2, HbA1c: hemoglobin A1c, GA: glycated albumin, C-PEP: C-peptide, PPV: positive predictive value, NPV: negative predictive value.

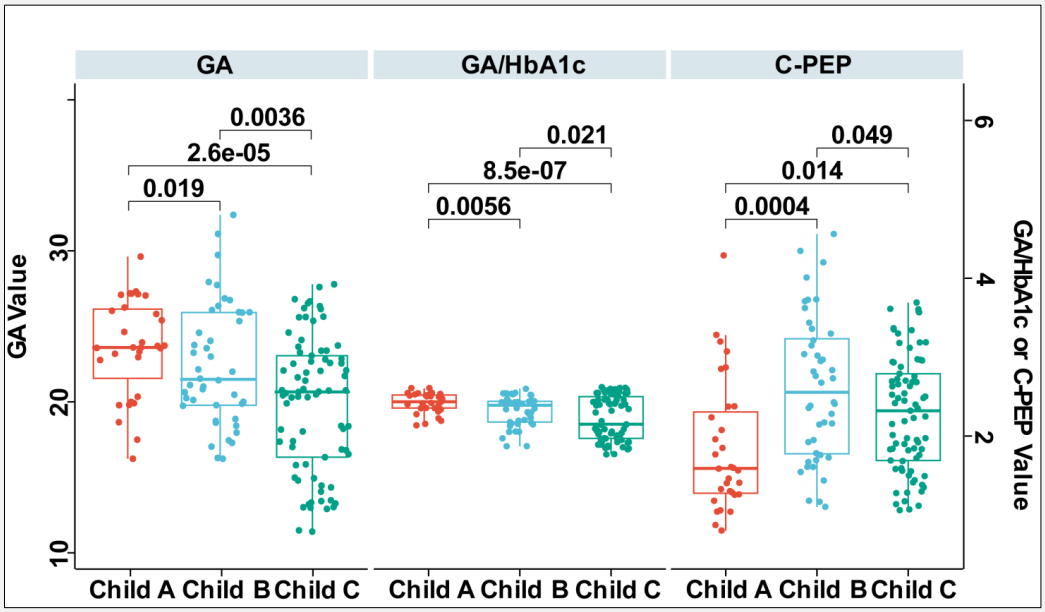

Figure 1. Comparison of GA, GA/HbA1c and C-PEP levels in patients with different Child Pugh classification in the liver injury group.

The horizontal coordinate is the degree of liver injury (Child-Pugh classification), the left vertical coordinate is the GA level, and the right vertical coordinate is the GA/HbA1c and C-PEP levels. Data were expressed as mean ± standard deviation. Continuous variables were tested by student's *t*-test. $p < 0.05$ was statistically different.

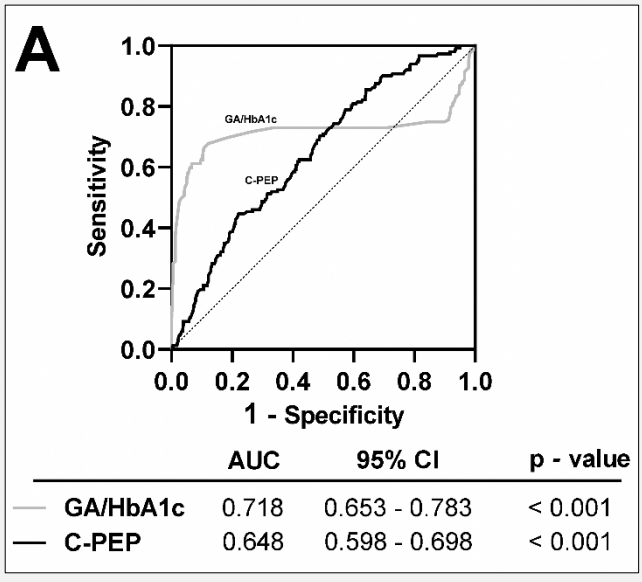

Figure 2. ROC curves of GA/HbA1c and C-PEP for predicting liver injury in T2DM patients.

The horizontal coordinate (X-axis) is the false-positive rate (1 - specificity); the vertical coordinate (Y-axis) is the true-positive rate (sensitivity). $p < 0.05$ was statistically significant.

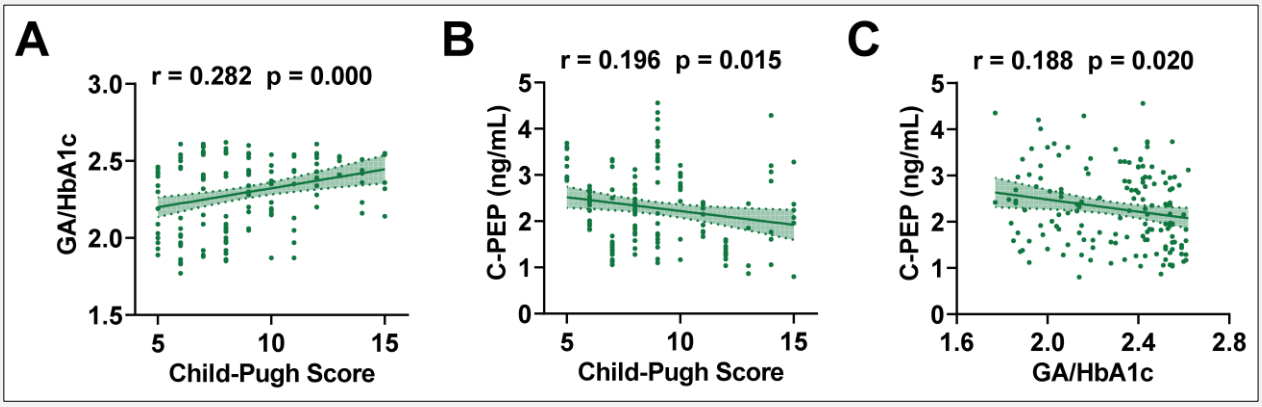

Figure 3. Pearson's analysis of the correlation between liver injury and GA/HbA1c and C-PEP in patients with T2DM.

A: Horizontal coordinate is the degree of liver injury (expressed as Child-Pugh score and vertical coordinate is the level of GA/HbA1c.
B: Horizontal coordinate is the degree of liver injury (expressed as Child-Pugh score) and vertical coordinate is the level of C-PEP.
C: Horizontal coordinate is the level of GA/HbA1c and vertical coordinate is the level of C-PEP.

3 weeks, and HbA1c, signifying the glycemic management status in the preceding 2 - 3 months, are extensively employed as the benchmark for glycemic regulation in clinical settings [13]. Initially, GA/HbA1c was identified as a predictor for upcoming alterations in blood glucose regulation and fluctuations [14,15]. Furthermore, a link exists between elevated GA/HbA1C ratios and liver fibrosis in individuals with chronic hepatitis [16]. Consequently, the GA/HbA1C ratio could serve as a marker for evaluating liver injury in patients. It was noted that cirrhosis patients had an average GA/HbA1c ratio of 3.14, markedly surpassing the 2.85 GA/HbA1c ratio found in cirrhosis patients [17]. This aligns with the current study's findings, where patients with T2DM and liver injury exhibited elevated GA/HbA1c levels compared to those with T2DM. Crucially, even when accounting for additional variables like GA and HbA1c, the heightened GA/HbA1c ratio remained closely linked to the severity of liver injury in T2DM patients. Notably, the association between GA and HbA1c was statistically significantly higher than normal in this study. GA and HbA1c are both blood glucose-related indicators, and their metabolic pathways are closely related. Even after controlling for confounders in the multivariate model, the ratio variable might not have fully adjusted for covariance with other blood glucose-related factors, leading to increased regression coefficients. Therefore, the conclusion of GA/HbA1c as an independent influencing factor still needs to be validated by larger sample size and multicenter studies. In this regard, it is recommended that GA/HbA1c be used as an auxiliary indicator for liver injury risk assessment, combined with clinical symptoms and other liver function indicators to make a comprehensive judgment.

In human pancreatic tissues, insulinogen produces insulin and C-PEP under the shearing action of enzymes. In the detection of DM patients, the functional status of pancreatic islets can be accurately reflected by the determination of serum C-PEP levels in the fasting state [18]. For patients with T2DM, the fasting serum C-PEP level is significantly higher than the normal range, but after the development of DM, the pancreatic islet β-cells fail in a large scale, and the C-PEP level is also significantly reduced [19]. This is consistent with the results of the present study, in which C-PEP levels were significantly lower in patients with combined liver injury than in patients with T2DM, suggesting that liver injury in patients with T2DM may not occur in the early stages of DM. The present study also found that fasting C-PEP was significantly correlated with liver injury in T2DM patients by multivariate logistic analysis. Fasting C-PEP is a protective factor against liver injury in T2DM, and low C-PEP levels may accelerate the occurrence of liver injury in T2DM patients. This study provides further evidence for the biological effect of C-PEP. It is currently believed that C-PEP has the ability to reduce DM complications for the following reasons: (1) C-PEP may act in coordination with insulin to help reduce postprandial hyperglycemia, thereby reducing vascular injury due to elevated blood glucose [20]. (2) Activation of intracellular second messengers by C-PEP binding to G protein-coupled receptors on the cell membrane can elevate intracellular calcium ion concentration, improve endothelial cell permeability, and ameliorate microvascular blood flow and neurological dysfunction [21,22]. (3) C-PEP can also stimulate adenosine monophos-

phate-activated protein kinase q, inhibiting reactive oxygen species-mediated endothelial cell apoptosis [23]. Although all current studies have shown that C-PEP is highly resistant to interference and is not easily affected by exogenous insulin, it is still necessary to judge whether it is suitable for T2DM patients receiving insulin therapy according to the actual situation in the clinic. In this study, the GA/HbA1c ratio (cutoff value > 2.17) was moderately effective in predicting liver injury in patients with T2DM (AUC = 0.72), and was positively correlated with the Child-Pugh classification. This suggests that the GA/HbA1c ratio can be used as a primary screening indicator for liver injury in T2DM patients with poor long-term glycemic control, especially in short-term fluctuations in blood glucose. For patients with elevated GA/HbA1c ratio, the glucose-lowering regimen should be prioritized to reduce short-term glucose fluctuations in clinical treatment. And further refinement of liver function biochemical tests and liver imaging assessment are needed for early identification of liver injury risk. Meanwhile, C-PEP level (cutoff value < 1.98 ng/mL), although with low predictive efficacy (AUC = 0.65), can be used in combination with GA/HbA1c as a direct reflection of islet function. This provides a therapeutic direction for the treatment of patients with T2DM combined with liver injury. In parallel with glucose lowering, drugs to improve pancreatic islet function can be considered, and changes in C-PEP levels can be monitored to assess the response to treatment.

Our study has some limitations. This cross-sectional study confirmed the correlation between GA/HbA1c, C-PEP, and liver injury, but it did not establish a causal connection with liver function impairment. Therefore, a prospective cohort study is needed to further elucidate the correlation between the GA/HbA1c ratio and the occurrence of liver injury in patients with T2DM. In clinical practice, a comprehensive judgment should be made in combination with the course of the patient's disease. In addition, this study is a single-center study, the sample size (530 cases) is large, but there are only 31 patients with Child-Pugh class C. The small sample size of the subgroup may lead to insufficient stability of the statistical results of the subgroup with severe liver injury. Secondly, oxidative stress and inflammatory responses caused by blood glucose fluctuations also exacerbate insulin resistance in T2DM patients, which in turn affects their glycemic control. However, this study could not further prove this point. The OR of GA/HbA1c (361.89) was significantly higher than the common clinical range and cannot be used alone as the sole basis for diagnosis or risk assessment; it must be combined with traditional liver function markers such as ALT and AST, as well as imaging findings.

In conclusion, the GA/HbA1c ratio is significantly increased and C-PEP level is significantly decreased in T2DM patients with liver injury. Both elevated GA/HbA1c and decreased C-PEP are independent risk factors for the development of liver injury in T2DM patients. This suggests that GA/HbA1c and C-PEP may be used as auxiliary indicators for screening and evaluating the risk of liver injury and disease progression in patients with T2DM in the clinical setting. However, their clinical application should be limited to scenarios combining traditional liver function indexes and imaging tests, and the application of GA/HbA1c in the clinic needs to be further validated in multicenter, large-sample prospective studies. Future studies should focus on the validation of causality and the specificity of GA/HbA1c in different liver injury etiologies to enhance its clinical value.

Availability of Data and Materials:

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval:

The present study was approved by the Ethics Committee of Xinyang Central Hospital and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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