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Association between hemoglobin glycation index and non-alcoholic fatty liver disease in the patients with type 2 diabetes mellitus

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Keywords
Hemoglobin glycation index, Non-alcoholic fatty liver disease, Type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: The hemoglobin glycation index (HGI) represent the disparity between actual glycated hemoglobin measurements and predicted HbA1c. It serves as a proxy for the degree of non-enzymatic glycation of hemoglobin, which has been found to be positively correlated with diabetic comorbidities. In this study, we investigated the relationship between HGI and non-alcoholic fatty liver disease (NAFLD), along with other relevant biological markers in patients with diabetes.

Materials and Methods: This cross-sectional study consisted of 3,191 adults diagnosed with type 2 diabetes mellitus. We calculated the predicted glycated hemoglobin levels based on fasting blood glucose levels. Multivariate binary logistic regression analysis was conducted to examine the correlation between the HGI and NAFLD. Hepatic steatosis was diagnosed using ultrasonography.

Results: Among all participants, 1,784 (55.91%) were diagnosed with NAFLD. Participants with confirmed NAFLD showed elevated body mass index, diastolic blood pressure, liver enzyme, total cholesterol, triglyceride, low-density lipoprotein and uric acid levels compared with those without NAFLD. In the unadjusted model, participants in the last tertile of HGI were 1.40-fold more likely to develop NAFLD than those in the first tertile (95% confidence interval 1.18–1.66; $P < 0.001$). In the fully adjusted model, those in the last tertile of HGI had a 39% increased risk of liver steatosis compared with confidence interval in the first tertile of HGI (95% confidence interval 1.12–1.74; $P < 0.001$).

Conclusions: A higher HGI suggests an elevated risk of developing NAFLD in patients with type 2 diabetes.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most widespread liver diseases in the world[1]. It encompasses a spectrum of conditions, ranging from simple steatosis without inflammation to non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma[2, 3]. Furthermore, its prevalence continues to rise globally due to the high prevalence of diabetes[4]. There is a significant correlation between NAFLD and type 2 diabetes mellitus, as >70% of patients with type 2 diabetes mellitus have NAFLD, and a personal or pedigree history of diabetes mellitus is associated with NASH and fibrosis in individuals with NAFLD[5, 6]. Therefore, it is essential to identify the parameters associated with a high risk of NAFLD in patients with diabetes.

Glycated hemoglobin (HbA1c) is a marker that reflects the glycemic control of patients with diabetes over the past 8–12 weeks. It is also used as a diagnostic criterion for diabetes and prediabetes[7, 8]. However, HbA1c levels are influenced by various factors, including the lifespan of blood cells. Changes in the rate of intracellular glycosylation can also lead to an under- or overestimation of HbA1c at current glucose concentrations[9]. This means that, in some cases, HbA1c is not a very suitable indicator. Therefore, to address this limitation, the hemoglobin glycation index (HGI) has been introduced to compensate for deficiencies in HbA1c levels. HGI is a non-enzymatic measure

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of HbA1c that represents the difference between the actual measured HbA1c and the predicted HbA1c derived from blood glucose levels through a linear regression equation. HGI has been found to be actively associated with diabetic comorbidities[10, 11]. A study on a cohort of USA adults showed a strong correlation between high HbA1c levels and an increased risk of NAFLD in healthy individuals, as well as the severity of hepatic steatosis in individuals with prediabetes[12]. Furthermore, Hong SH *et al.* found a positive link between fasting glucose variability and the occurrence of NAFLD in a large cohort study[13]. Given the close relationship between HGI, HbA1c and fasting blood glucose (FBG), researchers sought to determine if HGI could potentially serve as an indicator for NAFLD. Recent studies in Western and Asian non-diabetic populations have shown that elevated HGI levels can effectively identify individuals with an increased risk of developing hepatic steatosis[14, 15]. Nevertheless, the association between the HGI and NAFLD in Asian populations with diabetes remains unclear.

Considering the inextricable association between type 2 diabetes and NAFLD development, it is crucial to identify NAFLD using multiple methods in the diabetic population, where blood glucose and HbA1c levels are routinely measured. Hence, the present study aimed to examine the relationship between HGI and NAFLD in Chinese patients with type 2 diabetes mellitus, providing valuable insight into the potential of HGI as an indicator for NAFLD in this population.

MATERIALS AND METHODS

Study population

We collected inpatient records from May 2003 to July 2019 for 5,875 hospitalizations diagnosed with diabetes mellitus at discharge at the Endocrinology and Metabolism Department of the General Hospital of Tianjin Medical University, Tianjin, China. We excluded individuals based on the following criteria: (1) patients with type 1 diabetes mellitus and other specific types of diabetes mellitus; (2) those with viral or autoimmune hepatitis or medication-induced hepatic disease; (3) men with alcohol intake ≥30 g/day and women with alcohol intake ≥20 g/day; (4) those who did not undergo abdominal ultrasound; (5) those who lacked fasting glucose and HbA1c values; (6) those aged <18 years; and (7) extreme data. Ultimately, 3,191 hospitalized patients were included in this study for analysis (Figure 1).

Data collection

Using a computerized e-Inpatient data collection proforma, we gathered information on patient sex, age, diabetes history, smoking status, current alcohol consumption, systolic blood pressure, diastolic blood pressure, HbA1c, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), uric acid (UA), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and alanine aminotransferase (ALT). On admission, a trained physician measured the patients' height, weight and blood pressure using a standard regimen[16]. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[17]. Current smoking was defined as smoking a minimum of one cigarette per day in the past year. Blood pressure was recorded twice using a sphygmomanometer after each patient had been in a quiet state for at least 5 min, and the mean measurement was reported. This study was approved by the Institutional Review Board of the Tianjin Medical University General Hospital (approval number: IRB2020-YX-027-01). Informed consent was not obtained, because patient data were sourced from electronic medical records and prior medical history files in the Endocrinology and Metabolism Department, and the patients' identities were anonymous, except for the date of birth.

Calculation of HGI

After excluding participants with missing fasting glucose and HbA1c data, and those not diagnosed with type 2 diabetes, we used a random subsample of 4,919 participants to assess the linear relationship between fasting glucose and HbA1c. Predicted values of HbA1c were obtained by plugging FBG concentrations into a linear regression formula (Figures 2: HbA1c = 0.3 × fasting blood glucose [mmol/L] + 5.8). HGI was calculated as the actual measured value of HbA1c minus the predicted value of HbA1c, as mentioned earlier[10].

Definitions

Diabetes was diagnosed when the FBG value ≥7.0 mmol/L, 2-h postprandial blood glucose value ≥11.1 mmol/L, HbA1c ≥ 6.5%, previous confirmation of diabetes or application of antidiabetic drugs[18].

NAFLD was diagnosed by an experienced radiologist using liver ultrasonography, ruling out secondary causes of liver damage, such as viral hepatitis or drug-related hepatitis.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation, categorical variables as percentages, and continuous variables with biased distributions as median and interquartile range. Student's *t*-test and Mann–Whitney *U*-test were used for continuous variables with normal and skewed distributions, respectively. Comparison of categorical variables was carried out using the χ^2-test. The relationships among the variables were characterized using Pearson's correlation coefficient (*r*). The HGI values were separately categorized into tertiles, with the lowest tertile (T1) as the reference group. The relationship between HGI and NAFLD was determined using binary logistic regression analysis to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Logistic regression analyses were adjusted for the following variables: model 1 was not adjusted as a blank group; model 2 was adjusted for age and sex; model 3 was adjusted for the duration of diabetes,

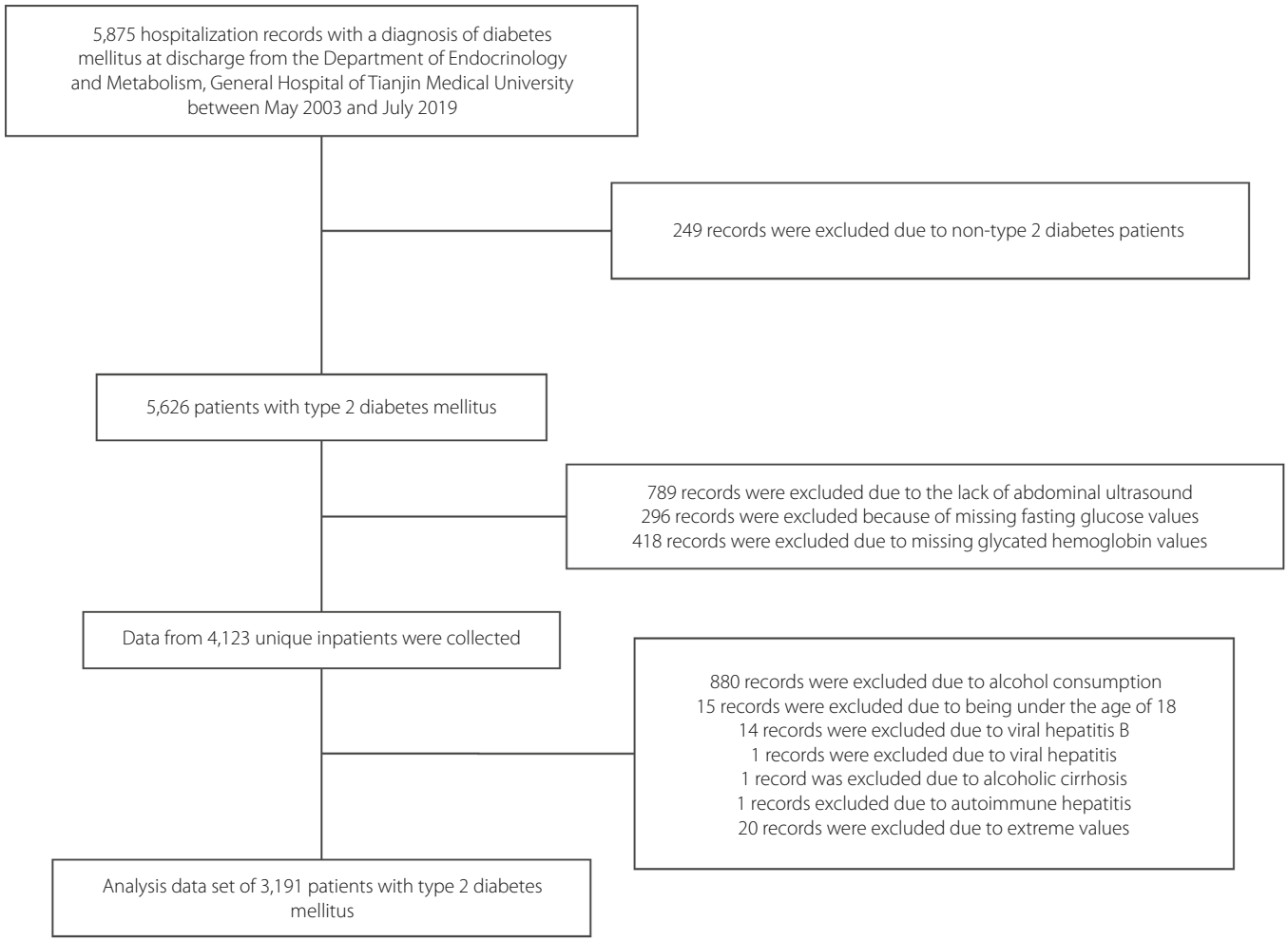

Figure 1 | Flowchart of identification of study population. Based on the exclusion criteria, a total of 3,191 patients with type 2 diabetes mellitus were included. Of the 5,875 patients who visited the Department of Endocrinology and Metabolism at Tianjin Medical University General Hospital from May 2003 to July 2019, 5,626 type 2 diabetes patients remained after excluding 249 non-type 2 diabetes patients. A total of 789 were excluded because they did not have abdominal ultrasound, 296 were excluded because they did not have fasting glucose data, 418 were excluded because they did not have glycated hemoglobin data, 880 were excluded due to excessive alcohol consumption (men with alcohol intake ≥30 g/day and women with alcohol intake ≥20 g/day), 15 were excluded due to age <18 years, 15 had confirmed viral hepatitis, one had confirmed alcoholic cirrhosis, one had confirmed autoimmune liver disease and 20 were excluded due to the presence of extreme values, resulting in the inclusion of 31,912 individuals with type 2 diabetes.

BMI, TC, TG, HDL-c and LDL-c on the basis of model 2; and model 4 was adjusted for ALT, AST and GGT based on model 3. All analyses were carried out using IBM SPSS for Windows (version 27.0; Armonk, NY, USA).

RESULTS

Baseline characteristics of the study participants

Detailed baseline patient information is presented in Table 1. The study included 3,191 patients with type 2 diabetes mellitus, of whom 1,784 (55.91%) were diagnosed with NAFLD. The average age of the study participants was 60.06 ± 12.58 years, with a mean BMI of 26.85 ± 4.33 kg/m^2, fasting glucose of 8.20 ± 3.36 mmol/L and HbA1c level of 8.26 ± 1.91%. Men accounted for 33.90%, and the percentage of smokers was 17.60%. The study revealed that men were more likely to develop NAFLD than were women ($P = 0.026$). Patients with NAFLD were younger and had a shorter duration of diabetes mellitus compared with those without NAFLD ($P < 0.001$). In addition, FBG, HbA1c, UA, BMI, systolic blood pressure, diastolic blood pressure, ALT, AST, GGT, lipid and HGI levels were significantly higher in participants with NAFLD than in those without ($P < 0.05$).

Correlation of HGI with clinical variables

In all subjects, the HGI was positively associated with diabetes duration ($r = 0.069$, $P < 0.001$), HbA1c ($r = 0.832$, $P < 0.001$),

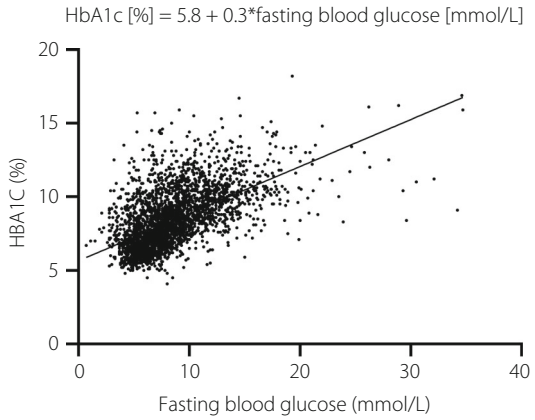

Figure 2 | Scatterplot of glycated hemoglobin (HbA1c) versus fasting blood glucose. There was a significant linear relationship between HbA1c and fasting blood glucose level (HbA1c [%] = 5.8 + 0.3 fasting blood glucose [mmol/L], $P < 0.001$, adjusted $R^2 = 0.306$). After excluding 295 patients without fasting glucose data and 1,414 without HbA1c data and four extreme values, and 249 non-type 2 diabetes patients among 5,875 patients who attended the Department of Endocrinology and Metabolism of Tianjin Medical University General Hospital (Tianjin, China) from May 2003 to July 2019, the fasting glucose data of the remaining 4,912 participants were used as horizontal coordinates, and the HbA1c data were used as vertical coordinates to make regression curves in IBM SPSS for Windows (version 27.0; Armonk, NY, USA).

FBG ($r = 0.127$, $P = 0.014$), LDH ($r = 0.040$, $P = 0.028$), TC ($r = 0.117$, $P < 0.001$) and LDL ($r = 0.133$, $P < 0.001$). Negative correlations were observed between the HGI and total bilirubin ($r = –0.054$, $P = 0.003$), direct bilirubin ($r = –0.052$, $P = 0.004$) and UA ($r = –0.036$, $P = 0.041$). No significant correlation was found between the HGI and sex, smoking status, family history of diabetes, BMI, blood pressure, AST, ALT, GGT, TG or HDL levels (Table 2).

Relationship between FBG, HbA1c, HGI and NAFLD

The associations between FBG, HbA1c, HGI and the risk of NAFLD are shown in Table 3. Fasting glucose and HbA1c levels were significantly associated with the risk of NAFLD, regardless of the model used. The odds of NAFLD increased significantly as the HGI level increased in model 1 (unadjusted; OR [tertile 3 vs tertile 1] 1.40, 95% CI 1.18–1.66; $P < 0.001$ for trend). This significant correlation remained even after adjusting for age, sex, BMI, TG, TC, LDL, HDL, duration of diabetes, and ALT, AST and GGT levels in model 4. The fully adjusted OR (95% CI) for tertile3 versus tertile1 was 1.39 (1.12–1.74; $P < 0.001$ for trend) in the fully adjusted model.

Subgroup analyses

Subgroup analysis of the association between HGI and NAFLD incidence was stratified by sex (male or female), smoking (yes or no), family history of diabetes (yes or no), age (<60 or ≥60 years) and BMI (≤28 or >28) in model 4. As shown in Table 4, a higher HGI levels were associated with an increased incidence of NAFLD in the following subgroups aged ≥60 years (OR [tertile 3 vs tertile 1] 1.42, 95% CI 1.06–1.91; $P < 0.001$ for trend), those with a family history of diabetes (OR [tertile 3 vs tertile 1] 1.65, 95% CI 1.18–2.31; $P < 0.001$ for trend), non-smokers (OR [tertile 3 vs tertile 1] 1.42, 95% CI 1.11–1.81; $P < 0.001$ for trend), participants with a BMI >28 (OR [tertile 3 vs tertile 1] 1.53, 95% CI 1.06–2.19; $P = 0.010$ for trend) and female patients (OR [tertile 3 vs tertile 1] 1.53, 95% CI 1.17–1.99; $P < 0.001$ for trend).

DISCUSSION

In the present cross-sectional study involving participants with type 2 diabetes, the HGI was found to have a significant association with NAFLD, which persisted even after adjusting for various risk factors associated with NAFLD.

As previously mentioned, HbA1c, which is commonly used as an indicator of glycemic fluctuations among patients with diabetes, can be influenced by several factors. Relying solely on HbA1c to assess glycemic fluctuations can lead to erroneous estimations, resulting in clinical evaluation and stewardship errors. Including HGI in the assessment of glycemic control can assist in determining the extent to which HbA1c differs from other glycemic assessments, thereby preventing misinterpretations of glycemic management and inappropriate treatment. HGI is associated with various comorbidities of diabetes. In patients with type 1 diabetes enrolled in the Diabetes Control and Complications Trial, a higher HGI was related to the risk of retinopathy and nephropathy[11]. Furthermore, a high HGI level is an independent predictive indicator of major adverse cardiovascular events in patients with cardiovascular disease and type 2 diabetes mellitus[19]. Among individuals with prediabetes or the primary treatment population, HGI is related to cardiovascular disease in patients with impaired glucose metabolism[20]. Furthermore, relatively high HGI levels might increase the likelihood of vascular atherosclerosis in individuals without diabetes[21]. A prospective study carried out in a Chinese population showed an increased risk of stroke in individuals with high HGI, regardless of diabetes status[22].

Previous studies have established that fasting glucose levels and mean HbA1c levels are independent risk factors for NAFLD[12, 23]. Researchers have also explored the relationship between HGI and NAFLD, primarily focusing on non-diabetic populations. Yoo *et al.*[14] and Fiorentino *et al.*[15] found that with higher HGI levels in white and Asian populations, individuals might recognize themselves as having an increased risk of developing hepatic lipid degeneration. In a white population, after adjusting for age, sex and BMI, the highest quartile of HGI had a 1.6-fold higher occurrence of hepatic steatosis compared to the lowest quartile[15]. Similarly, in an Asian population, after adjusting for factors, such as age, sex, BMI, high-sensitivity C-reactive protein, AST, ALT and FBG, the risk of hepatic steatosis was shown to increase 1.56-fold with elevated HGI levels[14]. Furthermore, a recent report by Hu *et al.*[24] proposed a

Table 1 | Baseline characteristics of the study participants

Variables	Overall	NAFLD	Non-NAFLD	*P*-value
No. participants	3,191	1,784	1,407	
Age (years)	60.06 ± 12.58	58.56 ± 12.94	61.96 ± 11.85	<0.001
Duration of DM (years)	12 (5, 18)	10 (4, 17)	13 (7, 20)	<0.001
Male (%)	33.90	32.29	36.03	0.026
Smoker (%)	17.60	17.04	18.27	0.367
FH of DM (%)	45.50	46.92	43.78	0.077
FBG (mmol/L)	8.20 ± 3.36	8.61 ± 3.18	7.68 ± 3.52	<0.001
HbA1c (%)	8.26 ± 1.91	8.42 ± 1.79	8.05 ± 2.02	<0.001
BMI (kg/m^2)	26.85 ± 4.33	28.36 ± 4.13	24.93 ± 3.80	<0.001
SBP (mmHg)	136.79 ± 19.09	137.44 ± 18.13	135.94 ± 20.21	0.041
DBP (mmHg)	80.45 ± 10.66	81.67 ± 10.76	78.90 ± 10.32	<0.001
ALB (g/L)	40.99 ± 4.21	41.50 ± 3.82	40.33 ± 4.58	<0.001
ALT (U/L)	22.82 ± 22.13	25.84 ± 22.60	19.00 ± 20.91	<0.001
AST (U/L)	20.18 ± 15.59	21.10 ± 14.86	19.03 ± 16.40	<0.001
ALKP (U/L)	72.58 ± 30.03	72.41 ± 26.23	72.79 ± 34.26	0.113
GGT (U/L)	29.84 ± 39.65	32.19 ± 31.26	26.86 ± 48.09	0.004
LDH (U/L)	195.04 ± 55.76	193.47 ± 55.33	197.03 ± 56.26	0.197
TBIL (μmol/L)	9.73 ± 5.17	9.814 ± 4.62	9.63 ± 5.80	0.545
DBIL (μmol/L)	3.31 ± 1.76	3.30 ± 1.60	3.33 ± 1.96	0.239
TC (mmol/L)	5.04 ± 1.51	5.16 ± 1.62	4.88 ± 1.33	<0.001
TG (mmol/L)	2.05 ± 2.09	2.51 ± 2.52	1.48 ± 1.12	<0.001
HDL-c (mmol/L)	1.16 ± 0.36	1.07 ± 0.30	1.26 ± 0.41	<0.001
LDL-c (mmol/L)	3.04 ± 1.15	3.11 ± 1.18	2.96 ± 1.12	<0.001
eGFR (mL/min/1.73m^2)	92.23 ± 21.05	94.35 ± 20.67	89.54 ± 21.24	<0.001
UA (μmol/L)	302.67 ± 97.57	319.05 ± 103.29	281.88 ± 85.43	<0.001
HGI	−0.0025 ± 1.54	0.042 ± 1.441	−0.059 ± 1.648	0.034

Data was presented as mean ± standard deviation, weighted median (25th percentile, 75th percentile) or *n* (%). ALB, albumin; ALKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBIL, direct bilirubin; DBP, diastolic blood pressure; eGFR, estimate glomerular filtration rate; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; HGI, hemoglobin glycation index; LDH, lactate dehydrogenase; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TBIL, total bilirubin; TC, total cholesterol; TG, total triglycerides; UA, uric acid.

phantom to forecast the risk of NAFLD in individuals without diabetes based on the HGI. The present study is the first to identify a positive association between HGI and NAFLD in a population with diabetes, a relationship that has not been previously investigated.

Insulin resistance and diabetes mellitus are considered risk factors for the development of more serious hepatic disorders in NAFLD, even in individuals without abnormal liver enzyme levels. Hepatic fibrosis might evolve over the disease course, even if it initially presents as only simple steatosis without hepatocellular damage[25, 26]. Type 2 diabetes mellitus is usually accompanied by NAFLD, resulting in a high incidence of NASH in individuals with both conditions[27–29]. Diabetes patients also have an elevated incidence of end-stage liver diseases, such as cirrhosis and hepatocellular carcinoma[30]. Therefore, there is a need to identify individuals at risk for NAFLD in the diabetes population at an early stage. The present study showed that participants with a high HGI had an increased risk of NAFLD compared with those with a low HGI, even after adjusting age, sex and liver enzymes.

As found in the present study, the HGI is an indicator that correlates strongly with NAFLD. However, the precise underlying mechanism of this association remains unclear. Several potential mechanisms have been proposed to explain the relationship between HGI and NAFLD. First, advanced glycation end-products (AGEs) are covalent complexes composed of non-enzymatic reactions between amino acids and reducing sugars or oxidized lipids[31]. The role of the HGI in reflecting AGEs is partially evident. AGEs contribute to tissue damage by activating receptors for AGEs and facilitating the generation of reactive oxygen species. In diabetes patients, the excess of reducing sugars due to hyperglycemia leads to an increased rate of AGE formation[32]. Increasing evidence suggests that AGEs activity on receptor for AGEs downstream pathways might facilitate pro-inflammatory responses and damage signaling pathways of insulin, thereby promoting the evolution and worsening of NAFLD[33, 34]. Additionally, AGEs are also associated with the severity of fibrosis in patients with NAFLD[31].

Second, obesity and the resulting dysfunction of fat metabolism are significant risk elements for the progression of

Table 2 | Univariate correlations between hemoglobin glycation index and anthropometric and metabolic variables

Variables	HGI	
	r	*P*
Age (years)	−0.046	0.009
Duration of DM (years)	0.069	<0.001
Male (%)	0.006	0.750
Smoker (%)	0.008	0.634
Family history of DM (%)	0.017	0.329
FBG (mmol/L)	0.127	0.014
HbA1c (%)	0.832	<0.001
BMI (kg/m^2)	−0.008	0.674
SBP (mmHg)	−0.010	0.565
DBP (mmHg)	0.004	0.806
ALT (U/L)	−0.005	0.797
AST (U/L)	−0.012	0.492
ALKP (U/L)	0.020	0.263
GGT (U/L)	0.033	0.062
LDH (U/L)	0.040	0.028
TBIL (μmol/L)	−0.054	0.003
DBIL (μmol/L)	−0.052	0.004
TC (mmol/L)	0.117	<0.001
TG (mmol/L)	0.035	0.050
HDL-c (mmol/L)	−0.015	0.389
LDL-c (mmol/L)	0.133	<0.001
eGFR (mL/min/1.73m^2)	0.048	0.007
UA (μmol/L)	−0.036	0.041

ALB, albumin; ALKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBIL, direct bilirubin; DBP, diastolic blood pressure; eGFR, estimate glomerular filtration rate; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TBIL, total bilirubin; TC, total cholesterol; TG, total triglycerides; UA, uric acid.

NAFLD[35]. Obesity might result in an imbalance of the secretion of pro- and anti-inflammatory factors by adipose tissue, thereby inducing NAFLD. The present findings showed that patients without NAFLD had a lower BMI than those with NAFLD. Both BMI and waistline showed a positive correlation with the existence of NAFLD and illness advancement[36]. In middle-aged overweight individuals who have type 2 diabetes mellitus, the existence of NAFLD is associated with worse steatotic organization and hepatic insulin resistance, hyperinsulinemia, together with more severe dense dyslipidemia[37]. Several studies have shown that the risk of NAFLD increases with higher BMI[38–40]. Gluconeogenesis contributes significantly in the overall production of endogenous glucose in obese individuals compared with leaner populations[41]. Increased gluconeogenesis is the primary cause of fasting hyperglycemia[42]. The present study also confirms this finding, as the association between HGI and NAFLD is more significant in diabetes patients with BMI >28 kg/m^2. Additionally, chronic inflammation plays a crucial role in the development of NAFLD, and insulin resistance is associated with the etiopathogenesis of NAFLD and its progression from steatosis to NASH. Inflammation might impair insulin signaling, worsen hepatic fat infiltration, induce endoplasmic reticulum and oxidative stress, and eventually lead to the development of more severe forms of liver disease. Previous studies have shown that individuals with higher HGI values tend to show elevated levels of inflammatory markers that might cause liver damage by mediating chronic inflammation[15].

Research has shown that the global incidence of NAFLD is lower in men than in women[43–45]. However, young women with abnormal blood glucose levels are equally likely to develop NAFLD at a comparable age to men[46]. The highest incidence of NAFLD in men occurs between the ages of 40 and 60 years, whereas in women, it is observed at age ≥60 years[47]. In a survey investigating the prevalence of NAFLD in women, 7.5% of menopausal women and 6.1% of postmenopausal women were observed to have NAFLD, compared with 3.5% of premenopausal women[48]. According to yearly healthcare screening results in Japan, the frequency of NAFLD in males aged >30 years is approximately 27%, compared with a gradual increase from 7% in their 30s to 23% in women aged >60 years[49]. These findings show the need for early detection and prevention of NAFLD in women. Furthermore, a higher percentage of women diagnosed with NAFLD had hypertension, diabetes, obesity and cirrhosis at the time of diagnosis[50]. The present study also showed that the relationship between HGI and NAFLD was more pronounced in women. Therefore, HGI could be considered a potential tool for identifying NAFLD risk in women. However, whether this strong association is related to factors such as hormones and age remains unclear.

It is important to note that the present study had several limitations. First, it was an observational study; therefore, further studies are necessary to establish more reliable and convincing results. Second, hepatic steatosis was diagnosed using sonography instead of intrusive approaches, such as hepatic biopsy, or more expensive non-invasive methods, such as proton magnetic resonance spectroscopy or computed tomography. Ultrasonography is the most frequently used tool in clinical and epidemiological studies for detecting liver steatosis. In addition, the use of fiber scans for the detection and follow up of hepatic steatosis might be considered when invasive procedures cannot be carried out; however, they were not implemented owing to issues, such as hospital equipment and patient willingness. Finally, the present study only included patients with type 2 diabetes mellitus, which limits the generalizability of the findings to other populations.

In conclusion, we found an association between NAFLD and HGI levels in patients with type 2 diabetes mellitus. These findings have important implications for the management and treatment of NAFLD in diabetic individuals. By including HGI as an assessment of glycemic control alongside traditional

Table 3 | Odds ratios (95% confidence intervals) for association of fasting blood glucose, glycated hemoglobin and hemoglobin glycation index with the prevalence of non-alcoholic fatty liver disease

	T1	T2	T3	*P* for trend
FBG				
n	1,111	1,021	1,059	
Model 1	Ref.	2.41*** (2.02, 2.87)	2.27*** (1.91, 2.70)	<0.001
Model 2	Ref.	2.42*** (2.03, 2.89)	2.17*** (1.82, 2.58)	<0.001
Model 3	Ref.	2.10*** (1.69, 2.59)	1.74*** (1.40, 2.17)	<0.001
Model 4	Ref.	2.03*** (1.64, 2.52)	1.69*** (1.35, 2.11)	<0.001
HbA1c				
No.	1,076	1,057	1,058	
Model 1	Ref.	2.05*** (1.72, 2.43)	1.95*** (1.64, 2.31)	<0.001
Model 2	Ref.	2.09*** (1.76, 2.49)	1.84*** (1.54, 2.19)	<0.001
Model 3	Ref.	2.09*** (1.69, 2.60)	1.73*** (1.39, 2.16)	<0.001
Model 4	Ref.	2.02*** (1.62, 2.51)	1.68*** (1.34, 2.10)	<0.001
HGI				
No.	1,067	1,063	1,061	
Model 1	Ref.	1.58*** (1.33, 1.88)	1.40*** (1.18, 1.76)	<0.001
Model 2	Ref.	1.61*** (1.35, 1.91)	1.35*** (1.13, 1.60)	<0.001
Model 3	Ref.	1.63*** (1.32, 2.02)	1.43** (1.15, 1.77)	<0.001
Model 4	Ref.	1.60*** (1.29, 1.99)	1.39** (1.12, 1.74)	<0.001

Fasting blood glucose (FBG; mmol/L): tertile 1 (T1) ≤6.50, 6.51 ≤ tertile 2 (T2) ≤ 8.80, T3 ≥8.81; glycated hemoglobin (HbA1c; %): T1 ≤7.10, 7.11 ≤ T2 ≤ 8.90, tertile 3 (T3) ≥8.91; hemoglobin glycation index (HGI; %): T1 ≤−0.840, −0.839 ≤ T2 ≤ 0.400, T3 ≥0.401. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for Model 2 plus body mass index (BMI), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and duration of diabetes (DM). Model 4: adjusted for model 3 plus alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. CI, confidence interval; OR, odds ratio.

Table 4 | Subgroup analysis for the association of hemoglobin glycation index with the prevalence of non-alcoholic fatty liver disease

Subgroup	Cases	T1	T2	T3	*P* for trend
Sex					
Male	1,083	Ref.	1.82** (1.23, 2.69)	1.12 (0.75, 1.68)	<0.001
Female	2,108	Ref.	1.53** (1.17, 1.99)	1.53** (1.17, 1.99)	<0.001
Smoker					
Yes	561	Ref.	1.95* (1.14, 3.33)	1.35 (0.77, 2.35)	<0.001
No	2,630	Ref.	1.51*** (1.19, 1.93)	1.42** (1.11, 1.81)	<0.001
Family history of DM					
Yes	1,453	Ref.	1.59** (1.15, 2.21)	1.65** (1.18, 2.31)	<0.001
No	1,738	Ref.	1.63** (1.22, 2.19)	1.23 (0.92, 1.66)	<0.001
Age (years)					
<60	1,458	Ref.	1.89*** (1.33, 2.69)	1.43 (0.96, 1.91)	<0.001
≥60	1,103	Ref.	1.45* (1.09, 1.91)	1.42** (1.06, 1.91)	<0.001
BMI					
≤28	1,945	Ref.	1.60*** (1.24, 2.05)	1.34* (1.04, 1.73)	0.001
>28	1,246	Ref.	1.65** (1.17, 2.33)	1.53* (1.06, 2.19)	0.010

Fasting blood glucose (FBG; mmol/L): tertile 1 (T1) ≤6.50, 6.51 ≤ tertile 2 (T2) ≤ 8.80, tertile 3 (T3) ≥8.81; glycated hemoglobin (HbA1c; %): T1 ≤7.10, 7.11 ≤ T2 ≤ 8.90, T3 ≥8.91; HGI (%): T1 ≤ −0.840, −0.839 ≤ T2 ≤ 0.400, T3 ≥ 0.401. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. CI, confidence interval; OR, odds ratio.

indicators, such as HbA1c, clinicians can gain a more comprehensive understanding of glycemic fluctuations, potentially preventing misinterpretations and guiding appropriate treatment strategies. However, the causative relationship between HGI levels and NAFLD in patients with diabetes remains unclear and requires further investigation.

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DISCLOSURE

The authors declare no interest conflict.

Approval of the research protocol: The Institutional Review Board of Tianjin Medical University General Hospital approved the study. Informed consent was not obtained, because the patient information was extracted from electronic medical records at the Department of Endocrinology and Metabolism, and the patients' identities were kept anonymous, except for date of birth. (approval number: IRB2020-YX-027-01).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

DATA AVAILABILITY STATEMENT

The data set generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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