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Association between glucose time-in-range and the severity of metabolic dysfunction-associated steatotic liver disease in Chinese adults with type 2 diabetes mellitus

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Abstract

Background This study investigated the correlation between glucose time-in-range (TIR) and hepatic steatosis severity or liver fibrosis risk in Chinese adults with type 2 diabetes mellitus (T2DM) comorbid with metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods Participants with T2DM were evaluated for hepatic steatosis and fibrosis using vibration-controlled transient elastography. TIR was calculated based on data from a retrospective continuous glucose monitoring system.

Results A total of 184 T2DM patients with MASLD were enrolled. The controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) decreased with increasing TIR ($p < 0.05$). Spearman correlation showed negative correlations between CAP, LSM, and TIR (r = -0.824 and −0.842, $p < 0.05$) and positive correlations with basal insulin resistance (HOMA-IR) ($r = 0.205$ and 0.208, $p < 0.01$). Multiple linear regression revealed TIR and HOMA-IR independently correlated with CAP (std. regression coefficients = -0.695 and 0.103, $p < 0.05$) and LSM (std. regression coefficients = -0.735 and 0.083, $p < 0.05$), wit0.34 h TIR having a stronger impact. Binary logistic regression showed TIR Groups 3 (70% ≥ TIR < 85%) and 4 (TIR ≥ 85%) were protective for MASLD (OR = 0.26 and 0.11, 95% CI 0.10–0.66 and 0.04–0.29, $P = 0.005$ and < 0.001) and liver fibrosis (OR = 0.29 and 0.13, 95% CI 0.12–0.74 and 0.05–0.36, $P = 0.010$ and < 0.001) compared to TIR Group 1 (lowest quartile).

Conclusion In T2DM patients with coexisting MASLD, a significant and independent association existed between TIR and the severity of hepatic steatosis.

Clinical trial number Not applicable.

Keywords Glucose time-in-range, Metabolic dysfunction-associated steatotic liver disease, Type 2 diabetes mellitus, Controlled attenuation parameter, Liver stiffness measurement

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a hepatic condition intricately linked with several metabolic disturbances within the body, including obesity, hypertension, hyperlipidemia, and type 2 diabetes mellitus (T2DM). Its defining pathological feature is the widespread accumulation of lipids within hepatocytes [1]. Over time, MASLD can advance to liver fibrosis, cirrhosis, and even hepatocellular carcinoma. In China, the prevalence of MASLD has shown a consistent upward trajectory. A 2016 survey has revealed that 17.6% of the Chinese population is affected by MASLD, with a projected prevalence anticipated to reach up to 22% by 2030 [2]. Similarly, epidemiological statistical analyses worldwide show that 38% of adults and 7–14% of children and adolescents suffer from MASLD [3].

T2DM often presents concomitantly with MASLD, and these two conditions frequently exert causative influences on each other. Individuals who experience the coexistence of MASLD and T2DM face a notable 2 to 3-fold heightened risk of mortality resulting from chronic liver diseases in comparison to those who do not have this comorbidity [4]. Recent investigations have unveiled that individuals with both T2DM and MASLD exhibit significantly elevated susceptibility to cardiovascular diseases and proliferative retinopathy when juxtaposed with those lacking comorbid MASLD [5–6]. Compared to those without MASLD, patients with type 1 diabetes mellitus (T1DM) and MASLD might have more difficulties in controlling glucose owing to more significant insulin resistance [7]. Therefore, achieving glycemic control in these patients with both T2DM and MASLD also may present greater challenges.

"Time-in-range" (TIR), a burgeoning parameter for assessing glycemic control, has garnered endorsement from both domestic and international guidelines. It quantifies the duration or percentage of time spent within a specified glucose target range, typically ranging from 3.9 to 10.0 mmol/L, throughout a 24-hour period. In contrast to glycated hemoglobin (HbA1c), TIR offers a more precise and comprehensive evaluation of glycemic control. Research has demonstrated that patients with identical HbA1c levels can exhibit significantly disparate TIR values [8–9].

In our present study, we harnessed a continuous glucose monitoring system (CGMS) to calculate TIR and employed transient elastography (FibroScan) for the measurement of the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). Moreover, our research endeavored to investigate the correlation between TIR and the extent of liver fat accumulation, as well as the risk of developing liver fibrosis in patients concurrently afflicted with T2DM and MASLD.

Methods

Study design and participants

This observational study was conducted on T2DM patients comorbid with MASLD who were admitted to the Endocrinology Department of the First People's Hospital of Nantong, China, from May 2020 to July 2022. The study encompassed 99 men and 85 women participants, all meeting specific inclusion criteria: age within the range of 18 to 60 years, a body mass index (BMI) not exceeding 30 kg/m^2, and a diagnosis of T2DM in accordance with the 2020 American Diabetes Association (ADA) guidelines [10]. The T2DM diagnosis criteria encompassed fasting plasma glucose levels of at least 7.0 mmol/L following an 8-hour fast, 2-hour plasma glucose levels equal to or greater than 11.1 mmol/L during the oral glucose tolerance test, HbA1c levels of 6.5% or higher, presence of typical symptoms of hyperglycemia or hyperglycemic crisis, or random plasma glucose levels measuring 11.1 mmol/L or higher. These stringent criteria were applied to ensure the uniformity of the study population. The exclusion criteria were as follows: T1DM, gestational diabetes, diabetes associated with pregnancy, or other specialized forms of diabetes; severe acute diabetes complications, such as diabetic ketoacidosis or hyperosmolar coma; the presence of coexisting conditions, including malignancies, severe wasting diseases, severe anemia, severe hepatic or renal dysfunction, severe mental disorders, among others; recent cardiovascular events occurring within the preceding 3 months; excessive alcohol consumption (exceeding 30 g/day for men, or 20 g/day for women); a history of viral hepatitis, hepatic cirrhosis, autoimmune hepatitis, or other conditions known to induce liver steatosis; recent use of medications recognized to induce liver steatosis, such as estrogen analogs, and glucocorticoids.; and refusal to participate in the study. These stringent exclusion criteria were meticulously applied to ensure the clarity and specificity of the study cohort. Ethical approval for this research protocol was obtained from the Ethics Committee of the First People's Hospital of Nantong, and all participants provided informed consent.

Basic data collection

Upon admission, comprehensive clinical data were meticulously gathered from all participants, encompassing key variables such as age, sex, height, weight, duration of diabetes, presence of hypertension, and precise measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP). BMI was calculated employing the standard formula: BMI = weight (kg) / (height (m))^2.

Analysis of body composition

Subsequent to admission, all participants underwent body composition analysis utilizing a body composition

analyzer (Inbody370, South Korea). The analysis yielded the following parameters: lean mass of the whole body (LMWB), fat mass of the whole body (FMWB), body fat percentage (FAT%), and waist-hip ratio (WHR).

Collection and analysis of blood specimens

Blood specimens were meticulously collected and analyzed from all participants on the second day following admission, with participants adhering to an 8-hour fasting requirement before blood collection. Venous blood samples were procured and subjected to the following analyses. HbA1c was assessed using an HbA1c analyzer (BIO-RAD10, USA). Additionally, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (Alb), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood urea nitrogen (BUN), serum creatinine (Cr), uric acid (UA), and fasting blood glucose were quantified employing a fully automated biochemical analyzer (Hitachi 7600, Japan). Fasting insulin levels were quantified utilizing an automated chemiluminescent immunoassay analyzer (UniCel DxI800, USA), and platelet (PLT) counts were performed by fully automated blood analyzer (Sysmex xs 800i, Japan). The basal insulin resistance index (HOMA-IR) was computed employing the HOMA steady-state model, following the formula: HOMA-IR = (fasting blood glucose (mIU/L) × fasting insulin (mmol/L))/22.5. The Zhejiang University (ZJU) index [11] and hepatic steatosis index (HSI) [12] were noninvasive tests for evaluating liver steatosis, while the fibrosis-4 (FIB-4) and non-alcoholic fatty liver disease fibrosis score (NFS) were for liver fibrosis [13]. The corresponding formulas are as follows: ZJU index = BMI + fasting glucose + TG + 3×ALT/AST + 2, HSI = 8 × ALT/AST + BMI + 2 + 2 (if female), FIB-4 = age × AST/(PLT × √ALT) and NFS = -1.675 + 0.037 × age + 0.094 × BMI + 1.13 + 0.99 × ALT/AST − 0.013 × PLT − 0.66 × Alb.

CGMS measurement and grouping

TIR, time-above-range (TAR) and time-below-range (TBR) was determined through a retrospective CGMS (iPro2, Medtronic, USA). Each participant wore the CGMS device for a duration of 72 h, commencing on the second day following admission. The device sensor probe was subcutaneously placed to monitor interstitial glucose levels at 5-minute intervals, and the collected data were stored within a glucose recorder. A total of 288 glucose measurements were recorded every 24 h, with fingerstick capillary glucose values (measured using Johnson & Johnson VerioVue, USA) entered into the device for calibration purposes four times daily. Following the 72-hour monitoring period, an automatic glucose profile was generated, facilitating the calculation of the average TIR, TAR and TBR. Participants were categorized into the following groups based on their TIR with reference to previous researches [14]: Group 1: TIR ≤ 40%; Group 2: 40% < TIR < 70%; Group 3: 70% ≤ TIR < 85%; and Group 4: TIR ≥ 85%.

CAP and LSM

The analyses of CAP and LSM were conducted using transient elastography (FibroScan). These examinations were performed by the same experienced operator. Patients assumed a supine position with their right arm raised to expose the right intercostal space. A tightly secured M-type probe (or XL-type probe for BMI ≥ 28 kg/m²) was applied perpendicularly against the skin in the right intercostal space for measurement. The final median value was calculated as the median of 10 valid measurements taken at each measurement point. Validity as established if the relative deviation (interquartile range of measurements/median 156 * 100%) for each measurement was ≤ 30%. The CAP results were interpreted as follows, based on the instrument's reference standards: CAP < 240 dB/m: no hepatic steatosis; 240 dB/m ≤ CAP < 265 dB/m: mild hepatic steatosis; CAP ≥ 265 dB/m: moderate hepatic steatosis; and CAP ≥ 295 dB/m: severe hepatic steatosis.

Diagnose of MASLD and liver fibrosis

MASLD was diagnosed if a patient had hepatic steatosis and met 1 cardiometabolic adult criteria and without other causes of hepatic steatosis or excessive alcohol consumption [15]. Since the population included in this study was T2DM, each participant met 1 cardiometabolic criterion. According to the criteria outlined in the "Expert Consensus on Management of Nonalcoholic Fatty Liver Disease in Adults with Type 2 Diabetes in China" [16], an LSM value of ≥ 8.0 kPa was indicative of the presence of liver fibrosis.

Statistical analyses

Statistical analysis was performed using SPSS 19.0 software. Quantitative data were initially subjected to a normality test using the Shapiro-Wilk method. Data following normal distribution were presented as mean ± SD, while non-normally distributed data were presented as median with interquartile range [M (QL, QU)]. Categorical data were presented as counts or percentages (%). For normally distributed quantitative data, between-group comparisons were conducted using one-way ANOVA, followed by pairwise comparisons within the analysis of variance. For non-normally distributed quantitative data, between-group comparisons were performed using the independent samples Kruskal-Wallis test, followed by pairwise comparisons. Categorical data between groups were analyzed using the $\chi 2$ test. To assess the factors correlated with the indicators of hepatic steatosis and liver

fibrosis, spearman's correlation analysis and multiple linear regression analysis were used. The correlation between TIR and the severity of MASLD, as well as liver fibrosis, was analyzed using multivariate binary logistic regression. A *p* value of less than 0.05 was considered statistically significant.

Results

General clinical data based on TIR groups

Table 1 presents the comparison of general clinical data among the four TIR groups. In Group 4, participants had a shorter duration of diabetes and lower BMI, WHR, HbA1c, LDL-C, and HOMA-IR levels. They also had

Table 1 Comparison of clinical traits of four groups

Variables	Group 1	Group 2	Group 3	Group 4	*p* value
n	47	49	42	46	
Male/female (*n*)	26/21	29/20	19/23	25/21	0.602
Age (year)	60.26 ± 14.67	56.06 ± 15.63	55.38 ± 14.36	52.24 ± 15.33	0.805
Disease duration (year)	10.00(3.00,15.00)	8.00(1.00,10.00)	3.50(0.53,10.00)	2.00(0.10,6.25)	0.001
BMI (kg/m^2)	26.76 ± 2.786	25.59 ± 3.17	24.54 ± 3.33	24.19 ± 3.10	< 0.001
FAT% (%)	34.14 ± 5.93	32.38 ± 5.54	34.48 ± 5.43	31.80 ± 5.47	0.063
FMWB (kg)	23.95 ± 4.98	23.64 ± 4.00	24.55 ± 4.87	22.00 ± 4.12	0.051
LMWB (kg)	42.92 ± 5.63	44.06 ± 7.25	42.67 ± 6.74	45.53 ± 8.24	0.201
WHR	0.94 ± 0.07	0.86 ± 0.08	0.82 ± 0.10*	0.80 ± 0.10	< 0.001
SBP (mmHg)	131.17 ± 21.33	138.08 ± 21.25	136.02 ± 14.91	133.65 ± 17.15	0.322
DBP (mmHg)	78.45 ± 12.11	79.33 ± 12.69	80.71 ± 11.70	82.15 ± 10.28	0.449
HbA1c (%)	10.20(9.10,12.30)	9.10(7.70,10.60)	7.50(6.45,8.35)	6.80(6.00,7.95)	< 0.001
ALT (U/L)	24.50 ± 11.10	19.84 ± 11.97	19.81 ± 10.35	18.37 ± 11.77	0.055
AST (U/L)	17.79 ± 6.95	19.29 ± 6.59	17.07 ± 5.92	20.04 ± 6.98	0.135
TG (mmol/L)	2.62 ± 1.87	1.87 ± 1.12	2.00 ± 1.49	1.97 ± 1.63	0.081
TC (mmol/L)	4.50 ± 1.21	4.26 ± 1.13	4.34 ± 0.96	4.60 ± 1.02	0.418
LDL-C (mmol/L)	3.23 ± 1.12	2.96 ± 1.02	2.72 ± 0.87	2.60 ± 1.02	0.018
HDL-C (mmol/L)	1.10 ± 0.28	1.12 ± 0.27	1.16 ± 0.25	1.11 ± 0.33	0.771
BUN (mmol/L)	5.74 ± 1.82	5.26 ± 1.85	5.42 ± 1.77	4.95 ± 1.96	0.221
Cr (μmol/L)	61.14 ± 18.38	61.48 ± 22.09	57.22 ± 17.65	56.76 ± 18.79	0.511
UA (μmol/L)	318.13 ± 97.74	325.47 ± 112.63	305.30 ± 114.71	331.28 ± 106.69	0.702
HOMA-IR	8.55(6.19,15.87)	7.15(3.67,12.99)	7.74(2.94,12.33)	5.43(1.97,9.71)	0.039
Hypertension, *n* (%)	27(57.4)	20(40.8)	21(50.0)	12(26.1)	0.016
Antidiabetic treatments					
Drug naive, *n* (%)	4(8.5)	6(12.2)	5(11.9)	8(17.4)	0.635
Sulfonylureas, *n* (%)	3(6.4)	6(12.2)	5(11.9)	7(15.2)	0.598
Metformin, *n* (%)	22(46.8)	19(38.8)	13(31.0)	17(37.0)	0.489
TZDs, *n* (%)	8(17.0)	6(12.2)	9(21.4)	7(15.2)	0.692
AGIs, *n* (%)	5(10.6)	5(10.2)	3(7.1)	6(13.0)	0.842
DPP-4Is, *n* (%)	3(6.4)	6(12.2)	4(9.5)	5(10.9)	0.797
GLP-1RAs, *n* (%)	6(12.8)	5(10.2)	9(21.4)	8(17.4)	0.458
SGLT-2Is, *n* (%)	7(14.9)	7(14.3)	11(26.2)	9(19.6)	0.446
Glinides, *n* (%)	3(6.4)	5(10.2)	4(9.5)	2(4.3)	0.686
Insulin, *n* (%)	12(25.5)	14(28.6)	9(21.4)	7(15.2)	0.445
CAP (dB/m)	301.79 ± 19.52	292.76 ± 18.38	250.12 ± 18.69	234.00 ± 22.61	< 0.001
LSM (kPa)	8.81 ± 0.43	8.50 ± 0.37	7.74 ± 0.38	7.28 ± 0.45	< 0.001
ZJU index	43.13 ± 3.61	39.94 ± 2.65	37.11 ± 2.84	36.02 ± 5.19	< 0.001
HSI	36.55 ± 9.55	34.31 ± 6.92	34.71 ± 5.49	31.52 ± 7.33	0.016
FIB-4	2.23 ± 0.31	2.22 ± 0.35	2.14 ± 0.24	1.99 ± 0.35	0.001
NFS	0.17 ± 0.07	0.14 ± 0.06	0.12 ± 0.07	-0.02 ± 0.08	< 0.001

Normally distributed values in the table are given as the mean ± SD, skewed distributed values are given as the median (25 and 75% interquartiles), and categorical variables are given as frequency (percentage)

BMI: body mass index; FMWB: fat mass of the whole body; LMWB: lean mass of the whole body; WHR: waist-hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; BUN: blood urea nitrogen; Cr: serum creatinine; UA: uric acid; HOMA-IR: basal insulin resistance index; TZDs: thiazolidinediones; AGIs: α-glucosidase inhibitors; DPP-4Is: dipeptidyl peptidase-4 inhibitors; GLP-1RAs: glucagon-likepeptide-1 receptor agonists; SGLT-2Is Sodium-glucose cotransporter-2 inhibitors; CAP: controlled attenuation parameter; LSM: liver stiffness measurement; ZJU: Zhejiang University index; HSI hepatic steatosis index; FIB-4 fibrosis-4; NFS: non-alcoholic fatty liver disease fibrosis score

Table 2 Spearman correlation analysis results of CAP and related indicators

Variables	*r*	*p*
TIR	-0.824	< 0.001
BMI	0.224	0.002
FAT%	0.403	< 0.001
FMWB	0.295	< 0.001
LMWB	-0.189	0.010
WHR	0.400	< 0.001
Hypertension	0.041	0.581
Course of disease	0.271	< 0.001
Drug naive	-0.032	0.668
Sulfonylureas	-0.029	0.693
Metformin	0.209	0.004
TZDs	-0.026	0.730
AGIs	0.020	0.784
DPP-4Is	-0.020	0.784
GLP-1RAs	-0.066	0.371
SGLT-2Is	-0.052	0.483
Glinides	0.066	0.372
Insulin	0.211	0.004
Gender	-0.008	0.918
Age	0.209	0.004
SBP	-0.042	0.570
DBP	-0.116	0.118
HbA1c	0.558	< 0.001
ALT	0.128	0.083
AST	-0.083	0.265
TG	0.101	0.172
TC	-0.065	0.384
HDL-C	-0.012	0.875
LDL-C	0.156	0.035
BUN	0.067	0.368
CR	0.047	0.529
UA	-0.057	0.446
HOMA-IR	0.205	0.005

Table 3 Spearman correlation analysis results of LSM and related indicators

Variables	*r*	*p*
TIR	-0.842	< 0.001
BMI	0.234	0.001
Body weight	0.171	0.020
FAT%	0.418	< 0.001
FMWB	0.301	< 0.001
LMWB	-0.194	0.008
WHR	0.413	< 0.001
Hypertension	0.042	0.575
Course of disease	0.273	< 0.001
Drug naive	-0.044	0.556
Sulfonylureas	-0.051	0.495
Metformin	0.189	0.010
TZDs	-0.032	0.666
AGIs	-0.002	0.976
DPP-4Is	-0.041	0.579
GLP-1RAs	-0.065	0.377
SGLT-2Is	-0.066	0.372
Glinides	0.051	0.492
Insulin	0.195	0.008
Gender	0.000	0.996
Age	0.210	0.004
SBP	-0.056	0.450
DBP	-0.117	0.114
HbA1c	0.557	< 0.001
ALT	0.139	0.060
AST	-0.097	0.189
TG	0.123	0.097
TC	-0.058	0.435
HDL-C	-0.012	0.868
LDL-C	0.169	0.022
BUN	0.072	0.330
CR	0.043	0.566
UA	-0.064	0.386
HOMA-IR	0.208	0.005

a lower prevalence of hypertension and lower values of CAP, LSM, ZJU index, HSI, FIB-4 and NFS (all $p < 0.05$, Table 1). There were no statistically significant differences in sex distribution, age, weight, FAT%, FMWB, LMWB, SBP, DBP, ALT, AST, TG, TC, HDL-C, BUN, Cr, UA and antidiabetic treatments (all $p > 0.05$, Table 1).

Correlation analysis of the indicators of hepatic steatosis and liver fibrosis and related factors

CAP was negatively correlated with TIR and LMWB (with correlation coefficients of -0.824 and −0.189, respectively; both $p < 0.05$). CAP was positively correlated with BMI, weight, FAT%, FMWB, WHR, duration of diabetes, age, HbA1c, LDL-C, and HOMA-IR (with correlation coefficients of 0.224, 0.165, 0.403, 0.295, 0.400, 0.271, 0.209, 0.558, 0.156, and 0.205, respectively; all $p < 0.05$). CAP showed no significant correlation with hypertension (yes = 1, no = 0), sex (men = 1, women = 2), SBP, DBP, ALT, AST, TG, TC, HDL-C, BUN, Cr, or UA (all $p > 0.05$). LSM was negatively correlated with TIR and LMWB (with correlation coefficients of -0.842 and −0.194, respectively; both $p < 0.05$). Among antidiabetic treatments, CAP was positively associated with metformin and insulin use (with correlation coefficients of 0.209 and 0.211, respectively; both $p < 0.05$).

LSM was positively correlated with BMI, weight, FAT%, FMWB, WHR, duration of diabetes, age, HbA1c, LDL-C, and HOMA-IR (with correlation coefficients of 0.234, 0.171, 0.418, 0.301, 0.413, 0.273, 0.210, 0.557, 0.169, and 0.208, respectively; all $p < 0.05$). LSM showed no significant correlation with hypertension (yes = 1, no = 0), sex (men = 1, women = 2), SBP, DBP, ALT, AST, TG, TC, HDL-C, BUN, Cr, or UA (all $p > 0.05$). Tables 2 and 3 show detailed results. Among antidiabetic treatments, CAP was positively associated with metformin

Table 4 Multiple linear regression analysis with CAP as a dependent variable

Variables	β	Standardized regression coefficients	t	*p*	95% CI
TIR	-0.991	-0.695	-9.533	< 0.001	-1.196–0.786
BMI	-0.752	-0.070	-1.028	0.306	-2.195-0.692
FAT%	-2.743	-0.448	-1.594	0.113	-6.141-0.655
FMWB	4.000	0.526	2.430	0.016	0.751–7.250
LMWB	-1.478	-0.301	-1.763	0.080	-3.132-0.177
WHR	-0.894	-0.003	-0.033	0.973	-53.711-51.924
Course of disease	0.142	0.031	0.557	0.578	-0.360-0.643
Age	0.146	0.064	1.195	0.234	-0.095-0.388
HbA1c	1.459	0.099	1.730	0.085	-0.206-3.123
LDL-C	-1.490	-0.044	-0.974	0.332	-4.511-1.531
HOMA-IR	0.349	0.103	2.201	0.029	0.036–0.662
Metformin	-3.946	-0.056	-0.924	0.357	-12.372-4.481
Insulin	2.817	0.034	0.588	0.557	-6.634-12.268

Table 5 Multiple linear regression analysis with LSM as a dependent variable

Variables	β	Standardized regression coefficients	t	*p*	95% CI
TIR	-0.022	-0.735	-10.575	< 0.001	-0.026–0.018
BMI	-0.018	-0.079	-1.225	0.222	-0.047-0.011
FAT%	-0.051	-0.395	-1.472	0.143	-0.119-0.017
FMWB	0.079	0.492	2.388	0.018	0.014–0.144
LMWB	-0.029	-0.277	-1.702	0.090	-0.062-0.005
WHR	0.028	0.004	0.052	0.959	-1.034-1.090
Course of disease	0.003	0.030	0.560	0.576	-0.007-0.013
Age	0.003	0.060	1.166	0.245	-0.002-0.008
HbA1c	0.024	0.077	1.408	0.161	-0.010-0.057
LDL-C	-0.026	-0.036	-0.834	0.406	-0.086-0.035
HOMA-IR	0.006	0.083	1.875	0.063	0.000-0.012
Metformin	-0.104	-0.069	-1.211	0.228	-0.273-0.065
Insulin	0.045	0.026	0.471	0.639	-0.145-0.235

and insulin use (with correlation coefficients of 0.189 and 0.195, respectively; both $p < 0.05$).

In Supplementary Table 1, TIR was significantly and negatively associated with ZJU index, HSI, FIB-4 and NFS (with correlation coefficients of -0.659, -0.238, -0.307 and – 0.607, respectively; all $p < 0.05$).

Furthermore, using CAP and LSM as dependent variables, we included the independent variables TIR, LMWB, BMI, FAT%, FMWB, WHR, diabetes duration, age, HbA1c, LDL-C, HOMA-IR, use of metformin and insulin, which were found to be correlated with CAP and LSM in the Spearman correlation analysis, in a stepwise multiple linear regression model analysis. The results revealed that TIR and HOMA-IR exhibited independent correlations with CAP ($p < 0.05$). BMI, FAT%, FMWB, LMWB, WHR, duration of diabetes, age, HbA1c, HDL-C, and CAP showed no significant correlation ($p > 0.05$, Table 4).

Similarly, TIR and HOMA-IR demonstrated independent correlations with LSM ($p < 0.05$), while BMI, FAT%, FMWB, LMWB, WHR, duration of diabetes, age, HbA1c, HDL-C, and CAP exhibited no significant correlation ($p > 0.05$, Table 5). Notably, TIR exhibited a greater impact on both CAP and LSM, as determined by the magnitude of the standardized regression coefficients.

As shown in Supplementary Tables 2–5, after adjustment for the independent variables selected by spearman correlation analysis, TIR was independently and negatively associated with ZJU index, FIB-4 and NFS (all $p < 0.05$), but not with HSI ($p = 0.085$).

Multifactorial binary logistic regression analysis of TIR with the severity of hepatic steatosis and liver fibrosis

Table 6 presents the results of multifactorial binary logistic regression analysis, which assessed the relationship between TIR groupings (Groups 1 to 4) and the severity of hepatic steatosis and liver fibrosis. The dependent variables in this analysis were the severity of MASLD (mild MASLD: CAP < 265 dB/m, moderate to severe MASLD: CAP ≥ 265 dB/m) and the presence of liver fibrosis (non-liver fibrosis: LSM < 8.0 kPa, liver fibrosis: LSM ≥ 8.0 kPa). TIR groupings served as the independent variables, while gender, age, duration of diabetes, BMI, FAT%, FMWB, LMWB, WHR, SBP, DBP, HbA1c, ALT, AST, TG, TC,

Table 6 Correlation analysis of TIR with liver fibrosis and moderate and severe MASLD

TIR	Moderate to severe MASLD		Liver fibrosis	
	OR(95%CI)	*P*	OR(95%CI)	*P*
Group 1	1		1	
Group 2	0.51(0.22–1.21)	0.126	0.62(0.26–1.50)	0.287
Group 3	0.26(0.10–0.66)	0.005	0.29(0.12–0.74)	0.010
Group 4	0.11(0.04–0.29)	< 0.001	0.13(0.05–0.36)	< 0.001

TIR: time-in-range

HDL-C, LDL-C, BUN, Cr, UA, HOMA, and hypertension status were controlled variables included in the multifactorial binary logistic regression model. The forward (LR) analysis method was employed to select significant independent variables. The results indicate that, when compared to TIR Group 1 (the lowest quartile of TIR), both TIR Group 3 and TIR Group 4 were independent protective factors against moderate to severe hepatic steatosis and liver fibrosis ($p < 0.05$ for both, Table 6).

Discussion

MASLD encompasses metabolic dysfunction-associated steatotic liver (MASL), metabolic dysfunction-associated steatohepatitis (MASH), and advanced liver diseases associated with MASLD, such as cirrhosis and liver cancer. In China, there has been a steady increase in the prevalence of MASLD. A meta-analysis conducted in 2019 among the Chinese population has revealed that one-third of individuals in China are affected by MASLD [17]. The relationship between T2DM and MASLD is intricately intertwined and characterized by a complex bidirectional association. Both conditions share common risk factors, including obesity and insulin resistance, which disrupt metabolic processes. Furthermore, they often lead to complications or damage in each other's target organs. When coexisting, patients with concurrent liver and diabetes issues have a notably poor prognosis, with a significantly elevated risk [6]. As early as 2011, Sung et al. have demonstrated that individuals with MASLD have more than a 2-fold increased risk of developing diabetes compared to the general population, with even higher risks in cases of obesity [18]. Concurrently, MASLD has a higher incidence rate among T2DM patients. A cross-sectional study conducted in 2020, examining regional differences in MASLD susceptibility in China, has found that among the 2,420 participants, the prevalence of MASLD is 55.3% among T2DM patients, 44.0% among those with prediabetes, and 23.3% among non-diabetic individuals [19]. Thus, MASLD and T2DM mutually influence and exacerbate each other, leading to an increase in the incidence rates of both conditions.

In individuals with T2DM who also have concurrent MASLD, achieving glycemic control becomes increasingly challenging, while disturbances in lipid metabolism become more severe. This acceleration in metabolic disruption contributes to the onset and progression of complications related to diabetes. A study conducted in 2018 by Afolabi, which involves 80 Nigerian T2DM patients aged 40–80, has revealed that T2DM patients with concurrent MASLD have a 1.96-fold higher risk of cardiovascular events and a 3.46-fold higher risk of cardiovascular mortality compared to those without MASLD [20]. Furthermore, T2DM is closely linked to adverse liver outcomes in individuals with MASLD. T2DM can enhance the influx of free fatty acids, including cholesterol and ceramides, into the liver, resulting in direct liver fat toxicity and the initiation of liver inflammation and fibrosis [21].

In 2019, the "International Consensus on Time in Range as an Important Metric for Glycemic Control" put forth a recommendation endorsing TIR as a critical parameter for monitoring blood glucose [22]. In contrast to HbA1c, which reflects the average blood glucose levels over the past 2 to 3 months, TIR offers a more comprehensive insight into blood glucose fluctuations. These two metrics complement each other in evaluating glycemic control and have been garnering increasing attention and recognition. Numerous studies have now established a close association between TIR and various diabetes-related complications. In 2020, Mayeda et al. [23] have identified a robust correlation between TIR and symptoms of diabetic peripheral neuropathy (DPN) in T2DM patients who have a longer disease duration and concurrent chronic kidney disease (CKD), whereas HbA1c exhibits no significant correlation with DPN symptoms. In 2021, Wang Danyu et al. [24] have conducted a study on T2DM patients with concomitant coronary artery disease, investigating the relationship between TIR and the severity of coronary artery lesions and the risk of acute coronary syndrome. Their research unveils a significant independent correlation between TIR and the severity of coronary artery lesions as well as the risk of the acute coronary syndrome, even after controlling for confounding factors such as BMI and HbA1c. In the same year, Lu et al. [25] have conducted a prospective cohort study involving 6,225 adult T2DM patients in Shanghai, China. They have identified a close association between TIR and adverse cardiovascular outcomes as well as all-cause mortality. Consequently, they recommend TIR as one of

the effective metrics for assessing long-term adverse clinical outcomes in T2DM patients.

According to the latest research [26], different levels of TIR are associated with varying risks of complications in T2DM. The study suggests that TIR can be used as a research cutoff point for assessing blood glucose control in T2DM patients, with suggested thresholds of 85% (excellent control), 70% (adequate control), and 40% (poor control). In our study involving 185 T2DM patients with concomitant MASLD, four groups were defined based on TIR levels: TIR ≥ 85%, 70% ≤ TIR < 85%, 40% < TIR < 70%, and TIR ≤ 40%. The single-factor analysis revealed that except that variables, such as diabetes duration, blood glucose indicators like HbA1c, HOMA-IR, the proportion of hypertension, lipid parameters (LDL-C), BMI, and WHR, exhibited significant trends among the groups, both CAP and LSM, interestingly, showed a gradual decrease as TIR groups increased. However, due to the numerous confounding factors involved, it was unclear whether there was an independent correlation between TIR and CAP/LSM or if these trends were a result of cumulative effects. To explore this further, we conducted Spearman correlation analysis and subsequent stepwise multiple linear regression analysis. The Spearman correlation analysis indicated that CAP had a negative correlation with TIR and LMWB but a positive correlation with BMI, body weight, FAT%, FMWB, WHR, diabetes duration, age, HbA1c, LDL-C, and HOMA-IR. This finding suggested that as TIR and LMWB decreased and BMI, body weight, and FMWB increased, CAP, representing hepatic steatosis, became more severe. Similar results were found for LSM, which had a negative correlation with TIR and LMWB but a positive correlation with BMI, body weight, FAT%, FMWB, WHR, diabetes duration, age, HbA1c, LDL-C, and HOMA-IR. In other words, lower TIR and LMWB were associated with higher BMI, body weight, FMWB, and increased LSM, signifying more severe liver fibrosis. After incorporating confounding factors into a stepwise multiple linear regression model, the analysis revealed that TIR and HOMA-IR were independently correlated with CAP. Specifically, lower TIR and higher HOMA-IR were associated with higher CAP, indicating more severe hepatic steatosis. The same held true for LSM, where lower TIR and higher HOMA-IR were independently correlated with increased LSM, suggesting more severe liver fibrosis. Notably, TIR had a greater impact on CAP and LSM compared to other factors.

Furthermore, when liver steatosis severity and the presence of liver fibrosis were treated as binary dependent variables, multiple logistic regression analysis revealed that compared to TIR ≤ 40%, TIR ≥ 85% and 70% ≤ TIR < 85% were independent protective factors against moderate to severe hepatic steatosis. This finding suggested an independent correlation between TIR and the severity of hepatic steatosis, with lower TIR associated with more severe steatosis. The analysis also showed an independent correlation between TIR and the occurrence of liver fibrosis, with lower TIR associated with a higher risk of liver fibrosis. These findings aligned with the 2021 study by Wu et al. [27], which has found that TIR is an independent risk factor for liver fibrosis in T2DM patients with metabolic-associated fatty liver disease.

HbA1c represents the average blood glucose level over the past 2–3 months and serves as an indicator of overall blood glucose control. On the other hand, TIR reflects the percentage of time during the day when glucose levels are within the target range, offering insights into blood glucose fluctuations. When combined, these two metrics enhance blood glucose monitoring, making it more comprehensive and precise. In comparison to HbA1c, TIR may provide a more intuitive understanding of blood glucose control. Previous studies [28, 29] have indicated that patients with the same HbA1c levels can have significantly different TIR values, resulting in completely different blood glucose profiles. Solely relying on HbA1c may lead to the misconception that a patient's blood glucose levels are stable, while they may actually be experiencing severe blood glucose fluctuations with alternating episodes of hypoglycemia and hyperglycemia. Recognizing this, several national and international guidelines now recommend the inclusion of TIR as an important metric for blood glucose monitoring. As science advances and healthcare professionals' knowledge evolves, the increasing clinical use of CGMS is making TIR, derived from CGMS data, a feasible and valuable indicator for blood glucose monitoring. It is expected hat in the near future, TIR will be widely accepted as a key metric for assessing blood glucose control in diabetic patients and as a predictor of diabetes-related complications. Ultimately, it may be used to guide changes in clinical treatment plans, benefiting individuals with diabetes.

This study has certain limitations. Firstly, it is a clinical observational study. While we found a correlation between TIR and both hepatic steatosis and liver fibrosis, causality cannot be established. Secondly, in this study, the TIR was derived from a 72-hour CGMS. There are other measures available for evaluating glucose fluctuation, such as the coefficient of variation (CV), mean amplitude of glycemic excursions (MAGE), and mean of daily differences (MODD). The TIR might not comprehensively represent overall glucose variability. Furthermore, the short monitoring duration might not fully reflect historical glucose control levels. Given that hepatic steatosis and liver fibrosis are long-term chronic processes, our results might be influenced by this factor. Thirdly, our study had a small sample size and did

not utilize random grouping. There were significant differences in multiple datasets between groups, indicating that there might be uncontrolled confounding factors affecting our results. Fourthly, the gold standard for the diagnosis of hepatic steatosis and hepatic fibrosis is liver biopsy. Although transient elastography is a commonly used method for liver disease examination, it still has its shortcomings. To compensate, we further calculated commonly used non-invasive tests for liver steatosis and liver fibrosis, and these results further confirmed the results of the present study. Lastly, socioeconomic status could affect MASLD, glycemic control, and the use of CGMS, but these were not collected at the time of data collection. In subsequent studies, the influence of socioeconomic status needs to be taken into account.

Conclusion

In summary, this study demonstrates that in T2DM patients with coexisting MASLD, even after adjusting for potential confounding factors such as BMI, FMWB, LDL-C, and HbA1c, a significant independent association existed between TIR and the severity of hepatic steatosis, as well as the risk of developing liver fibrosis. Lower TIR levels were correlated with higher CAP and LSM values, indicating a more pronounced degree of hepatic steatosis and an elevated risk of liver fibrosis. These findings suggested that TIR might serve as a predictive factor for the progression of MASLD in T2DM patients. However, it is important to acknowledge the limitations of our study. Further research, including prospective, large-scale, multicenter, randomized controlled clinical studies, is required to validate and extend these findings.

Supplementary Information

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Supplementary Material 1

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Author contributions
CW and CL participated in the design of the study, data collection, analysis of the data, and drafting of the manuscript. HX and XW conceived of the study, participated in its design and revised the manuscript. XJ, NJ, QY and XC participated in data collection. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study conformed to the guidelines of the Declaration of Helsinki, and the study procedures were reviewed and approved by the medical research ethics committee of Second Affiliated Hospital of Nantong University (No.2022KT120). Each patient agreed to participate and signed the informed consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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