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Association of point in range with β-cell function and insulin sensitivity of type 2 diabetes mellitus in cold areas

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Abstract

Background and Objective: Self-monitoring of blood glucose (SMBG) is crucial for achieving a glycemic target and upholding blood glucose stability, both of which are the primary purpose of anti-diabetic treatments. However, the association between time in range (TIR), as assessed by SMBG, and β-cell insulin secretion as well as insulin sensitivity remains unexplored. Therefore, this study aims to investigate the connections between TIR, derived from SMBG, and indices representing β-cell functionality and insulin sensitivity. The primary objective of this study was to elucidate the relationship between short-term glycemic control (measured as points in range [PIR]) and both β-cell function and insulin sensitivity. **Methods:** This cross-sectional study enrolled 472 hospitalized patients with type 2 diabetes mellitus (T2DM). To assess β-cell secretion capacity, we employed the insulin secretion-sensitivity index-2 (ISSI-2) and (ΔC-peptide$_{0–120}$/Δglucose$_{0–120}$) × Matsuda index, while insulin sensitivity was evaluated using the Matsuda index and HOMA-IR. Since SMBG offers glucose data at specific point-in-time, we substituted TIR with PIR. According to clinical guidelines, values falling within the range of 3.9–10 mmol were considered "in range, " and the corresponding percentage was calculated as PIR. **Results:** We observed significant associations between higher PIR quartiles and increased ISSI-2, (ΔC-peptide$_{0–120}$/Δglucose$_{0–120}$) × Matsuda index, Matsuda index (increased) and HOMA-IR (decreased) (all $P < 0.001$). PIR exhibited positive correlations with log ISSI-2 ($r = 0.361$, $P < 0.001$), log (ΔC-peptide$_{0–120}$/Δglucose$_{0–120}$) × Matsuda index ($r = 0.482$, $P < 0.001$), and log Matsuda index ($r = 0.178$, $P < 0.001$) and negative correlations with log HOMA-IR ($r = -0.288$, $P < 0.001$). Furthermore, PIR emerged as an independent risk factor for log ISSI-2, log (ΔC-peptide$_{0–120}$/Δglucose$_{0–120}$) × Matsuda index, log Matsuda index, and log HOMA-IR. **Conclusion:** PIR can serve as a valuable tool for assessing β-cell function and insulin sensitivity.

Keywords

time in range; points in range; self-monitoring of blood glucose; β-cell function; insulin sensitivity

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1 Introduction

Type 2 diabetes mellitus (T2DM) represents one of the most prevalent risk factors contributing to stroke and cardiovascular diseases. Strikingly, the prevalence of T2DM in high-latitude cold regions significantly surpasses that in low-latitude warmer areas. Consequently, it is imperative for these colder regions to promptly implement measures to curb this alarming trend and mitigate associated risk factors. The pathophysiology of T2DM is characterized by impaired β-cell secretory responses and decreased insulin sensitivity[1-2]. A previous study showed a progressive annual decline of approximately 6%–7% in β-cell insulin secretion, even in the presence of ongoing glucose-lowering medications[3]. Identifying factors linked to β-cell dysfunction and developing interventions to delay or prevent deterioration hold substantial significance. Intensive glycemic control plays a pivotal role in reducing the incidence and progression of vascular events associated with T2DM[3]. It also helps sustain β-cell function and improve insulin resistance[4-5]. Hence, the quest for cost-effective, precise, convenient, and

user-friendly parameters to evaluate long-term and short-term glycemic control is of paramount importance in clinical practice and daily diabetes self-management.

Glycated hemoglobin (HbA_1c) serves as a marker for assessing average glucose levels over the past three months, providing insight into long-term glycemic control, but it does not capture rapid changes day-to-day fluctuations in glucose levels[6]. It is important to note that HbA_1c measurements may be inaccurate in various situations, including hemoglobinopathies, anemia, iron deficiency, and pregnancy[7]. In contrast to HbA_1c, time in range (TIR), as determined by continuous glucose monitoring (CGM), offers a comprehensive view of intra- and inter-day glucose fluctuations. TIR is not only a critical metric for assessing glycemic control but also in evaluating the risk of diabetes-related complications[8]. Despite the consensus on the importance of TIR in managing blood sugar levels, the widespread use of CGM is hindered by issues of availability and affordability. On the other hand, Self-monitoring of blood glucose presents an attractive alternative; It is a relatively cost-effective and convenient tool that provides greater accuracy in estimating both short-term and long-term glycemic control[9]. Consequently, SMBG finds extensive use, especially in developing countries, including some undeveloped regions[10-11].

SMBG provides a solitary point of glucose measurement, but an adequate frequency of SMBG readings can create a continuous trend that effectively replaces the need for CGM[12]. However, in contrast to a single-point capillary glucose measurement, points in range (PIR) provides a more comprehensive view of blood glucose variability[13]. Moreover, PIR, as determined by SMBG, proves to be a more dependable metric than HbA_1c in various clinical conditions such as anemia and uremia[10]. It is worth noting that PIR is evaluated using capillary samples, which are known for their higher accuracy compared to the interstitial fluid used in CGM systems. Moreover, PIR stands out for its simplicity and intuitiveness when compared to other indices measuring glucose variations, such as the standard deviation of mean blood glucose (SDBG). Notably, there is evidence suggesting a correlation between oral blood glucose control, as estimated by CGM, and postprandial β-cell secretion in individuals with T2DM[14].

Due to the SMBG, we opted to utilize PIR rather than TIR in our study. Much like TIR, PIR proves to be a cost-effective, precise, and user-friendly indicator of glycemic control. However, its relationship with β-cell dysfunction and insulin insensitivity remains to be elucidated. In this cross-sectional study involving Chinese patients with T2DM, we investigated the connections between PIR, as measured through SMBG, and both β-cell glucose-reflection capacity and insulin sensitivity.

2 Methods

2.1 Study design and subjects

We enrolled a total of 472 adult patients diagnosed with T2DM between January 1, 2019, and December 31, 2020, from the Second Affiliated Hospital of Harbin Medical University, following the guidelines outlined in the 2017 Guidelines for the Prevention and Treatment of T2DM in China.

At the commencement of the study, participants ceased their use of antidiabetic medications, including metformin, sulfonylurea, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, acarbose, or glucagon-like peptide-1 agonists, for at least 72 h prior to the study. During this period, they exclusively relied on an insulin pump until the conclusion of an oral glucose tolerance test (OGTT). Exclusion criteria encompassed other diabetes types, acute complications of diabetes or concurrent infectious disease, hematologic or endocrinologic disorders, anemia, malignancies, corticosteroid usage, end-stage organ failure, or an aged below 18 years. Prior to enrollment, participants provided signed, written consent. The study complied with the Declaration of Helsinki and the Ethics Committee of No. 2 Affiliated Hospital of Harbin Medical University approved the study (No. 2022-096).

2.2 Clinical characteristics

All data was retrieved from the participants' electronic medical records, encompassing information such as age, gender, diabetes duration, history of smoking and drinking, family diabetes history, biochemical records, and anthropometric parameters. Blood pressure was measured twice using a sphygmomanometer after sitting for a 30-minute period of rest, and the results were subsequently averaged. Body mass index (BMI) was computed as kg/m^2. While hospitalized, a standardized dietary regimen was administered based on each patient's physical condition. Additionally, patients were instructed to maintain their customary physical exercises during their hospital stay, with the provision of snacks as needed, particularly in cases of hypoglycemia.

2.3 Biochemical measurements

Factors which might influence insulin secretion and sensitivity, including plasma glucose (PG), lipid profiles, liver enzymes, and renal function parameters, were assessed using established techniques applied to fasting blood samples. An electrochemiluminescence immunoassay was used to determine insulin and C-peptide concentrations, while high-performance liquid chromatography was used to measure HbA_1c levels. To

calculate the glomerular filtration rate (eGFR), we applied the creatinine-cystatin C equation[15].

Patients with fasting glucose levels ranging from 6 to 8 mmol/L, following an 8-hour fast, underwent a 75-gram, 50% OGTT, with plasma samples collected at 0, 30, 60, and 120 min, assuming the patient consumed the glucose within 5 min. The area under the curve (AUC) for each OGTT (AUCins and AUCgluc) was calculated using the trapezoidal rule. To assess dynamic pancreatic β-cell insulin secretion, we employed the ISSI-2 index, which is closely related to intravenous OGTT-derived indexes[16-18]. ISSI-2 is represented as follows: ISSI-2= (AUCins/AUCgluc) × Matsuda index[19-20]. The Matsuda index, as determined through OGTT, gauged peripheral insulin sensitivity and displayed a strong correlation with results from the hyperinsulinemic-euglycemic clamp test[19]. Meanwhile, HOMA-IR primarily reflected hepatic insulin sensitivity[20]. In addition, we utilized the (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index because a subgroup of our patients received insulin treatment, which could potentially affect insulin measurements[21].

2.4 SMBG data collection and analysis

We employed the Accu-Chek Inform II system to measure capillary blood glucose during levels during the patients' hospitalization. Each patient underwent a regimen of seven finger-prick tests, spanning no fewer than five consecutive days. This regimen included three tests before meals, three 2-h postprandial tests, and one test before bedtime. Before recording, all blood glucose measurements underwent verification by two nurses. In cases where a patient experienced hypoglycemia, the glucose test was consistently recorded. In this study, PIR was calculated as the percentage of the seven-point tests conducted during hospitalization that fell within the range of 3.9 to 10.0 mmol/L with each value used only once[22]. Our aim was to maintain pre-meal glucose levels between 4.0 to 6.0 mmol/L and 2-h post-prandial glucose levels between 8.0 to 9.0 mmol/L.

2.5 Statistical methods

Data analysis was performed using SAS 9.13 (SAS Institute Inc. Shanghai, China). To test the normality of data distribution, tests were applied, revealing some skewed variables that necessitated log-transformation. Continuous variables with abnormal distributions were presented as median with interquartile ranges (25th-75th quartiles) and compared using the Wilcoxon rank-sum test. Normally distributed variables were compared using ANOVA and *t*-tests. Categorical data were expressed as frequencies and percentages and comparisons were performed using the chi-square test. Correlations were evaluated through Pearson and Spearman correlation analysis. To explore relationships between PIR and conventional risk factors (age, sex, BMI, systolic blood pressure [SBP] and diastolic blood pressure [DBP], diabetes duration, eGFR, lipid profiles, HbA_1c, and log ISSI-2, log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index, log Matsuda index, and log HOMA-IR, multivariate linear regression analyses were employed. Statistical significance was defined as $P < 0.05$.

3 Results

3.1 Subject characteristics

Patients were categorized into quartiles based on their PIR as follows: Q1, PIR ≤ 51.5%; Q2, 51.5% < PIR ≤ 68.0%; Q3, 68.0% < PIR ≤ 80.0%; and Q4, PIR > 80.0%. Notably, the prevalence of extended diabetes duration and elevated HbA_1c levels exhibited a declining trend with higher PIR quartiles ($P < 0.001$), whereas levels of high-density lipoprotein cholesterol (HDL-C) displayed an increase ($P < 0.05$). Significant differences were observed in diabetes duration, HbA_1c, and HDL-C among the PIR quartiles (all $P < 0.05$). The PIR quartile Q4 encompassed both the lowest and highest levels of HDL-C. Conversely, age, gender distribution, BMI, SBP, DBP, smoking and drinking habits, family history of diabetes, eGFR, triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) demonstrated comparable distributions across the PIR groups (Table 1).

3.2 Differences in insulin secretion in the PIR quartiles

As illustrated in Fig. 1A, ISSI-2 levels exhibited a significant increase within the higher PIR quartiles, rising from 73.1 (53.3–102.1) in Q1 to 122.4 (92.7–159.5) in Q4 ($P < 0.001$). Given the equimolar secretion of insulin and C-peptide from the pancreas, we conducted a detailed analysis of (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda as an alternative measure of β-cell function. This analysis revealed a parallel ascending trend in ISSI-2 across the higher PIR quartiles ($P < 0.001$, Fig. 1C). Notably, log ISSI-2 levels experienced significant increases in Q2 and Q3 compared to Q1 ($P < 0.001$), with the highest level observed in Q4 in contrast to the other PIR quartiles ($P < 0.001$, Fig. 1B). Additionally, the highest log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index was recorded in Q4 ($P < 0.001$), while Q1 exhibited the lowest values ($P < 0.001$), with a notable distinction between Q2 and Q3 ($P < 0.05$, Fig. 1D).

The significant differences in PIR values for log ISSI-2 and log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index remained the same at all HbA_1c levels (all $P < 0.05$, Supplementary Table S1).

Table 1 Clinical characteristics of the participants according to PIR quartiles

Variables	Q1	Q2	Q3	Q4	*P*
Age (years)	53.0 (47.0-62.0)	55.0 (46.0-64.0)	55.0 (47.0-61.5)	53.0 (43.0-60.0)	0.395
Male (*n*, %)	69.0 (61.6)	67.0 (51.5)	65.0 (54.2)	56.0 (50.9)	0.345
BMI (kg/m^2)	25.0 (23.3-27.5)	25.4 (23.8-28.4)	25.5 (23.0-27.5)	26.1 (23.6-28.4)	0.203
Risk factors					
SBP (mmHg)	135.5 (125.5-149.0)	138.0 (125.0-151.0)	139.0 (124.0-150.0)	138.0 (124.0-153.0)	0.898
DBP (mmHg)	86.5 (78.0-95.5)	86.0 (79.0-93.0)	85.5 (79.0-97.0)	89.0 (82.0-95.0)	0.263
Current Smoking (*n*, %)	33.0 (29.5)	34.0 (26.2)	24.0 (20.0)	17.0 (15.5)	0.057
Current alcohol drinker (*n*, %)	20.0 (17.9)	13.0 (10.0)	17.0 (14.2)	11.0 (10.0)	0.221
Family history of diabetes (*n*, %)	21.0 (18.8)	27.0 (20.8)	16.0 (13.3)	18.0 (16.4)	0.451
Diabetes duration (years) (*n*, %)					
< 5 years	51.0 (45.5)	53.0 (40.8)	63.0 (52.5)	72.0 (65.4)	0.001
5-10 years	26.0 (23.2)	34.0 (26.1)	26.0 (21.7)	19.0 (17.3)	0.001
> 10 years	35.0 (31.3)	43.0 (33.1)	31.0 (25.8)	19.0 (17.3)	0.001
Laboratory data					
HbA_1c (%)	10.2 (9.1-11.1)	9.6 (8.2-10.7)	8.7 (7.8-10.7)	8.3 (7.1-9.6)	< 0.001
eGFR (mL/min)	94.0 (73.9-124.7)	96.4 (75.2-120.8)	101.8 (74.0-130.8)	104.6 (83.2-126.6)	0.270
TG (mmol/L)	2.07 (1.28-3.21)	1.78 (1.30-2.79)	1.76 (1.13-2.75)	1.67 (1.14-2.47)	0.089
TC (mmol/L)	4.98 (4.27-5.80)	4.69 (3.91-5.47)	4.84 (3.82-5.73)	5.04 (4.02-5.61)	0.204
HDL-C (mmol/L)	1.07 (0.92-1.26)	1.04 (0.90-1.19)	1.09 (0.90-1.27)	1.14 (1.01-1.33)	0.018
LDL-C (mmol/L)	3.03 (2.43-3.70)	2.85 (2.08-3.35)	2.65 (2.20-3.71)	2.95 (2.20-3.67)	0.216

Data are expressed as the median and interquartile range (25^{th}–75^{th}) for variables without a normal distribution. Categorical data are expressed as frequency and percentage. Between the four groups, the *P*-values were calculated using Wilcoxon rank sum test. BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA_1c: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; PIR: point in range; SBP: systolic blood pressure.

3.3 Differences in insulin sensitivity in the PIR quartiles

The Matsuda index exhibited a significant increase corresponding to PIR quartile ($P < 0.001$, Fig. 2A), while HOMA-IR showed a decrease ($P < 0.001$, Fig. 3A). Notably, the lowest log Matsuda index (Fig. 2B) and the highest log HOMA-IR values were observed in Q1 ($P < 0.001$), with a noticeable reduction in Q4 compared to Q2 ($P < 0.05$) (Fig. 3B). Interestingly, patients with varying PIR values displayed similar log Matsuda index and log HOMA-IR within the same HbA_1c group ($P < 0.001$, Supplementary Table S1).

3.4 The relationship between PIR and insulin secretion and sensitivity in the participants

Pearson correlation tests revealed a positive correlation between PIR and log ISSI-2 ($r = 0.361$, $P < 0.001$), log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index ($r = 0.361$, $P < 0.001$), as well as log Matsuda index ($r = 0.178$, $P < 0.001$). Conversely, PIR exhibited a negative correlation with log HOMA-IR ($r = -0.288$, $P < 0.001$, Fig. 4).

3.5 Univariate and multivariate linear regression models of β-cell function and insulin sensitivity associated with risk factors

In the univariate model, PIR, BMI (positively) and age, diabetes duration, HbA_1c, TC, and LDL-C (negatively) several factors exhibited associations with log ISSI-2 and log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index: PIR and BMI were positively correlated, while age, diabetes duration, HbA_1c, TC, and LDL-C showed negative correlations. Of note, eGFR was significantly associated with log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index but not with log ISSI-2. Moreover, log Matsuda index displayed associations with PIR (positive), HDL-C (positive) and BMI (negative), DBP (negative), HbA_1c (negative), SBP (negative), TG (negative), and TC (negative). Conversely, log HOMA-IR was associated with BMI (positive), HbA_1c (positive), LDL-C (positive), TG (positive), and TC (positive), while PIR (negative) and HDL-C (negative) displayed inverse associations (Supplementary Table S2).

Multivariate linear regression analysis revealed exhibited a

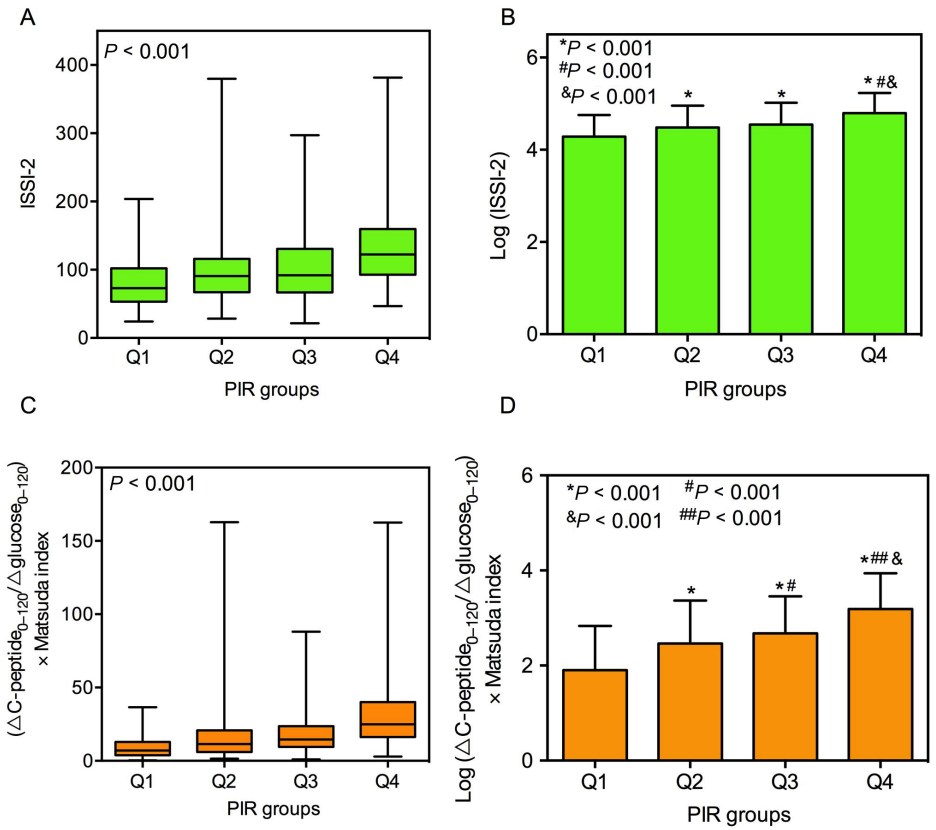

Fig. 1 Different levels of insulin secretion-sensitivity index-2 (ISSI-2), logISSI-2, (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index and log(ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index among patients with different point in range (PIR) quartiles. Comparisons of ISSI-2(A), logISSI-2(B), (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index (C) and log(ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index (D) among patients with different PIR quartiles (Q1-Q4). *P*-value for the significant difference among the groups was determined by Wilcoxon rank sum test (A, C), one-way ANCOVA (B, D). Q1: PIR ≤ 51.5%, Q2: 51.5% < PIR ≤ 68.0%, Q3: 68.0% < PIR ≤ 80.0%, Q4: PIR > 80.0%. Data are presented as the median and interquartile range (25^{th}–75^{th}) (A, C), mean ± SD (B, D). $^{*}P < 0.001$ *vs.* group Q1; $^{\#}P < 0.001$ *vs.* group Q2; $^{\&}P < 0.001$ *vs.* group Q3 in panel B; $^{*}P < 0.001$ *vs.* group Q1; $^{\#}P < 0.05$, $^{\#\#}P < 0.001$ *vs.* group Q2; $^{\&}P < 0.001$ *vs.* group Q3 in panel D.

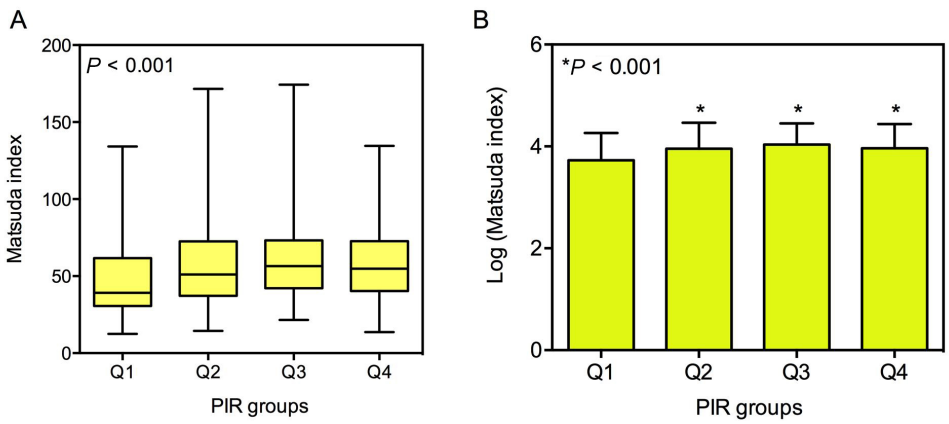

Fig. 2 Different levels of Matsuda index and log Matsuda index among patients with different PIR quartiles. Comparisons of Matsuda index(A) and log Matsuda index(B) among patients with different point in range (PIR) quartiles (Q1-Q4). *P*-value for the significant difference among the groups was determined by Wilcoxon rank sum test (A), one-way ANCOVA (B). Q1: PIR ≤ 51.5%, Q2: 51.5% < PIR ≤ 68.0%, Q3: 68.0% < PIR ≤ 80.0%, Q4: PIR > 80.0%. Data are presented as the median and interquartile range (25^{th}–75^{th}) (A), mean ± SD (B). $^{*}P < 0.001$ *vs.* group Q1.

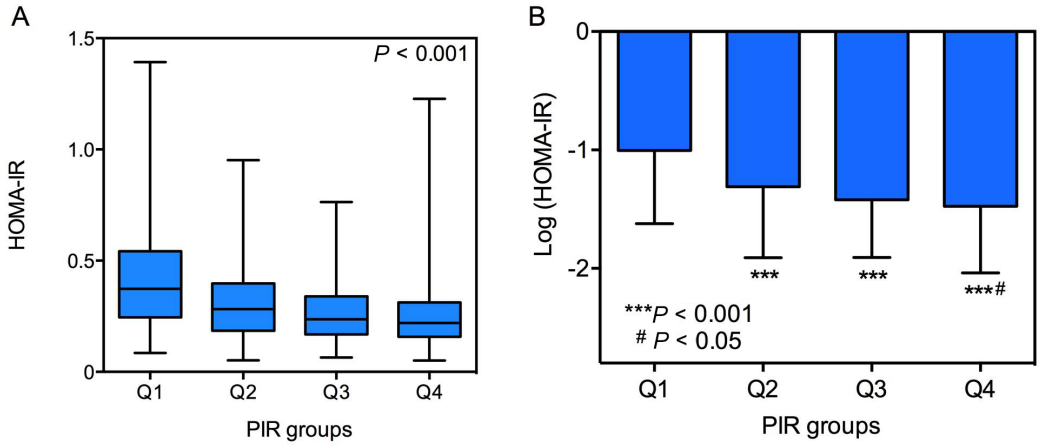

Fig. 3 Different levels of HOMA-IR and log HOMA of insulin resistance (HOMA-IR) among patients with different point in range (PIR) quartiles. Comparisons of HOMA-IR(A) and log HOMA-IR(B) among patients with different PIR quartiles (Q1-Q4). *P*-value for the significant difference among the groups was determined by Wilcoxon rank sum test(A), one-way ANCOVA(B). Q1: PIR ≤ 51.5%, Q2: 51.5% < PIR ≤ 68.0%, Q3: 68.0% < PIR ≤ 80.0%, Q4: PIR > 80.0%. Data are presented as the median and interquartile range (25^{th}–75^{th}) (A), mean ± SD (B). $^{***}P < 0.001$ *vs.* group Q1; $^{\#}P < 0.05$ *vs.* group Q2.

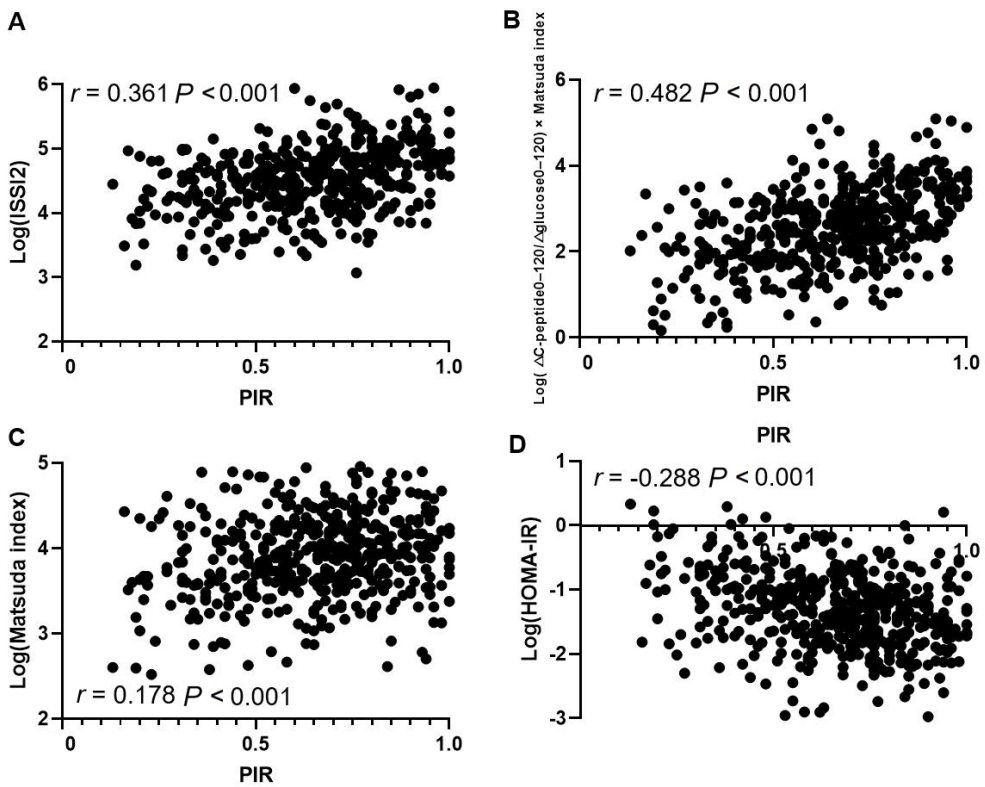

Fig. 4 The relationships of point in range (PIR) and log Insulin Secretion-Sensitivity Index-2 (ISSI-2) (A), log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index (B), log Matsuda index (C), and log HOMA-IR (D) in the participants. Pearson's correlation test was used to determine the relationship.

positive association with I that PIR exhibited a positive association with log ISSI-2 and log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index after adjustment for other variables, while HbA_1c and diabetes duration demonstrated negative associations after adjusting for other variables. PIR and HbA_1c exserted similar effects on log ISSI-2 and log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) ×

Matsuda index, with standardized regression coefficients of 0.243, -0.209 for log ISSI-2 and 0.307 and-0.329 for log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index, respectively. Furthermore, LDL-C exhibited a negative association with log ISSI-2, whereas eGFR displayed a positive association and TC had a negative association with log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index (Table 2). Specifically, TC was decreased, while log (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index was increased, with the other results remaining consistent (Table 2).

We conducted additional assessments of the association between the above mentioned variables insulin sensitivity (log Matsuda index, log HOMA-IR) and the risk factors, using both univariable and multivariate linear regression analyses. Following adjustments for other factors, PIR and HDL-C displayed positive associations, while male gender, BMI, TG, and LDL-C exhibited negative associations with log Matsuda index (Table 3). In terms of log HOMA-IR, we observed negative correlations with log HOMA-IR, PIR, and HDL-C, whereas male gender, BMI and TC displayed positive correlations (Table 4).

Table 2 Multiple linear regression models for logISSI-2 and log(ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index

Variables	β	standardized regression coefficient	*P*-value
For logISSI-2			
PIR (%)	0.110	0.243	< 0.001
Diabetes duration (years)	-0.120	-0.206	< 0.001
HbA_1c (%)	-0.054	-0.209	< 0.001
LDL-C (mmol/L)	-0.064	-0.125	0.001
For log(ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index			
PIR (%)	0.269	0.307	< 0.001
Diabetes duration (years)	-0.231	-0.206	< 0.001
HbA_1c (%)	-0.165	-0.329	< 0.001
eGFR (mL/min)	0.002	0.104	0.015
TC (mmol/L)	-0.059	-0.078	0.043

eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; ISSI-2: insulin secretion-sensitivity index-2; LDL-C: low-density lipoprotein cholesterol; PIR: point in range; TC: total cholesterol.

Table 3 Multiple linear regression models for log Matsuda index

Variables	β	standardized regression coefficient	*P*-value
PIR (%)	0.076	0.166	< 0.001
Male (%)	-0.156	-0.157	< 0.001
BMI (kg/m^2)	-0.035	-0.252	< 0.001
TG (mmol/L)	-0.032	-0.163	< 0.001
HDL-C (mmol/L)	0.214	0.119	0.011
LDL-C (mmol/L)	-0.049	-0.096	0.030

BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PIR: point in range; TG: triglyceride.

Table 4 Multiple linear regression models for log HOMA-IR

Variables	β	standardized regression coefficient	*P*-value
PIR (%)	-0.146	-0.269	< 0.001
Male (%)	0.107	0.089	0.039
BMI (kg/m^2)	0.036	0.215	< 0.001
TC (mmol/L)	0.079	0.169	< 0.001
HDL-C (mmol/L)	-0.357	-0.167	< 0.001

BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; HOMA-IR: HOMA of insulin resistance; PIR: point in range.

4 Discussion

This large-scale cross-sectional study investigated the effects of two distinct hypoglycemic drugs, insulin and metformin, in 472 T2DM patients, aiming to present a comprehensive understanding of the intricate interplay between glycemic control and β-cell dysfunction or insulin insensitivity. The principal discoveries encompassed four key insights: (1) β-cell functionality, as assessed by the logarithmic ISSI-2 and the logarithmic (ΔC-peptide$_{0-120}$/Δglucose$_{0-120}$) × Matsuda index, exhibited a notable decline within the lower quartiles of PIR; (2) Insulin sensitivity, as evaluated through the logarithmic Matsuda index and logarithmic HOMA-IR, exhibited a worsened state within these same lower PIR quartiles; (3) The duration of diabetes, HbA_1c levels, and the presence of dyslipidemia emerged as significant risk factors contributing to β-cell dysfunction. In contrast, factors such as gender, BMI, and the presence of dyslipidemia were identified as risk factors for insulin sensitivity; (4) Importantly, PIR was identified as an independent determinant associated with the decline in both β-cell functionality and insulin sensitivity. This study sheds light on the intricate web of factors influencing glycemic control in T2DM patients, highlighting the pivotal role of PIR as a key player in β-cell function and insulin sensitivity.

A prior study revealed an association between glycemic control, as assessed by CGM, and postprandial β-cell function[14]. Although CGM offers a more comprehensive daily monitoring of glycemic fluctuations than SMBG, SMBG remains a fundamental and universally recognized method for both self-care and clinical diabetes management, particularly in developing regions. This preference is attributed to its convenience, accuracy, and cost-effectiveness[23-24]. PIR represents a structured SMBG testing regimen that furnishes patients with detailed insights into the velocity and direction of their glycemic trends. Notably, it is more intuitive for patients when compared to other glycemic variability indices, which often involve complex algorithms. However, it is worth noting that PIR does not exhibit a significant correlation with HbA_1c. This disparity arises because HbA_1c reflects average blood glucose levels over the past 3–4 months, whereas PIR is

adept at identifying the nuances of inter- and intra-day glycemic fluctuations, even during hospitalization. PIR serves as a valuable tool for evaluating both short- and long-term glycemic control, a crucial aspect for tailoring treatment strategies and promoting positive lifestyle changes[24]. PIR values, therefore, act as surrogate markers for glucose control related, offering insights into islet β-cell function and insulin sensitivity, even when HbA_1c levels are comparable. Consequently, the use of PIR proves to be an effective approach for evaluating glycemic control, especially in situations where neither the HbA_1c assay nor CGM are readily available or affordable.

β-cell dysfunction and glycemic control exhibit a close interrelationship[25]. Our findings align, in part, with previously published results, that have underscored the hyperbolic association between glycemic variability indices and β-cell function[26]. Given the dynamic nature of the pancreatic β-cell responses, we opted for ISSI-2 as our metric for assessing β-cell function. ISSI-2 stands out as a dynamic, more precise, and comprehensive index compared to the static and basal index, HOMA-β. The utilization of a static index is deemed less than ideal when evaluating β-cell secretion. Indeed, as revealed in a prior observational study[27], short-term fluctuations in glucose levels can lead to a decline in β-cell capacity. Furthermore, sustained exposure of β-cells to hyperglycemia gradually erodes their responsiveness, resulting in decreased insulin production.

Conversely, impaired β-cell function can instigate clinically meaningful shifts in glycemic levels, manifesting as pronounced fluctuations in glucose levels and sustained hyperglycemia[28]. In our study, we observed that patients with lower PIR quartiles had significantly decreased β-cell function. Lower PIR values signify an elevated risk of hypoglycemia, reflecting diminished responsiveness of β-cells to abnormal glucose levels, whether excessively low or high[28]. Our study underscores the importance of maintaining tight and stable glycemic control as a potential necessity to safeguard endogenous β-cell insulin secretion. Moreover, our research highlights the utility of PIR, as assessed by SMBG, as a sensitive parameter for monitoring fluctuations in β-cell insulin secretion among individuals with T2DM. This underscores its potential as an invaluable tool for evaluating glucose control in this patient population.

Numerous mechanisms may underlie the relationship between deteriorated β-cell function and lower PIR quartiles. To begin, a prior study reported a significant reduction in the expression of several transcription factors (Foxo1, PDX1, NKX6.1, and MAFA) within β-cells in the context of severe chronic hyperglycemia or glucose fluctuation[29-30]. This decrease in transcription factor expression was shown to trigger β-cell dedifferentiation, resulting in detrimental alterations to pancreatic β-cells[31]. Furthermore, another study reported that rigorously normalizing blood glucose levels in individuals with T2DM could rescue "exhausted" β-cells, prompting a progress of dedifferentiation that subsequently led to the re-differentiate of cells into mature β-cells[32]. Additionally, a previous study has unveiled that glucose fluctuations and sustained hyperglycemia can elevate the levels of reactive oxygen species (ROS), instigating β-cell apoptosis and pyroptosis, ultimately culminating in a reduction in β-cell mass[33]. Moreover, there exists evidence suggesting that blood glucose fluctuations exert a more pronounced impact on oxidative stress than chronic hyperglycemia[34], although the precise underlying mechanisms remain incompletely elucidated.

Understanding β-cell function necessitates a concurrent consideration of insulin sensitivity, as these two facets of glucose regulation are inherently intertwined[35]. To illustrate, conditions like obesity characterized by insulin resistance, can culminate in hyperinsulinemia, primarily driven by the increased workload on β-cells rather than their optimal function. In individuals with pre-diabetes, decreased insulin sensitivity directly contributes to glycemic disturbances[36]. Furthermore, in the context of T2DM, β-cell dysfunction and insulin resistance act synergistically to impair glycemic control[36]. Our current study underscores that lower PIR quartile values are associated with heightened insulin resistance. Prior research has also demonstrated that hyperglycemia escalates oxidative stress and exacerbates insulin sensitivity[37]. Additionally, a noteworthy finding from our study suggests that early and intensive glycemic control can preserve β-cell secretion and ameliorate insulin insensitivity in individuals with T2DM[38]. This body of evidence indicates that maintaining tight glucose control not only upholds insulin sensitivity but also mitigates the burden on dysfunctional β-cells, thereby preventing their overuse.

Upon adjusting for various potential risk factors, our analysis revealed a clear association between lower PIR and compromised β-cell secretion as well as diminished insulin sensitivity. Intensified glycemic control plays a pivotal role in diminishing the detrimental effects of glucotoxicity and lipotoxicity, indirectly preserving β-cell function, and fostering improvements in insulin sensitivity. In this context, we posit that PIR serves as a reliable indicator of alterations in both β-cell insulin secretion and insulin sensitivity. The maintenance of stable glucose levels may yield further advantages in terms of averting complications associated with diabetes. Consequently, it becomes evident that an array of factors contributes to β-cell dysfunction and reduced insulin sensitivity, with elevated blood sugar levels representing just the tip of the iceberg. Nevertheless, intensive and stable glycemic control remains a universal benefit for every patient.

Our present study has illuminated the significant impact of

dyslipidemia on β-cell secretion function and the exacerbation of insulin resistance. Previous research has consistently demonstrated the role of lipotoxicity in precipitating both β-cell dysfunction and insulin insensitivity[39]. It is well-established that individuals with dyslipidemia often exhibit insulin resistance and a predictable decline in islet β-cell function[39]. Furthermore, independent investigations have highlighted that baseline HDL-C levels serve as a valuable predictor of the progressive decline in β-cell function during follow-up periods[40]. Experimental studies have further elucidated that the accumulation of cholesterol can impair insulin secretion and induce β-cell apoptosis[41]. Elevated circulating triglyceride levels have been linked to β-cell dysfunction and the onset of T2DM in high-risk populations. Interventions aimed at reducing circulating triglyceride levels have shown promise in restoring insulin secretion[42]. However, it is important to tread carefully in interpreting these associations, given that a significant proportion of T2DM patients are prescribed statins. Notably, an observational study has suggested that statins use may potentially lead to insulin resistance and the development of[43]. Additionally, our study has brought to light a notable gender disparity, with insulin resistance being more pronounced in men. This observation underscores the potential relationship between the prevalence of metabolic diseases and the gender of the patients[44].

This study has some limitations. Firstly, it is essential to recognize that this research is an observational cross-sectional study, making it impossible to establish cause-and-effect relationships definitively. Longitudinal studies would undoubtedly offer a more comprehensive understanding of the dynamics at play. Secondly, the study's participants were undergoing treatment with two different hypoglycemic drugs, and due to ethical constraints, we could not request patients to discontinue these medications solely for research purposes[45]. Consequently, we relied on C-peptide measurements to mitigate the potential influence of different glucose-lowering medications on the β-cell function assay[46]. Thirdly, it is important to acknowledge that various racial and ethnic groups may exhibit divergent insulin sensitivity and β-cell secretory responses[47], thereby limiting the generalizability of our findings to other populations. Fourthly, while we did not use the hyperglycemic clamp method for assessing β-cell function, as it represents the gold standard, this approach is often impractical for clinical use due to its resource-intensive and complex nature. Nonetheless, our use of OGTT methodology for assessing insulin sensitivity and β-cell function has been shown to strongly correlates with the gold standard methods. Moreover, the inclusion of a large sample size likely mitigated the increased variability in β-cell function measures associated with OGTT. Lastly, we did not directly compare SMBG with CGM since CGM is often financially prohibitive for patients and clinical departments. However, it is worth noting that a study employing both methods has reported similar glucose profiles[12], with point testing, such as SMBG, potentially offering comparable accuracy to CGM.

5 Conclusions

The study cohort, originating from a cold region of China, has provided valuable insights into the utility of PIR as a straightforward, intuitive, convenient, and cost-effective glycemic control index, relevant to both patients and clinicians. This index's association with β-cell function and insulin sensitivity in T2DM, independent of other risk factors and traditional parameters, underscores its significance as a clinical indicator for monitoring glucose control. To further enrich our understanding, future studies should aim to retrieve medication data and compare the clinical responses to hypoglycemic treatments across various PIR categories. This study implies that in clod, less developed regions and among economically disadvantaged patients, PIR can serve as a valuable tool for assessing β-cell function and insulin sensitivity.

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Author contributions

Ni Y N: conceptualization, data curation, writing- original draft, and writing- review& editing; Liu D: data curation, and formal analysis; Zhang X N: data curation; Qiao H: investigation, supervision, validation, and writing- review& editing.

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Conflict of interest

All authors have no competing interests.

Date availability statement

All data in this study can be obtained from the corresponding author, on request.

Ethical approval

The study complied with the Declaration of Helsinki and the Ethics Committee of No. 2 Affiliated Hospital of Harbin Medical University approved the study (No.2022-096).

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