Association of Time in Range with Cognitive Impairment in Type 2 Diabetic Patients

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Research Article

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Abstract

OBJECTIVE

This study investigated the association of Time In Range (TIR) obtained from Blood Glucose Monitoring (BGM) with Cognitive Impairment (CI) inpatients with Type 2 Diabetes Mellitus (T2DM) and further explored whether a TIR goal for T2DM in adults with > 70% possess a protective effect on cognitive function.

RESEARCH DESIGN AND METHODS

A total of 274 inpatients with T2DM aged 40–64 years, who underwent seven-point BGM (120 mins pre and post meals and at bedtime) were recruited in this cross-sectional study. TIR was defined as the percentage of blood glucose within the target range of 3.9-10.0mmol/L. Subjects were divided into Normal Cognitive Function (NCF) (n = 160) and CI (n = 114) groups according to the results of the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). The association of TIR and other glycemic metrics, calculated from seven-point BGM data, with cognitive dysfunction was analyzed.

RESULTS

The prevalence of CI was 41.6% in patients with T2DM (median age 58 years). TIR was lower in CI group than in NCF group (28.6% vs. 42.9%, P = 0.004). The prevalence of CI decreased with ascending tertiles of TIR (p for trend < 0.05). Binary logistic regression analysis showed a significant association between TIR and CI (odds ratio [OR] = 0.84, p < 0.001) after adjusting for confounders (age, education, marital status, age at Diabetes Mellitus (DM) onset, cerebrovascular disease). Further adjustment of Standard Deviation (SD)(OR = 0.84, p = 0.001) or Coefficient of Variation (CV)(OR = 0.83, p < 0.001), TIR was still associated with CI. While a TIR goal of > 70% probably possessed independent protective effect on cognitive function (OR = 0.25, p = 0.001) after controlling for confounders above.

CONCLUSIONS

TIR obtained from BGM was related to CI in T2DM patients and a TIR goal of > 70% probably possessed a protective effect on cognitive function for T2DM adults.

1. Introduction

Cognitive Impairment (CI) is one of the main complications of DM. It is a cognitive state between normal brain aging and dementia and is mainly characterized by the decline of cognitive abilities in memory, language, execution, attention and other cognitive domains[1]. Prior studies have shown that diabetes patients, especially those of middle-aged, have higher risk of cognitive decline than those without diabetes[2, 3]. The detection of cognitive dysfunction is important in diabetes patients, because diabetic management and cognition are bidirectional - cognitive dysfunction negatively impacts diabetes management, diabetes...
exacerbates cognitive dysfunction when inadequately managed[4]. Hemoglobin A1c (HbA1c) and Time In Range (TIR) are two important indicators in current blood glucose control. Most previous studies have focused on the effect of HbA1c, a measure of average blood glucose level on cognitive function, while little attention has been paid to TIR, which refers to the time an individual spends within their target glucose range (usually 3.9–10.0 mmol/L). However, persistent hyperglycemia[5–8]and severe hypoglycemia[9–12]in patients with diabetes could both cause progressive damage to the brain, affect cognitive function and contribute to the occurrence of CI and dementia. Therefore, the purpose of this study was to investigate the association between TIR and CI among patients with Type 2 Diabetes Mellitus (T2DM).

Currently, HbA1c is not only recognized as the gold standard for assessing glycemic management, but also a predictor of long-term diabetic complications[13, 14]. In previous studies, HbA1c has been linked to diabetic CI [2, 15, 16]. Higher HbA1c was associated with higher incidence of dementia in diabetes, while poor glycemic control was associated with worse cognitive outcomes[5]. However, HbA1c cannot provide information of hypoglycemia. Daily patterns of glycemia or glycemic variability may be relevant for cognitive function. Prior studies have shown that glucose fluctuation and CI are significantly correlated[17, 18]. Thus, we should pay more attention to the association between risk factors correlated to blood glucose fluctuations and cognitive dysfunction.

TIR can be used to determine whether the frequency and duration of hypoglycemia and hyperglycemia are improving over time. As an important metric to classify glycemic management[19], TIR can be calculated by BGM or Continuous Glucose Monitoring (CGM)[20]. TIR is correlated well with HbA1c in most studies[21–26], with a TIR of 70% aligning with an HbA1c of around 7%[26, 27]. While HbA1c remains the primary predictor, there is suggestive evidence from several recent studies showing correlations of TIR with diabetes complications. A cross-sectional study showed TIR assessed by CGM was associated with varying degrees of diabetes retinopathy in T2DM[28]. Another analysis of the 7-point BGM data from the Diabetes Control and Complications Trial (DCCT) indicated that reduced TIR was associated with risk of development of retinopathy and micro-albuminuria in Type 1 Diabetes Mellitus (T1DM)[29]. Other studies have also found TIR to be related with Diabetic Peripheral Neuropathy (DPN)[30], diabetic foot[31, 32]and carotid intima-thickness[33]. However, no study on TIR and CI has been measured thus far. Based on this, the purpose of the current study was to investigate whether TIR obtained from BGM was associated with CI in patients with T2DM, and further to explore whether a TIR goal of > 70% for T2DM adults possessed a protective effect on cognitive function.

2. Research Design and Methods

2.1 Inclusion and Exclusion Criteria

A total of 274 inpatients with T2DM were consecutively recruited at the Department of Endocrinology and Metabolism of the Tianjin Union Medical Center from July 2018 to September 2021. T2DM was diagnosed according to the 2013 American Diabetes Association criteria[34]. Inclusion criterion: (1) Age 40–64 years, presence of T2DM; (2) Capability to complete neuropsychological tests independently; (3) Seven-point BGM (at least 6 points included) completed within 72 hours of admission. Exclusion criterion: (1) Inability to
complete neuropsychological tests due to communication difficulties, physical disability, severe limitation of movement, severe vision, hearing, reading, language impairment or any other reasons (2) such as, Anemia (hemoglobin[Hb] < 90g/L), cachexia, liver insufficiency (ALanine Transaminase [ALT] ≥ 120U/L), renal insufficiency (creatinine[Cr] ≥ 265umol/L), severe cardiopulmonary insufficiency, thyroid dysfunction or severe infection (3) Parkinson's disease, epilepsy, brain trauma, encephalitis, brain tumor, schizophrenia, severe depression, diagnosed dementia, alcohol or drug addiction and long-term use of drugs affecting cognitive function. The study protocol was approved by the Medical Ethics Committee of Tianjin Union Medical Center in accordance with the principles of the Declaration of Helsinki. Participants were informed about the study objectives and examination procedures in detailed and were asked to sign an informed consent form before participating in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

2.2 Clinical and Biochemical Data

General clinical data of patients were collected, including gender, age, nationality, marital status, education level, sedentary lifestyle, diabetic diet control, age at DM onset, use anti diabetes agents (insulin, insulin secretagogues), diabetic microangiopathy, CerebroVascular Disease (CVD, including hemorrhagic and/or ischemic strokes) and hypertension (defined as a blood pressure ≥ 140/90mmHg or the use of antihypertensive medications). In addition, we collected data on diabetic microangiopathy, which includes diabetic nephropathy and/or diabetic retinopathy. After 10–12 hours of overnight fasting, venous blood was drawn in the early morning and samples were analyzed by the central laboratory within the hospital for the following indicators: White Blood Cell (WBC) count, neutrophil count, lymphocyte count, Red Blood Cell (RBC) count, Hb, ALT, Cr, TriGlyceride (TG), Total Cholesterol (TC), High-Density Lipoprotein Cholesterol (HDL-c), Low-Density Lipoprotein Cholesterol (LDL-c), Thyroid Stimulating Hormone (TSH) and HbA1c.

2.3 Glycemic Metrics

Subjects performed seven-point (120-min before and after meals and at bedtime) fingerstick capillary glucose monitoring with the Glupadblood glucose meter (GlupadPlus878; Sinomedisite, Beijing, China) during a 24-hour period within 72 hours of admission. TIR was computed by calculating the percentage of the seven-point profile samples that were 3.9-10.0mmol/L. In addition, the following glucose metrics were similarly computed. Time above Target Glucose Range (TAR) was assessed as the percentage of the seven-point profile samples that were > 10.0mmol/L. Glycemic Variability (GV) metrics included Standard Deviation (SD) and Coefficient of Variation (CV). SD was equal to the standard deviation of the seven-point profile samples. CV was obtained by dividing the SD by the arithmetic mean of the seven-point profile samples. All participants were required to maintain their original therapy regimen and original diet regimen during BGM period.

2.4 Screening Evaluation for Cognitive Impairment

Several feasible scales were available to screen for CI, such as the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). MMSE was widely used to screen for dementia. The score was bounded by 23/24 (score considered “positive” / “negative”) for dementia. MoCA was a valid screening
method for Mild Cognitive Impairment (MCI). The score was bounded by 25/26 for MCI. If the subjects had less than 12 years of education, 1 point was added to the total MoCA score. The sensitivity of MoCA for MCI screening was higher than MMSE, while the specificity of MMSE for dementia diagnosis was better. So we used neuropsychological scales above to screen for CI in the present study. The grouping situation of this study was as follows: NCF group: MMSE \( \geq 24 \) and MoCA \( \geq 26 \), CI group: MMSE \( \geq 24 \) and MOCA < 26 (Fig. 1).

### 2.5 Statistical Analysis

Mean \( \pm \) SD or the median with InterQuartile Range (IQR) \([M (P25, P75)]\) were used to present continuous variables, while categorical variables were presented as numbers (percentages). Tests for significance were conducted using Student’s t-test or non-parametric Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. The association between TIR, TAR and HbA1c was ascertained by using the Spearman correlation coefficient. Binary logistic regression analysis was used to evaluate the independent association of TIR with CI and whether a TIR goal of > 70% for T2DM adults possessed a protective effect on cognitive function. All statistical analyses were performed with SPSS software (version 26.0; IBM, Armonk, New York, USA). Significant differences were observed when \( p < 0.05 \) using a two-tailed test.

### 3. RESULTS

#### 3.1 Characteristics of the Study Subjects

Of the 274 participants, 114 were screened for CI, resulting in an overall prevalence of 41.6%. The characteristics of the participants are shown in Table 1. Compared with individuals in the NCF group, the proportion of participants with CVD (31.0% vs. 11.9%) was significantly higher in the CI group, while the education years (9.0 vs. 12.0) and the proportion of participants who were married (84.2% vs. 96.9%) were significantly lower in the CI group (Table 1).
<table>
<thead>
<tr>
<th>Variables</th>
<th>All subjects (n = 274)</th>
<th>CI (n = 114)</th>
<th>NCF (n = 160)</th>
<th>F/Z/χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>124 (45.3%)</td>
<td>53 (46.5%)</td>
<td>71 (44.4%)</td>
<td>0.120</td>
<td>0.729</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.0 (54.0,62.0)</td>
<td>58.0 (55.0,62.0)</td>
<td>57.0 (54.0,61.0)</td>
<td>-1.686</td>
<td>0.092</td>
</tr>
<tr>
<td>40–44(years)</td>
<td>8 (2.9%)</td>
<td>1 (0.9%)</td>
<td>7 (4.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–59(years)</td>
<td>150 (54.7%)</td>
<td>58 (50.9%)</td>
<td>92 (57.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–64(years)</td>
<td>116 (42.3%)</td>
<td>55 (48.2%)</td>
<td>61 (38.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education(years)</td>
<td>12.0 (9.0,12.0)</td>
<td>9.0 (9.0,12.0)</td>
<td>12.0 (9.0,12.0)</td>
<td>-2.469</td>
<td>0.014</td>
</tr>
<tr>
<td>Age at DM onset (years)</td>
<td>52.0 (45.0,57.0)</td>
<td>53.0 (46.0,57.5)</td>
<td>50.5 (44.0,56.0)</td>
<td>-1.179</td>
<td>0.238</td>
</tr>
<tr>
<td>Ethnic Han</td>
<td>244 (89.1%)</td>
<td>104 (91.2%)</td>
<td>140 (87.5%)</td>
<td>0.949</td>
<td>0.330</td>
</tr>
<tr>
<td>Married</td>
<td>251 (91.6%)</td>
<td>96 (84.2%)</td>
<td>155 (96.9%)</td>
<td>13.885</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>66 (24.2%)</td>
<td>25 (21.9%)</td>
<td>41 (25.8%)</td>
<td>0.539</td>
<td>0.463</td>
</tr>
<tr>
<td>diabetic dietary control</td>
<td>163 (59.7%)</td>
<td>64 (56.1%)</td>
<td>99 (62.3%)</td>
<td>1.035</td>
<td>0.309</td>
</tr>
<tr>
<td>Use antidiabetic agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin</td>
<td>135 (49.3%)</td>
<td>60 (52.6%)</td>
<td>75 (46.9%)</td>
<td>0.883</td>
<td>0.347</td>
</tr>
<tr>
<td>insulin secretagogues</td>
<td>121 (44.2%)</td>
<td>51 (44.7%)</td>
<td>70 (43.8%)</td>
<td>0.026</td>
<td>0.871</td>
</tr>
<tr>
<td>Diabetic microangiopathy</td>
<td>126 (46.2%)</td>
<td>56 (49.6%)</td>
<td>70 (43.8%)</td>
<td>6.182</td>
<td>0.103</td>
</tr>
<tr>
<td>CVD</td>
<td>54 (19.8%)</td>
<td>35 (31.0%)</td>
<td>19 (11.9%)</td>
<td>15.224</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>173 (63.4%)</td>
<td>71 (62.8%)</td>
<td>102 (63.7%)</td>
<td>0.688</td>
<td>0.876</td>
</tr>
<tr>
<td>WBC(10⁹/L)</td>
<td>5.9 (5.1, 7.2)</td>
<td>5.8 (5.1, 7.2)</td>
<td>5.9 (5.1, 7.1)</td>
<td>-0.236</td>
<td>0.813</td>
</tr>
<tr>
<td>NLR</td>
<td>1.7 (1.3, 2.2)</td>
<td>1.6 (1.3, 2.1)</td>
<td>1.7 (1.4, 2.2)</td>
<td>-0.820</td>
<td>0.412</td>
</tr>
<tr>
<td>RBC(10¹²/L)</td>
<td>4.5 (4.2, 4.8)</td>
<td>4.5 (4.1, 4.8)</td>
<td>4.5 (4.2, 4.8)</td>
<td>-0.116</td>
<td>0.908</td>
</tr>
<tr>
<td>Hb(g/L)</td>
<td>135.9 ± 14.9</td>
<td>136.3 ± 15.1</td>
<td>135.7 ± 14.8</td>
<td>0.485</td>
<td>0.753</td>
</tr>
</tbody>
</table>

The measurement data are shown as mean ± standard deviation (SD) or median and interquartile range [P25, P75], depending on the normality of data distribution. Categorical data are presented as the number of cases (percentage) [n (%)]. P < 0.05 was regarded as a significant difference.

CI, cognitive impairment; NCF, normal cognitive function; CVD, cerebrovascular disease; WBC, white blood cell count; NLR, neutrophil count to lymphocyte ratio; RBC, red blood cell count; Hb, hemoglobin; ALT, alanine aminotransferase; Cr, serum creatinine; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TSH, thyroid stimulating hormone.
<table>
<thead>
<tr>
<th>Variables</th>
<th>All subjects (n = 274)</th>
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<th>F/Z/χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT(U/L)</td>
<td>20.9 (14.2, 34.2)</td>
<td>31.4 (18.1, 53.6)</td>
<td>34.3 (21.8, 52.9)</td>
<td>-1.338</td>
<td>0.181</td>
</tr>
<tr>
<td>Cr(µmol/L)</td>
<td>55.0 (46.8, 63.0)</td>
<td>63.0 (56.0, 67.7)</td>
<td>64.0 (53.0, 73.7)</td>
<td>-0.919</td>
<td>0.358</td>
</tr>
<tr>
<td>TC(mmol/L)</td>
<td>5.0 (4.3, 5.6)</td>
<td>5.6 (5.0, 6.4)</td>
<td>5.7 (5.0, 6.5)</td>
<td>-0.524</td>
<td>0.600</td>
</tr>
<tr>
<td>TG(mmol/L)</td>
<td>1.7 (1.2, 2.48)</td>
<td>2.6 (1.6, 4.5)</td>
<td>2.5 (1.7, 4.5)</td>
<td>-0.059</td>
<td>0.953</td>
</tr>
<tr>
<td>LDL-c(mmol/L)</td>
<td>2.8 (2.5, 3.4)</td>
<td>3.4 (2.9, 3.9)</td>
<td>3.43 (2.9, 4.0)</td>
<td>-0.162</td>
<td>0.871</td>
</tr>
<tr>
<td>HDL-c(mmol/L)</td>
<td>1.2 (1.1, 1.4)</td>
<td>1.4 (1.2, 1.6)</td>
<td>1.4 (1.2, 1.6)</td>
<td>-0.799</td>
<td>0.424</td>
</tr>
<tr>
<td>TSH(µIU/mL)</td>
<td>2.8 (1.9, 4.4)</td>
<td>2.8 (1.8, 4.5)</td>
<td>2.8 (2.0, 4.2)</td>
<td>-0.203</td>
<td>0.839</td>
</tr>
</tbody>
</table>

The measurement data are shown as mean ± standard deviation (SD) or median and interquartile range [P25, P75], depending on the normality of data distribution. Categorical data are presented as the number of cases (percentage) [n (%)]. P < 0.05 was regarded as a significant difference.

CI, cognitive impairment; NCF, normal cognitive function; CVD, cerebrovascular disease; WBC, white blood cell count; NLR, neutrophil count to lymphocyte ratio; RBC, red blood cell count; Hb, hemoglobin; ALT, alanine aminotransferase; Cr, serum creatinine; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TSH, thyroid stimulating hormone.

### 3.2 Comparison of TIR and Other Glycemic Metrics Between Different Cognitive Status

Compared with the NCF group, TIR was significantly lower and TAR was higher in the CI group (Table 2).

There were no significant differences between the two groups in HbA1c, which reflects the average three-month glucose level and the GV measures including SD and CV. According to recommendations of the international consensus established by Advanced Technologies & Treatments for Diabetes (ATTD), a goal for non-pregnant T2DM adults was time in range (TIR) of > 70%[19]. Patients with TIR > 70% in the NCF group were significantly higher than those in the CI group (20.6% vs. 9.6%) (Table 2).
Table 2  
Comparison of TIR and Other Glycemic Metrics Between Different Cognitive Status

<table>
<thead>
<tr>
<th>Variables</th>
<th>All subjects (n = 274)</th>
<th>CI (n = 114)</th>
<th>NCF (n = 160)</th>
<th>F/Z/χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIR(%)</td>
<td>33.3 (14.3, 57.1)</td>
<td>28.6 (14.3, 50.0)</td>
<td>42.9 (14.3, 66.7)</td>
<td>-2.849</td>
<td>0.004</td>
</tr>
<tr>
<td>TAR(%)</td>
<td>66.7 (42.9, 85.7)</td>
<td>71.4 (48.2, 85.7)</td>
<td>57.1 (33.3, 85.1)</td>
<td>-2.641</td>
<td>0.008</td>
</tr>
<tr>
<td>SD(mmol/L)</td>
<td>2.83 (2.10, 3.63)</td>
<td>2.94 (2.14, 3.73)</td>
<td>2.80 (2.08, 3.59)</td>
<td>-1.285</td>
<td>0.199</td>
</tr>
<tr>
<td>CV(%)</td>
<td>23.1 (18.7, 29.2)</td>
<td>22.9 (18.4, 29.3)</td>
<td>23.3 (18.8, 29.2)</td>
<td>-0.200</td>
<td>0.841</td>
</tr>
<tr>
<td>HbA1c(%)</td>
<td>9.0 (7.8, 10.8)</td>
<td>8.8 (7.7, 10.6)</td>
<td>9.2 (7.9, 10.9)</td>
<td>-1.044</td>
<td>0.296</td>
</tr>
<tr>
<td>TIR≥70%</td>
<td>44 (16.1%)</td>
<td>11 (9.6%)</td>
<td>33 (20.6%)</td>
<td>5.949</td>
<td>0.015</td>
</tr>
</tbody>
</table>

TIR, time in range (3.9-10mmol/L); TAR, time above range (>10.0mmol/L); SD, standard deviation of blood glucose; CV, coefficient of variation; HbA1c, hemoglobin A1c.

Spearman correlation analysis revealed that TIR was negatively correlated with HbA1c (r = -0.450, p<0.001), while TAR was positively correlated with HbA1c (r = 0.456, p<0.001). The correlation of TIR with TAR was −0.996 (p<0.001).

3.3 Association of TIR with CI in Patients with T2DM

Binary logistic regression analysis was utilized to identify the association of TIR with CI in patients with T2DM. The dependent variable was coexisting CI. Four variables with P < 0.1 in univariate analysis (age, education level, marital status, CVD) and one variable that has been documented to be closely associated with CI (age at DM onset)[35] were introduced into the multivariate regression analysis as confounders. Table 3 showed the significant association between TIR and CI (OR = 0.84, p<0.001) after adjusting for confounders above. Further adjustment of SD (OR = 0.84, p < 0.001) and CV (OR = 0.83, p < 0.001), TIR was still associated with CI. The results showed that the effect of TIR on cognitive dysfunction was GV-independent. Next, the participants were stratified according to tertiles of TIR (tertile 1 [T1]:≤17%; tertile 2 [T2]:17–50%; tertile 3 [T3]: 50%). Figure 2 showed the prevalence of CI decreased with ascending tertiles of TIR (p for trend < 0.05). It was found that the highest TIR tertile had an independent association with CI in comparison to the lowest tertile when included as a categorical variable in the binary logistic regression model (OR = 0.32, p = 0.001) (Table 4). Even after controlling for SD or CV, the statistical significance of the link between CI and TIR as a categorical variable remained.
### Table 3

**Association of TIR and Other Glycemic Metrics with Cognitive Impairment in Patients with T2DM**

<table>
<thead>
<tr>
<th>OR per increase of</th>
<th>Unadjusted</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>TIR 10%</td>
<td>0.85 (0.77–0.93)</td>
<td>0.84 (0.76–0.92)</td>
<td>0.84 (0.76–0.93)</td>
<td>0.83 (0.75–0.92)</td>
<td></td>
</tr>
<tr>
<td>TAR 10%</td>
<td>1.16 (1.06–1.28)</td>
<td>1.18 (1.07–1.29)</td>
<td>1.17 (1.06–1.29)</td>
<td>1.19 (1.08–1.31)</td>
<td></td>
</tr>
<tr>
<td>HbA1c 1%</td>
<td>0.95 (0.84–1.08)</td>
<td>0.95 (0.84–1.09)</td>
<td>0.92 (0.80–1.06)</td>
<td>0.95 (0.84–1.09)</td>
<td></td>
</tr>
</tbody>
</table>

TIR, time in range; TAR, time above range; HbA1c, hemoglobin A1c.

*a* Model 1: adjusted for age, education, marital status; Model 2: Model 1 + age at DM onset and cerebrovascular disease (CVD). Model 3: Model 2 + SD. Model 4: Model 2 + CV.

*ORs and P values were estimated for each 10% increase in TIR (0–100%) and TAR (0–100%), and each 1% increase in HbA1c. OR: odds ratio, 95% CI: 95% confidence interval.*

*p value<0.05, #p value<0.01.

### Table 4

**Association Between Tertials of TIR and Cognitive Impairment**

<table>
<thead>
<tr>
<th>Tertials of TIR</th>
<th>N</th>
<th>unadjusted</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td></td>
</tr>
<tr>
<td>T1(≤17%)</td>
<td>107</td>
<td>1.00 (ref)</td>
<td>1.00(ref)</td>
<td>1.00(ref)</td>
<td>1.00(ref)</td>
<td>1.00(ref)</td>
</tr>
<tr>
<td>T2(17–50%)</td>
<td>86</td>
<td>0.64(0.36–1.14)</td>
<td>0.61(0.33–1.11)</td>
<td>0.59(0.32–1.10)</td>
<td>0.59(0.32–1.11)</td>
<td>0.52(0.27–1.01)</td>
</tr>
<tr>
<td>T3(50%)</td>
<td>81</td>
<td>0.46(0.25–0.85)*</td>
<td>0.34(0.18–0.66)#</td>
<td>0.32(0.16–0.62)#</td>
<td>0.33(0.17–0.67)#</td>
<td>0.29(0.14–0.58)#</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.011</td>
<td>0.001</td>
<td>0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*a* Model 1: adjusted for age, education, marital status; Model 2: Model 1 + age at DM onset and cerebrovascular disease (CVD). Model 3: Model 2 + SD. Model 4: Model 2 + CV.

b P values for linear trends were calculated using the median value of tertials of TIR.

*p value<0.05,#p value<0.01.*
3.4 Association of Other Glycemic Metrics with CI in Patients with T2DM

Table 3 depicted significant association existed between TAR and CI after adjusting for age, education level, marital status, CVD and age at DM onset. The adjusted odds ratio of CI was increased by 18% (p = 0.001) for each 10 percentage points higher TAR. Further adjustment of SD (OR = 1.17, p = 0.002) and CV (OR = 1.19, p = 0.001), TAR was still associated with CI. The prevalence of CI increased with ascending tertiles of TAR (p for trend < 0.05) and higher TAR was associated with increased risk for CI (Supplementary Fig. 1, Supplementary table 1). There was no linear association of HbA1c with the risk of CI in our study (p 0.05 in all models) (Table 3).

3.5 Protective Effects on Cognitive Function in Patients with T2DM

According to recommendations of the international consensus, a goal for non-pregnant T1DM and T2DM adults was TIR > 70%. Therefore, using TIR as a marker of glucose management, binary logistic regression analysis was performed to examine the effect of achieving the TIR goal on CI. The data indicated that significant association existed between a TIR goal of > 70% and CI (OR = 0.25, p = 0.001) after adjusting for age, education level, marital status, CVD, age at DM onset (Table 5). Further adjustment of SD (OR = 0.25, p = 0.002) and CV (OR = 0.25, p = 0.001), TIR > 70% was still associated with CI. The results showed that a TIR goal of > 70% probably possessed a protective effect on cognitive function in patients with T2DM.

Table 5

<table>
<thead>
<tr>
<th>TIR (Unadjusted)</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>TIR (≤ 70%)</td>
<td>1.00(ref)</td>
<td>1.00(ref)</td>
<td>1.00(ref)</td>
<td>1.00(ref)</td>
</tr>
<tr>
<td>TIR (70%)</td>
<td>0.41(0.20–0.85)</td>
<td>0.31(0.14–0.69)</td>
<td>0.25(0.11–0.57)</td>
<td>0.25(0.10–0.60)</td>
</tr>
</tbody>
</table>

*Model 1: adjusted for age, education, marital status; Model 2: Model 1 + age at DM onset and cerebrovascular disease (CVD). Model 3: Model 2 + SD. Model 4: Model 2 + CV.

**P value < 0.01 for each model.

Conclusion

This is the first study that investigates the association between TIR obtained from BGM and CI in T2DM patients, as far as we know. Among 274 inpatients with T2DM (median age 58 years), the prevalence of CI was 41.6%. TIR, obtained from seven-point BGM, was lower in CI group than in NCF group. When the tertiles of TIR were used to stratify the patients, the prevalence of CI decreased with ascending tertiles of TIR. TIR was significantly associated with CI after adjusting for confounders (age, education, marital status, age at
DM onset and CVD). Further adjustment for SD or CV, TIR was still associated with CI. While a TIR goal for T2DM adults of > 70% probably possessed protective effect on cognitive function. Among other glycemic metrics, TAR was independently correlated to CI, and higher TAR was correlated with increased risk for CI. There was no linear association of HbA1c with the risk of CI in our study.

At present, HbA1c is widely recognized as the gold standard for evaluating glycemic management, and is associated with long-term complications in diabetic patients, including CI. However, current findings on the relationship between HbA1c and cognitive function were inconsistent. The English longitudinal study of aging comprised 5189 participants (mean age 65.6 ± 9.4 years), 1190 (22.9%) of whom were prediabetes and 446 (8.6%) of whom were diabetic. After controlling for age and sex, linear regression analyses (cross-sectional analyses) showed a significant correlation between baseline HbA1c levels and global cognitive function, but this relationship became insignificant after further adjusting for additional confounding factors. Followed up the duration of 8.1 ± 2.8 years, the significant correlations between HbA1c levels and rate of change in global cognitive scores were revealed in longitudinal analyses[16]. A cross-sectional study (n = 1109) in elderly T2DM in China showed that HbA1c was the risk factor for MCI after adjusting for age, gender and educational level (OR = 1.25, 95% CI 1.09−1.43)[36]. In contrast, in a diabetes and aging study[37], a cohort study for prediction of 10 year dementia risk in individuals with T2DM patients, comprised 29961 patients (mean age 70.6 ± 6.8 years at baseline). HbA1c was not included in the final prognostic model, but acute metabolic events (severe hyper and/or hypoglycemic events) was. A meta-analysis of 144 prospective studies proved positive correlation between higher HbA1c levels and dementia or MCI, but when HbA1c was considered as a continuous variable, no association of HbA1c with the risk of CI was found[38]. Another cross-sectional study (n = 4335) in patients with T2DM (mean age 64.7 ± 9.4 years) shows a non-linear correlation between HbA1c and CI[39]. In our study, there was no linear association of HbA1c as a continuous variable with the risk of CI in T2DM patients. The result is consistent with the literature above. The inconsistent relationship between HbA1c and cognitive dysfunction may be related to the following reasons. Firstly, subject profiles differ. Subjects had different conditions of pre-diabetes, T1DM and T2DM, as well as different ages, ranging from middle-aged to elderly. Secondly, the outcome events were different. Some studies had dementia as the outcome event, and some had MCI. Thirdly, the trial designs were different. Some were cross-sectional studies exploring the correlation between HbA1c and CI, and some were cohort studies exploring the causal relationship between them. Finally, it is probably related to the limitations of the measurement of HbA1c. HbA1c reflects average glucose level over the last 2–3 months, which cannot provide information on acute glycemic fluctuation, hypoglycemia or hyperglycemia, nor can it provide information on the magnitude and frequency of intra- and interday glycemic changes[19]. It has been shown that blood glucose fluctuations are associated with cognitive dysfunction[18, 40–44]. Moreover, certain conditions such as anemia, hemoglobinopathies, iron deficiency and pregnancy can confound HbA1c measurements[5]. So HbA1c may not be an ideal predictor of CI in diabetic patients.

The 2019 ATTD congress reached consensus on glycemic cut-off points (a target in range of 3.9–10.0mmol/L) for individuals with T1DM and T2DM[19]. A growing number of studies have shown that TIR is important for patient blood glucose management and prognosis[28, 29, 31], as a new metric of glycemic control. In our study, TIR was significantly correlated with HbA1c, which was consistent with previous studies[26, 27]. TIR is well correlated with HbA1c, suggesting that it would probably replace HbA1c for
predicting diabetes complications as the preferred metric. In fact, there is growing evidence from several recent studies that have shown correlations of TIR with diabetes complications[28–31, 45]. Furthermore, TIR can more accurately assess daily patterns of glycemia and glycemic variability, which may be relevant for cognitive function. Therefore, we predict that TIR may be used as a surrogate predictor of CI in diabetic patients beyond HbA1c. Our study revealed the significant association of TIR with CI, suggesting that TIR may be a suitable indicator for the cognitive dysfunction in people with T2DM. Moreover, we also found that higher TIR was related to lower risk for CI, that means high TIR probably had a protective effect for cognitive function in T2DM. For instance, higher TIR for a patient means the more time spent in the target glucose range (3.9–10.0mmol/L) and the less time spent above or below the target glucose range, means the less glycemic fluctuations and the fewer instances of hypo or hyperglycemia. Glucose fluctuations measured by CGM were associated with cognitive decline among older T2DM patients in two cross-sectional studies[46, 47]. Blood glucose fluctuation can damage the function of endothelial cells, aggravate chronic inflammation and increases the risk of diabetic complications[47]. Recently, GV metrics have aroused extensive attention as independent predictors of diabetes complication[48], including SD, CV and Mean Amplitude of Glycemic Excursions (ie. MAGE). Further adjustments on SD and CV, we found TIR was still associated with CI, so the present study provided evidence of a GV-independent effect of TIR on CI.

As a hyperglycemia metric, TAR was positively correlated with HbAlc (r = 0.456) and negatively correlated with TIR (r = −0.996) in our study. The result was consistent with the literature[29]. The present study showed that TAR probably was a risk factor for cognitive function in T2DM and higher TAR was associated with increased risk for CI. Hyperglycemia probably affect cognitive function by damaging vascular endothelium and blood-brain barrier, demyelination and axonal loss, or aggravation of oxidative stress[49].

According to recommendations of the American Diabetes Association (ADA), keeping an HbA1c level below 53.0 mmol/mol (7.0%) can prevent microvascular complications related to diabetes[50]. However, findings from clinical trials on the effect of achieving an HbA1c goal on cognitive decline in diabetic patients are conflicting[16, 51–53]. There was no effect on cognitive dysfunction when HbA1c level was reduced in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Memory In Diabetes Study (ACCORD-MIND)[51], while mild effects on cognitive decline could be observed when HbA1c level was controlled at 53.0mmol/mol (7.0%) or less in the Informatics in Diabetes Education and Telemedicine Study (IDEATel)[52]. In our study, an HbA1c level of <7.0% still had no effect on CI in T2DM (Supplementary Table 2), which is consistent with the literature. The above findings may be due to severe hypoglycemia or glycemic fluctuations, which were adverse events related to diabetes treatment[10]. However, HbA1c provides no indication of hypoglycemia or glycemic fluctuation, which may be relevant for cognitive function. As a new metric of glycemic control, TIR can provide valuable information on the probability and duration of hypoglycemia and hyperglycemia occurrence, thus may compensate for the limitations of HbA1c. According to recommendations of the international consensus, a goal for non-pregnant T1DM and T2DM adults was time in range (TIR) of > 70% [19]. Therefore, we supposed to examine the effect of achieving the TIR goal on CI. The results showed that a TIR goal for T2DM adults of > 70% probably possessed protective effect on cognitive function.

In the present study, we assessed the correlation between TIR obtained by BGM and the risk of CI in T2DM patients. Moreover, from a therapeutic perspective, we found that achieving the TIR goal probably had
protective effects on cognitive function. BGM is flexible, convenient, easy to operate, relatively economical and has a high feasibility and good correlation with CGM[54]. Previous studies have shown that TIR measured by CGM and BGM are similar [55, 56], so it is reasonable to assume that the correlation between the TIR measured by BGM and CI would also be applicable to the TIR measured by CGM. As CGM continuously captures the glucose profile over days, it can provide much more data to compute TIR than BGM, it is possible that CGM-measured TIR allows for more accurate assessment of the risk of CI than BGM.

There were several limitations of this study. Patients with hypoglycemia were not included in our study. On the one hand, it may be related to subject profiles. Young children with T1DM and elderly people, including those with T1DM and T2DM are particularly prone to hypoglycemia, while middle-aged and early elderly T2DM adults (median age 58 years) enrolled in this study are not. On the other hand, seven-point BGM data are only from daytime, and does not include the overnight period, thus it may reduce the opportunity of detecting hypoglycemia. In addition, our study is a cross-sectional study, and the sample size is not large. Therefore, we cannot determine the causal relationship between TIR and CI.

In conclusion, we provide evidence that TIR, as a supplemental metric of HbA1c for glycemic management is probably associated with CI in T2DM patients. In addition, according to recommendations of the international consensus established by ATTD, we find that achieving a TIR goal for T2DM adults of > 70% probably possessed protective effect on cognitive function. In the future, some large prospective cohort studies are needed to explore a definitive role of CGM-measured TIR in the onset and progression of CI.

Declarations

Acknowledgments

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Author Contributions

Conceptualization, J-NL. and Y-LL.; methodology, Y-LL.; software, Y-TL.; validation, Y-TL. and Y-LL.; formal analysis, Y-TL.; investigation, H-NQ.; resources, J-NL.; data curation, H-NQ., J-BL., FW., Y-SL. and L-FX., W-RJ., C-YL; writing—original draft preparation, Y-TL.; writing—review and editing, Y-LL and NH; visualization, Y-TL.; supervision, J-NL. and H-NQ.; project administration, J-NL.; funding acquisition, J-NL. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Tianjin Union Medical Center, Nankai University affiliated hospital. Participants signed written informed consent to participate in this study.

**Informed Consent Statement**

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

**Data Availability Statement**

The raw data used in this study were provided unconditionally by the authors.

**Conflicts of Interest**

The authors declare no conflict of interest.

**References**


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32. 2022, 14, 650-655.


**Figures**

**Figure 1**

Flow Chart for Screening Subjects with Inclusion and Exclusion Criteria
Figure 2

Prevalence of Cognitive Impairment as a Function of TIR Tertials

Supplementary Files

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- Supplementaryfiles.docx