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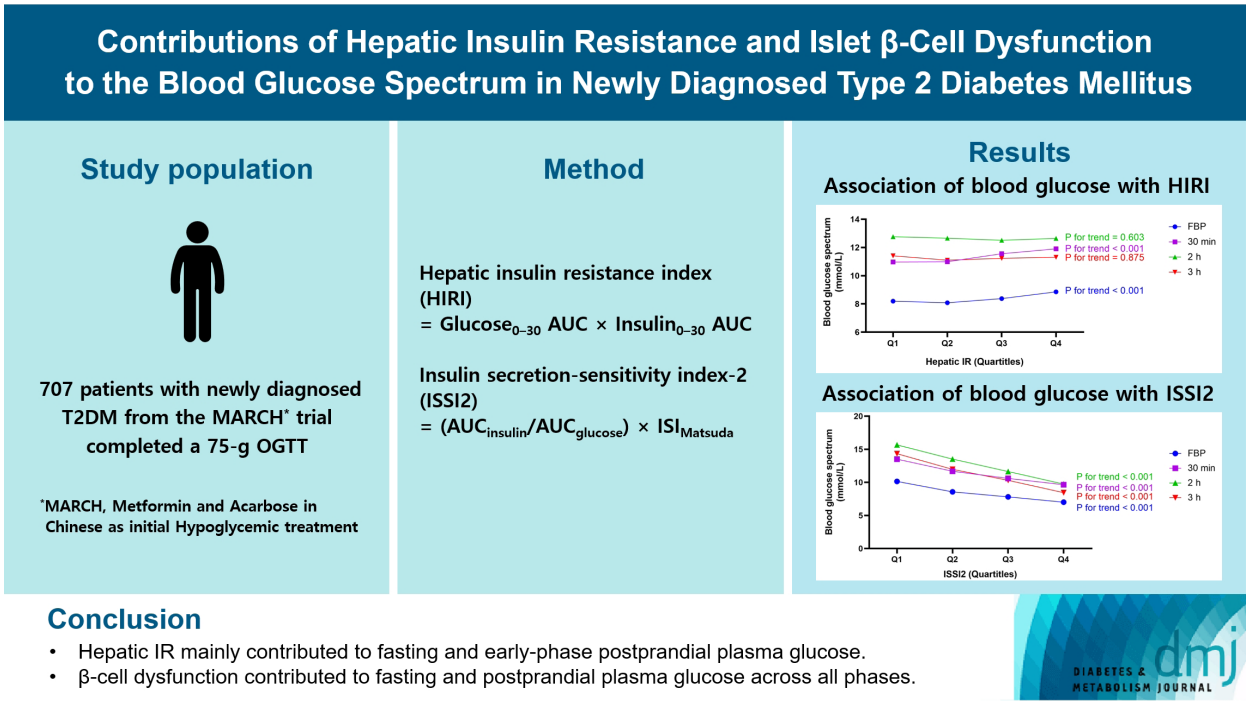


## Highlights

- **This study explores how hepatic IR and β-cell dysfunction contribute to glycemia.**
- **Hepatic IR primarily impacts fasting and early-phase postprandial plasma glucose.**
- **β-cell dysfunction affects fasting and postprandial plasma glucose at all phases.**
- **Hepatic IR and β-cell dysfunction jointly contribute to the pathogenesis of T2DM.**

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# Contributions of Hepatic Insulin Resistance and Islet β-Cell Dysfunction to the Blood Glucose Spectrum in Newly Diagnosed Type 2 Diabetes Mellitus

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**Background:** Our previous studies have investigated the role of hepatic insulin resistance (hepatic IR) and islet β-cell function in the pathogenesis of diabetes. This study aimed to explore the contributions of hepatic IR and islet β-cell dysfunction to the blood glucose spectrum in patients with newly diagnosed type 2 diabetes mellitus.
**Methods:** Hepatic IR was assessed by the hepatic insulin resistance index (HIRI). Islet β-cell function was assessed by insulin secretion-sensitivity index-2 (ISSI2). The associations between blood glucose spectrum and hepatic IR and ISSI2 were analyzed.
**Results:** A total of 707 patients with new-onset diabetes were included. The fasting blood glucose (FBG) and 30 minutes post-load blood glucose elevated with rising HIRI (both $P$ for trend <0.001). The FBG, 30 minutes, 2 hours, and 3 hours post-load blood glucose elevated with decreasing ISSI2 quartiles (all $P$ for trend <0.001). There was a negative correlation between ISSI2 and HIRI after adjusting blood glucose levels ($r$=–0.199, $P$<0.001).
**Conclusion:** Hepatic IR mainly contributed to FBG and early-phase postprandial plasma glucose, whereas β-cell dysfunction contributed to fasting and postprandial plasma glucose at each phase.

**Keywords:** Diabetes mellitus, type 2; Blood glucose; Insulin resistance; Insulin secretion

## INTRODUCTION

Insulin resistance is a state of decreased insulin sensitivity, which is the pathophysiological basis of chronic metabolic diseases such as type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, and atherosclerotic cardiovascular disease [1,2]. The regulation of blood glucose by insulin depends on three target organs: liver, skeletal muscle, and adipose tissue [3].

Insulin secreted by the pancreas first reaches the liver from the portal vein, where insulin concentrations are two to four times as high as those in other peripheral insulin-target tissues. Thus, the liver is one of the main targets of insulin action and plays an important role in maintaining the homeostasis of hepatic glycogenolysis and glycogenesis. Under normal physiological conditions, insulin can regulate the synthesis of glycogen, lipids, proteins and other biological macromolecules in the liver, inhibit gluconeogenesis, and maintain blood glucose homeostasis [4]. However, in a state of hepatic insulin resistance (hepatic IR), the insulin signaling pathway is damaged, and insulin cannot play its normal physiological role, such as the decreased ability to promote glycogen synthesis and inhibit gluconeogenesis, resulting in glucose and lipid metabolism disorders, and eventually developing into diabetes.

The Metformin and Acarbose in Chinese as initial Hypogly-

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cemic treatment (MARCH) trial was the first study to compare the efficacy of metformin and acarbose as the initial treatment in newly diagnosed T2DM. Our team has conducted several clinically oriented subgroup analyses of MARCH to further explore the metabolic features of newly diagnosed T2DM. We found that during the progression of baseline fasting blood glucose (FBG), β-cell dysfunction and insulin resistance worsened in newly diagnosed T2DM patients [5]. In addition, we explored the distinction in the curative effect of metformin treatment among patients with different hepatic IR levels, and the results showed that patients with higher levels of hepatic IR obtained better curative effects from metformin in terms of glycemic control.

The progression of T2DM is accompanied by the decline of insulin secretion [6]. A study showed that fasting and postload glucose homeostasis seem to be independent to a large extent [7]. However, the contributions of hepatic IR and β-cell dysfunction to fasting and postprandial glucose levels has not been studied. In this study, 707 patients with newly diagnosed T2DM from the MARCH trial were included. All patients underwent a 75 g oral glucose tolerance test (OGTT), and the levels of hepatic IR and β-cell dysfunction were assessed by hepatic insulin resistance index (HIRI) and insulin secretion-sensitivity index-2 (ISSI2), respectively. The relationship between the blood glucose spectrum and HIRI and ISSI2 was analyzed to assess contributions of hepatic IR and islet β-cell dysfunction to the blood glucose spectrum in patients with newly diagnosed T2DM.

## METHODS

### Subjects

The study involved individuals from the MARCH trial [8], which recruited patients with newly diagnosed T2DM from 11 clinical centers in China. Inclusion and exclusion criteria were as described previously, and all patients met the following criteria: aged between 30 and 70 years; diagnosed with T2DM according to 1999 World Health Organization criteria; not received oral antidiabetic drugs or received short-term (1 month) treatment but had been discontinued 3 months before enrolment. This study initially enrolled 788 patients, but four patients withdrew from the study before the start of the trial, and 77 of the remaining 784 patients did not complete the OGTT; thus, a total of 707 patients were included in this study. Informed consent was submitted by all subjects when they were enrolled. The protocol was approved by an ethics committee (Beijing Chao-Yang Hospital: No. 2008-28) from each clinical site and was implemented in accordance with provisions of the Declaration of Helsinki. The study was registered in the Chinese Clinical Trials Registry (ChiCTR-TRC-08000231). The flow of the study is shown in Fig. 1.

The baseline information of each subject was collected including age, gender, height, body weight, waist circumference, hip circumference, body mass index (BMI), blood pressure, past medical history, operation history, and medication history. Baseline blood biochemical indexes were measured at baseline including FBG, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, estimated glomerular filtration rate (eGFR), and uric acid, glycosylated hemoglobin (HbA1c). A 75 g OGTT was performed in all patients at baseline. Blood glucose and insulin concentration were tested at 0, 30, 120, and 180 minutes through OGTT.

### Definitions and calculations

Baseline hepatic IR was assessed by HIRI, which was calculated as $glucose_{0-30}$ [area under the curve (AUC)] × $insulin_{0-30}$ [AUC] [9]. Higher HIRI indicates higher hepatic IR levels. Baseline islet β-cell function was assessed by insulin ISSI2. $ISSI2 = (AUC_{insulin}/AUC_{glucose}) \times ISI_{Matsuda}$, where $AUC_{insulin}$ and $AUC_{glucose}$ are the areas under the insulin curve and glucose curve within 120 minutes of OGTT [10]. Higher ISSI2 reflects better islet β-cell function.

$AUCinsulin = 0.5 \times (insulin_{0min} + insulin_{30min}) \times 30 + 0.5 \times (insulin_{30min} + insulin_{2hr}) \times 90$; $AUCglucose = 0.5 \times (glucose_{0min} + glucose_{30min}) \times 30 + 0.5 \times (glucose_{30min} + glucose_{2hr}) \times 90$. $ISI_{Matsuda} = 10{,}000/\sqrt{(MG \times MI) \times (FG \times FI)}$,

where MG is mean glucose within 120 minutes of OGTT, MI is mean insulin within 120 minutes of OGTT, FG is fasting glucose, and FI is fasting insulin. All of the above indexes are validated surrogate measures. The upper quartile of HIRI and ISSI2 were defined as high HIRI and high ISSI2 and the lower quartile of HIRI and ISSI2 were defined as low HIRI and low ISSI2 respectively.

### Statistical analysis

IBM SPSS Statistics version 26.0 software (IBM Co., Armonk, NY, USA) was used for statistical analysis. Graphpad 8.0 (GraphPad Software Inc., San Diego, CA, USA) and BioRender (To-

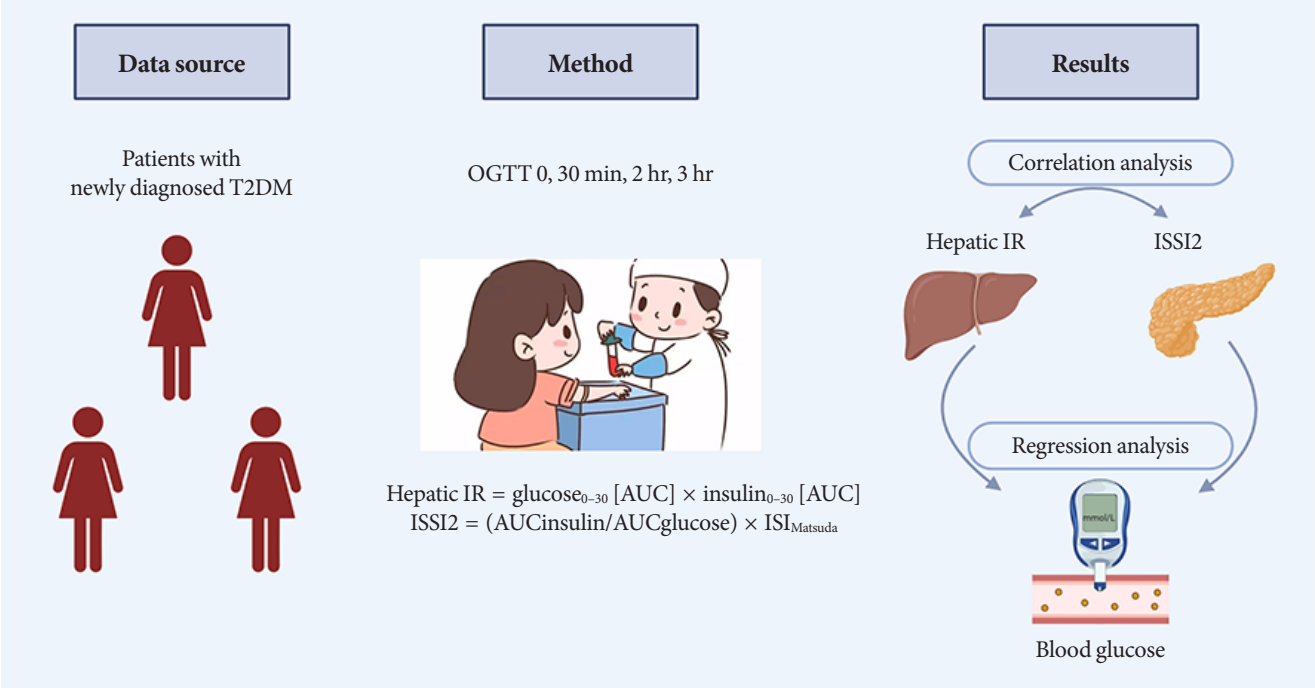


**Fig. 1.** Flow chart of the study. The study recruited patients with newly diagnosed type 2 diabetes mellitus (T2DM). A 75 g oral glucose tolerance test (OGTT) was performed. Baseline hepatic insulin resistance index (HIRI) and insulin secretion-sensitivity index-2 (ISSI2) were calculated. The relationship between the blood glucose spectrum and HIRI and ISSI2 was analyzed to assess contributions of hepatic insulin resistance (hepatic IR) and islet β-cell dysfunction to the blood glucose spectrum in patients with newly diagnosed T2DM. AUC, area under the curve.

ronto, ON, Canada) were used for graphics drawing. Continuous variables were presented as mean±standard deviation or median (interquartile range). Categorical variables were presented as frequencies and percentages. Kolmogorov-Smirnov test was used for normality test. The clinical characteristics of patients with different FBG levels were compared, analysis of variance (ANOVA) and Kruskal-Wallis test were used to compare normally distributed data and non-normally distributed data respectively. Chi-square test was applied to the comparison of categorical variables. The patients were divided into four groups according to the quartile of HIRI, and ANOVA was used to analyze the blood glucose profiles of patients with different hepatic IR levels. The patients were divided into four groups according to the quartile of ISSI2, and ANOVA was used to analyze the blood glucose profiles of patients with different ISSI2 levels. The associations between blood glucose spectrum and hepatic IR and β-cell function were analyzed by unary linear regression, and multiple linear regression was used to adjust for confounding factors. The correlation between hepatic insulin resistance and β-cell function was assessed by Spearman and partial correlation analysis. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

## RESULTS

### The baseline information of included subjects according to FBG

A total of 707 patients with newly diagnosed T2DM were included, and 58.8% ($n=416$) of whom were male. According to FBG quintiles, the patients were divided into five groups. Table 1 shows the characteristics of the patients with different FBG in baseline. Patients with higher FBG showed higher HIRI and lower ISSI2 in baseline ($P<0.001$).

### The association between blood glucose spectrum and hepatic IR

The association between blood glucose spectrum in OGTT and hepatic IR in patients with newly diagnosed T2DM was analyzed (Table 2, Fig. 2). The patients were divided into four

**Table 1.** The baseline information of included subjects according to FBG

| Variable | FBG, mmol/L | | | | | Total | *P* value |
|---|---|---|---|---|---|---|---|
| | <7.1 | ≥7.1–<7.7 | ≥7.7–<8.51 | ≥8.51–<9.7 | ≥9.7 | | |
| Number | 145 | 135 | 138 | 150 | 139 | 707 | |
| Male sex | 80 (55.2) | 75 (55.6) | 84 (60.9) | 84 (56.0) | 93 (66.9) | 416 (58.8) | 0.209 |
| Age, yr | 50.83±8.78 | 49.69±9.51 | 52.39±9.14 | 50.47±9.02 | 48.66±9.31 | 50.41±9.20 | 0.013 |
| BMI, kg/m$^2$ | 25.61±2.51 | 25.86±2.53 | 25.88±2.52 | 25.59±2.49 | 25.17±2.54 | 25.62±2.52 | 0.133 |
| Waist circumference, cm | 88.83±8.39 | 89.12±8.43 | 90.96±8.08 | 89.09±7.92 | 88.51±8.07 | 89.30±8.20 | 0.108 |
| Hip circumference, cm | 98.35±6.99 | 98.68±7.88 | 100.23±7.38 | 98.58±7.23 | 97.79±7.18 | 98.72±7.35 | 0.075 |
| SBP, mm Hg | 124.44±12.50 | 124.09±13.12 | 125.36±12.54 | 126.77±12.37 | 123.11±11.32 | 124.79±12.41 | 0.124 |
| DBP, mm Hg | 80.32±7.70 | 79.23±7.90 | 79.83±7.40 | 80.57±7.90 | 79.77±7.52 | 79.96±7.69 | 0.627 |
| TC, mmol/L | 5.04 (4.44–5.73) | 5.24 (4.56–6.00) | 5.22 (4.51–5.94) | 5.20 (4.52–5.90) | 5.27 (4.49–5.90) | 5.18 (4.48–5.90) | 0.503 |
| TG, mmol/L | 1.63 (1.23–2.44) | 1.88 (1.30–2.75) | 1.89 (1.26–2.56) | 2.07 (1.49–2.93) | 1.93 (1.24–2.76) | 1.90 (1.29–2.73) | 0.034 |
| LDL-C, mmol/L | 3.03±0.94 | 3.15±0.93 | 3.12±0.93 | 2.96±0.93 | 3.08±0.85 | 3.07±0.92 | 0.442 |
| HDL-C, mmol/L | 1.20 (1.01–1.39) | 1.23 (1.06–1.44) | 1.17 (1.02–1.35) | 1.18 (1.03–1.37) | 1.24 (1.04–1.48) | 1.20 (1.03–1.40) | 0.257 |
| HbA1c, % | 6.8 (6.3–7.4) | 7.1 (6.5–7.6) | 7.4 (6.8–8.0) | 7.7 (7.0–8.3) | 8.4 (7.4–9.1) | 7.4 (6.7–8.2) | <0.001 |
| HIRI | 107,701.65 (79,435.04–156,850.65) | 120,454.76 (82,983.60–156,179.70) | 136,938.23 (98,998.48–185,153.51) | 145,873.01 (85,226.93–218,637.91) | 153,063.68 (103,734.00–215,072.55) | 129,858.59 (90,148.73–188,409.49) | <0.001 |
| ISSI2 | 203.68 (161.76–237.54) | 163.26 (133.97–191.91) | 128.66 (113.71–159.16) | 106.52 (91.09–124.87) | 72.08 (58.94–85.90) | 127.12 (93.84–173.99) | <0.001 |

Values are presented as number (%), mean±standard deviation, or median (interquartile range). According to FBG quintiles, the patients were devided into five groups.
FBG, fasting blood glucose; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; HIRI, hepatic insulin resistance index; ISSI2, insulin secretion-sensitivity index-2.

**Table 2.** The association between blood glucose spectrum and hepatic insulin resistance

| | | Model 1 | | Model 2 | |
|---|---|---|---|---|---|
| | | β | *P* value | β | *P* value |
| OGTT, mmol/L | 0 min | 0.173 | <0.001 | 0.196 | <0.001 |
| | 30 min | 0.158 | <0.001 | 0.187 | <0.001 |
| | 2 hr | −0.050 | 0.183 | −0.003 | 0.928 |
| | 3 hr | −0.056 | 0.137 | −0.004 | 0.926 |

Model 1: unadjusted; Model 2: adjusted for age, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, alanine aminotransferase, aspartate aminotransferase, and estimated glomerular filtration rate.
OGTT, oral glucose tolerance test.

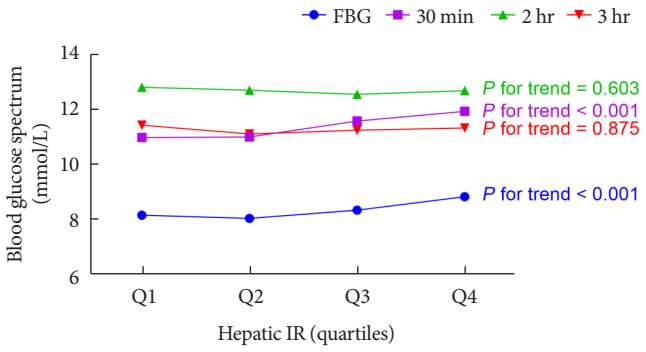


**Fig. 2.** The association of blood glucose in oral glucose tolerance test with the hepatic insulin resistance (hepatic IR) index quartiles. Q1 <90,148.73; 90,148.73≤ Q2 <129,858.59; 129,858.59≤ Q3 <188,409.48; Q4 ≥188,409.48. FBG, fasting blood glucose.

groups according to the quartile of HIRI, and ANOVA test showed that the FBG and 30 minutes post-load blood glucose of the patients elevated with the increase of HIRI (both *P* for trend <0.001) (Fig. 2). Univariate regression analysis showed

**Table 3.** The association between blood glucose spectrum and β-cell function

| | | Model 1 | | Model 2 | |
|---|---|---|---|---|---|
| | | β | *P* value | β | *P* value |
| OGTT, mmol/L | 0 min | −0.729 | <0.001 | −0.737 | <0.001 |
| | 30 min | −0.634 | <0.001 | −0.649 | <0.001 |
| | 2 hr | −0.717 | <0.001 | −0.728 | <0.001 |
| | 3 hr | −0.679 | <0.001 | −0.687 | <0.001 |

Model 1: unadjusted; Model 2: adjusted for age, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, alanine aminotransferase, aspartate aminotransferase, and estimated glomerular filtration rate.
OGTT, oral glucose tolerance test.

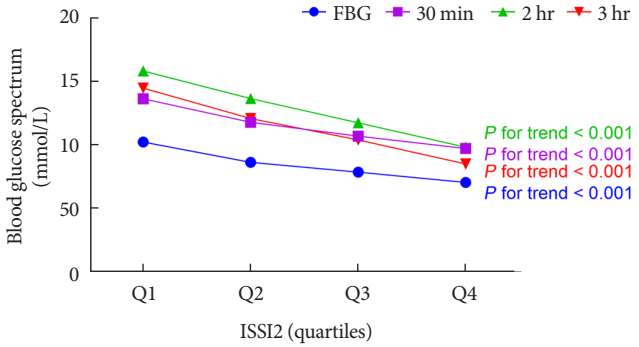


**Fig. 3.** The association of blood glucose in oral glucose tolerance test with the insulin secretion-sensitivity index-2 (ISSI2) quartiles. Q1 <93.83; 93.83≤ Q2 <127.12; 127.12≤ Q3 <173.99; Q4 ≥173.99. FBG, fasting blood glucose.

that FBG and 30 minutes post-load blood glucose were positively associated with HIRI ($P<0.001$). Multiple regression analysis showed that after adjustment of age, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, and eGFR, the positive correlations remained ($P<0.001$). But the correlations were not observed between 2 and 3 hours post-load blood glucose and HIRI whether adjusted for the confounders or not ($P>0.05$).

### The association between blood glucose spectrum and β-cell function

ISSI2 was used to assess the β-cell function of the patients and the association between ISSI2 and blood glucose spectrum in OGTT was analyzed (Table 3). The patients were divided into four groups according to the quartile of ISSI2, and ANOVA test showed that the FBG, 30 minutes, 2 hours, and 3 hours post-load blood glucose of the patients decreased with the increase of ISSI2 (all *P* for trend <0.001) (Fig. 3). Univariate regression analysis showed that ISSI2 was negatively associated with FBG, 30 minutes, 2 hours, and 3 hours post-load blood glucose ($P<0.001$). Multiple regression analysis showed that after adjustment of age, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, and eGFR, the negative correlations remained ($P<0.001$).

### The clinical characteristics of included subjects based on the levels of hepatic IR and ISSI2

The clinical characteristics of included subjects stratified by the levels of hepatic IR were analyzed (Supplementary Table 1). As HIRI increased, patients exhibited progressively higher BMI, accompanied by elevated levels of AST, ALT, eGFR, TC, and TG (all *P* for trend <0.001). The clinical characteristics of included subjects stratified by the levels of hepatic IR combined with ISSI2 were presented in Supplementary Table 2. Patients with high HIRI and high ISSI2 exhibited the highest BMI and the lowest HbA1c levels, whereas those with low HIRI and low ISSI2 had the lowest BMI and the highest HbA1c levels. Moreover, regardless of HIRI levels, patients with high ISSI2 consistently showed lower TG levels compared to those with low ISSI2.

### The association between hepatic IR and β-cell function

The relationship between hepatic IR and β-cell function was further evaluated. Spearman correlation analysis showed that there was a negative correlation between ISSI2 and HIRI ($r=-0.163$, $P<0.001$) (Supplementary Fig. 1). Partial correlation analysis showed the negative correlation remained after adjusting blood glucose levels at different time points in OGTT ($r=-0.111$, $P=0.003$) (Supplementary Fig. 2).

## DISCUSSION

Hepatic IR and β-cell dysfunction are important pathogenesis of T2DM [11]. Our previous study shows that metformin is more effective in patients with severe hepatic insulin resistance; thus, clarifying the contribution of hepatic IR and β-cell dysfunction to the glycemic profile is of great importance for the treatment of patients with newly diagnosed T2DM, however, which has not been investigated. Our study involved 707 patients with newly diagnosed T2DM and was the first to explore the association between the blood glucose spectrum at

different phases with hepatic IR and β-cell dysfunction. HIRI was used to represent the hepatic IR levels, and we found that HIRI was significantly positively correlated with FBG and 30-minute post-load blood glucose, but there were no significant correlations between HIRI and 2-hour and 3-hour post-load blood glucose. ISSI2 was used to reflect islet β-cell function, and the study showed that ISSI2 was associated with FBG, 30-minute, 2-hour, and 3-hour post-load plasma glucose after adjusting for confounding factors such as age, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, and eGFR. The above results suggest that hepatic IR mainly affects fasting and early-phase postprandial blood glucose, whereas β-cell function affects blood glucose at all phases.

Insulin resistance can occur in many organs, including adipose tissue, liver, muscle and even the brain [12,13]. Adipose tissue is an insulin-sensitive organ that is critical for maintaining glucose and lipid metabolic homeostasis, which is the initiating factor of systemic metabolic disorders [14]. Patients with high BMI are more likely to have adipose tissue insulin resistance; thus, adipose tissue dysfunction and inflammation lead to the release of excessive free fatty acids and inflammatory factors, causing lipotoxicity and ectopic fat deposition in liver, which in turn leads to hepatic insulin resistance [15,16]. In addition, TG can be broken down into free fatty acids, and excess free fatty acids can be deposited in the liver, exacerbating hepatic insulin resistance. Therefore, patients with severe hepatic insulin resistance had higher BMI and TG levels. Liver is the major organ for gluconeogenesis and plays a crucial role in the balance of glucose [17]. The most important physiological significance of gluconeogenesis is to maintain a relatively constant blood glucose concentration during fasting or starvation conditions [18]. Insulin can inhibits gluconeogenesis, and the liver is the main target organ of insulin action [19]. Due to the stimulation of endogenous or exogenous signals, the insulin transduction signal pathway is abnormal, and insulin cannot play its normal physiological role. In this case, the liver will lead to increased gluconeogenesis and high FBG. Understanding the contribution of hepatic insulin resistance to fasting plasma glucose and early-phase postprandial hyperglycemia is of great importance, since patients with newly diagnosed T2DM are a special group, and the rational use of antidiabetic drugs is very important for the subsequent blood glucose control and prognosis of patients. Our previous study showed that patients with more severe hepatic insulin resistance had a better response to metformin treatment [20]. The results of this study suggest that patients with higher FBG and early postprandial plasma glucose may have greater clinical benefit from metformin.

We also observed that as hepatic insulin resistance increases, levels of AST and ALT progressively rose in patients. On the one hand, the abnormal metabolism of fatty acids produces toxic metabolites that can exert lipotoxic effects on hepatocytes, damaging cell membranes and causing enzyme leakage [21]. On the other hand, excessive hepatic lipid deposition leads to increased production of reactive oxygen species and inflammatory mediators, causing oxidative stress and further hepatocyte injury, which exacerbates the elevation of liver enzymes [22]. In our study, as hepatic insulin resistance increases, patients exhibit an elevated eGFR. Another obese non-diabetic cohort study shows that insulin resistance but not adiposity was related to eGFR [23]. Insulin resistance may be a key driver in the development of glomerular hyperfiltration [24]. Hepatic insulin resistance can lead to compensatory hyperinsulinemia, which can induce renal vasodilation, increase fractional sodium reabsorption, and activate the renin-angiotensin system, thereby leading to an increase in eGFR. Insulin also promotes the production of insulin-like growth factor, which has been shown to elevate renal plasma flow [25]. Moreover, hyperinsulinemia is associated with increased sympathetic nervous system activity and elevated levels of adipokines, contributing to chronic low-grade inflammation and endothelial dysfunction [26,27]. These factors can result in hemodynamic changes in renal blood flow, which may ultimately lead to glomerular hyperfiltration.

Unary and multiple linear regression showed that β-cell function affected not only FBG but also postprandial plasma glucose at all phases. In addition to insulin resistance, patients with T2DM often have islet β-cell dysfunction, which leads to decreased insulin secretion. In the stage of impaired glucose tolerance (IGT), islet β-cell function significantly decreases by 50% and further decreases in the process from the IGT stage to diabetes [28]. On the one hand, hepatic gluconeogenesis cannot be inhibited in the fasting state, causing an increase in FBG. Besides, the negative correlation between blood glucose and insulin secretion may be the result of glucose toxicity, as well as a cause of elevated blood glucose [29]. On the other hand, the first phase of insulin secretion disappears after a glucose load, leading to postprandial hyperglycemia. Hepatic IR and β-cell dysfunction together contribute to elevated FBG. For postprandial hyperglycemia, β-cell dysfunction seems to

contribute more than hepatic IR.

Patients with high HIRI combined with high ISSI2 have the highest BMI, accompanied by the lowest HbA1c levels. Obesity is associated with adipose tissue dysfunction, leading to excessive deposition of free fatty acids in the liver, which contributes to hepatic insulin resistance and increased FBG levels [30]. This finding suggests that newly diagnosed obese diabetic patients may exhibit a pronounced degree of hepatic insulin resistance while retaining partial β-cell function. Consequently, pancreatic β-cells in these individuals are still capable of mounting a compensatory response to hyperglycemia. Magkos et al. [31] reported that a 5% reduction in body weight significantly improves β-cell function and hepatic insulin sensitivity in obese individuals. In contrast, patients with the lowest BMI exhibited low hepatic insulin resistance combined with low β-cell function, indicating that newly diagnosed lean T2DM patients are characterized by early β-cell dysfunction in the setting of insulin resistance, which is reflected in higher HbA1c levels. Additionally, regardless of the degree of hepatic insulin resistance, patients with higher ISSI2 levels exhibit lower TG levels and reduced pancreatic lipotoxicity. TG, when excessively accumulated, are hydrolyzed into free fatty acids, which can deposit in the pancreas and liver, impairing β-cell function and exacerbating hepatic insulin resistance, ultimately contributing to the progression of T2DM in susceptible individuals [32,33].

T2DM is often a 'second-hit' phenomenon in which insulin resistance is accompanied by β-cell dysfunction, thereby preventing the compensatory upregulation of insulin secretion [34]. But there has been much debate about the relative importance of these two abnormalities. Many studies have shown that insulin resistance is a primary abnormality and that β-cell dysfunction is a late event caused by a prolonged increase in the secretory demand of β-cells due to insulin resistance [35, 36]. Conversely, it has also been suggested that β-cell dysfunction, manifested as reduced insulin release, is a prerequisite for the progression of normal glucose tolerance to hyperglycemia [37-39]. It is well established that when hyperglycemia develops in patients with T2DM, both insulin sensitivity and β-cell function are impaired.

In a study of pregnant women [40], results showed that hepatic IR was associated with early deterioration of β-cell function in the first year postpartum, and increased hepatic insulin sensitivity independently predicted decreased β-cell function. However, the relationship between hepatic IR and β-cell function in patients with newly diagnosed T2DM has not been studied. To clarify whether hepatic IR was related to β-cell function, we performed a correlation analysis, which showed an inverse correlation between insulin resistance and β-cell function. Hyperglycemia itself causes 'glucose toxicity,' manifested as the inhibition of β-cell function [29]. To exclude the influence of glucose status, partial correlation analysis was performed again, and the results showed that insulin resistance was negatively correlated with β-cell function within the same glucose levels. When insulin resistance develops, insulin sensitivity is reduced and β-cells secrete insulin in compensation to maintain normoglycemia [41]. Over time, the β-cells cannot maintain their high insulin secretion rate, and the relative decrease in insulin leads to IGT, which eventually develops into overt diabetes [41]. The results were consistent with the closed-loop hypothesis proposed by Bergman et al. [34] that T2DM is the result of a dysregulated closed-loop relationship between insulin resistance and impaired insulin secretion. On the basis of hepatic IR, the insulin signaling pathway is damaged, and insulin cannot play its normal physiological role, which leads to the reduction of the ability to promote glycogen synthesis and inhibit gluconeogenesis, resulting in glucose and lipid metabolism disorders, and eventually diabetes mellitus [42]. Therefore, it is not surprising that hepatic insulin resistance and β-cell function show an inverse relationship, which enriches the theoretical system of the pathogenesis of diabetes.

Our study is the first to assess the contributions of hepatic IR and β-cell function to fasting plasma glucose and postprandial plasma glucose at different phases. These results shed light on the contributions of hepatic IR and β-cell function to the pathogenesis of T2DM, which has guiding significance for the treatment of diabetes. For patients with high FBG, insulin sensitizers should be used as appropriate, especially our recent study has demonstrated that metformin is more effective in patients with more severe hepatic IR [20]. For patients with elevated postprandial blood glucose, insulin secretokines are particularly important. There are a few limitations to consider. This was a cross-sectional study, and it was unable to observe glucose profile changes with changes in hepatic insulin sensitivity and islet β-cell function in individuals as diabetes progresses. Therefore, subsequent cohort studies are needed to further evaluate the changes in hepatic insulin sensitivity and β-cell function during the development of diabetes. Additionally, the study only included Chinese patients, which may have a certain ethnic bias. Future studies involving different ethnic populations are needed to support our conclusions.

In summary, hepatic IR mainly contributed to FBG and early-phase postprandial plasma glucose, whereas β-cell dysfunction contributed to fasting and postprandial plasma glucose at each phase. Hepatic IR and β-cell dysfunction jointly contribute to the pathogenesis of T2DM.

## SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2024.0537.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## AUTHOR CONTRIBUTIONS

Conception or design: J.L., G.W.
Acquisition, analysis, or interpretation of data: M.Y., Y.W. (Ying Wang)
Drafting the work or revising: Y.W. (Ying Wei)
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**Supplementary Table 1.** The clinical characteristics of diabetic patients based on HIRI

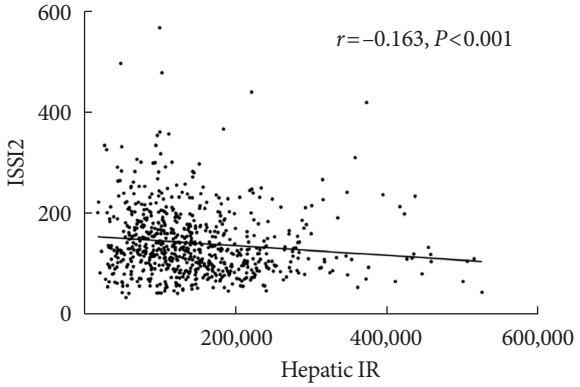
| Characteristic | HIRI | | | | *P* value | *P* for trend |
|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | | |
| Age, yr | 51.03±9.50 | 49.66±8.90 | 50.54±8.73 | 50.43±9.59 | 0.566 | 0.767 |
| BMI, kg/m$^2$ | 24.90±2.23 | 25.36±2.53 | 25.60±2.48 | 26.63±2.53 | <0.001 | <0.001 |
| SBP, mm Hg | 124.88±11.87 | 124.05±12.75 | 125.06±12.13 | 125.16±12.93 | 0.830 | 0.658 |
| DBP, mm Hg | 79.48±7.30 | 79.69±8.46 | 80.21±7.36 | 80.46±7.60 | 0.609 | 0.183 |
| AST, mmol/L | 22.47±7.66 | 23.09±8.23 | 23.99±8.80 | 26.13±10.08 | <0.001 | 0.005 |
| ALT, IU/L | 27.23±14.06 | 27.32±13.88 | 28.35±14.08 | 31.49±16.09 | 0.020 | <0.001 |
| eGFR, mL/min/1.73 m$^2$ | 99.86±30.74 | 107.53±34.54 | 115.98±91.98 | 119.49±38.03 | 0.004 | <0.001 |
| TC, mmol/L | 5.10 (4.31–5.86) | 5.09 (4.46–5.72) | 5.11 (4.40–6.01) | 5.44 (4.83–6.04) | 0.008 | 0.006 |
| TG, mmol/L | 1.70 (1.20–2.44) | 1.71 (1.26–2.65) | 1.99 (1.28–2.74) | 2.17 (1.50–3.02) | <0.001 | <0.001 |
| HDL-C, mmol/L | 1.22 (1.03–2.41) | 1.18 (1.04–1.42) | 1.21 (1.04–1.39) | 1.18 (1.01–1.40) | 0.839 | 0.695 |
| LDL-C, mmol/L | 3.15±1.00 | 3.00±0.85 | 3.01±0.92 | 3.10±0.88 | 0.347 | 0.620 |

Values are presented as mean±standard deviation or median (interquartile range).
HIRI, hepatic insulin resistance index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

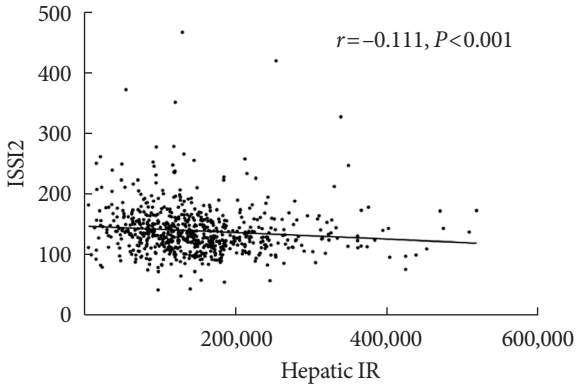
**Supplementary Table 2.** The clinical characteristics of diabetic patients based on HIRI combined with ISSI2

| HIRI | ISSI2 | Age, yr | BMI, kg/m$^2$ | SBP, mm Hg | DBP, mm Hg | AST, IU/L | ALT, IU/L | eGFR, mL/min/1.73 m$^2$ | TC, mmol/L | TG, mmol/L | HDL-C, mmol/L | LDL-C, mmol/L | HbA1c, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Q1 | Q1 | 50.76±10.05 | 24.00±2.46 | 122.67±12.17 | 79.27±7.24 | 20.23±6.84 | 24.60±11.93 | 98.29±36.54 | 5.37 (4.50–5.92) | 1.92 (1.20–2.66) | 1.20 (1.05–1.42) | 3.39±1.16 | 8.8 (8.0–9.6) |
| | Q4 | 50.37±9.16 | 25.38±2.12 | 126.67±11.91 | 79.93±6.75 | 24.12±8.72 | 29.20±16.64 | 100.50±29.68 | 5.10 (4.27–5.91) | 1.80 (1.22–2.36) | 1.25 (1.06–1.41) | 3.19±1.02 | 6.9 (6.3–7.5) |
| Q4 | Q1 | 48.18±9.37 | 26.45±2.42 | 122.11±2.42 | 79.66±8.32 | 24.50±8.10 | 29.84±15.10 | 126.29±42.08 | 5.35 (4.52–5.88) | 2.25 (1.50–3.30) | 1.18 (0.96–1.43) | 2.92±0.87 | 8.1 (7.4–8.6) |
| | Q4 | 52.35±8.60 | 26.83±2.57 | 125.84±12.89 | 81.26±7.29 | 26.81±10.98 | 31.93±17.29 | 111.22±23.91 | 5.48 (5.00–6.60) | 2.06 (1.53–2.75) | 1.10 (1.00–1.35) | 3.27±1.06 | 6.7 (6.1–6.9) |
| *P* value | | 0.216 | <0.001 | 0.165 | 0.727 | 0.024 | 0.269 | <0.001 | 0.315 | 0.062 | 0.589 | 0.146 | <0.001 |

Values are presented as mean±standard deviation or median (interquartile range).
HIRI, hepatic insulin resistance index; ISSI2, insulin secretion-sensitivity index-2; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin.




**Supplementary Fig. 1.** Spearman correlation analysis of insulin secretion-sensitivity index-2 (ISSI2) and hepatic insulin resistance (hepatic IR) index.




**Supplementary Fig. 2.** Partial correlation analysis of insulin secretion-sensitivity index-2 (ISSI2) and hepatic insulin resistance (hepatic IR) index.