BMC Endocrine Disorders

RESEARCH

Open Access

Association of time in range with cognitive impairment in middle-aged type 2 diabetic patients

Yanting Liu[1,3†], Yanlan Liu[2†], Huina Qiu[2], Nahal Haghbin[4], Jingbo Li[2], Yaoshuang Li[1,2], Weiran Jiang[5], Longfei Xia[1,2], Fan Wu[2,6], Chenying Lin[1,2], Jingna Lin[2*] and Chunjun Li[7*]

Abstract

Objective This study investigated the association of Time In Range (TIR) obtained from Blood Glucose Monitoring (BGM) with Cognitive Impairment (CI) inpatients with middle-aged 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 (pre meals and 120 min 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 middle-aged 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 middle-aged T2DM individuals and a TIR goal of > 70% probably possessed a protective effect on cognitive function for middle-aged T2DM .

Keywords Time in range (TIR), Cognitive impairment (CI), Type 2 diabetes mellitus (T2DM), Blood glucose monitoring (BGM)

†Yanting Liu and Yanlan Liu are co first authors.

*Correspondence:
Jingna Lin
13207628978@163.com
Chunjun Li
li_chunjun@126.com

Full list of author information is available at the end of the article

Introduction

Cognitive Impairment (CI) is one of the main complications of DM. It primarily manifests as cognitive decline 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 in diabetes patients is important, as CI can hinder effective diabetes management, and poorly managed diabetes can exacerbate cognitive decline [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 (typically 3.9–10.0 mmol/L). 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.

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 Type 2 Diabetes Mellitus (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 this study was to investigate the association between TIR and CI among middle-aged T2DM.

Research design and methods

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 h 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]$<$90 g/L), cachexia, liver insufficiency (ALanine Transaminase [ALT]$\geq$120U/L), renal insufficiency (creatinine[Cr]$\geq$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.

Clinical and biochemical Data

The participants completed a face-to-face survey questionnaire about their demographic characteristics, which included gender, age, ethnicity, marital status, education level, sedentary lifestyle, diabetic diet control, age at DM onset, use anti diabetes agents (insulin, insulin secretagogues). The prior history of diseases was provided through self-report and medical records, including diabetic microangiopathy (which includes diabetic nephropathy and/or diabetic retinopathy), hypoglycemia episode in last three months, CerebroVascular Disease (CVD, including hemorrhagic and/or ischemic strokes) and

hypertension (defined as a blood pressure ≥ 140/90mmHg or the use of antihypertensive medications).

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 (BC-6800, Mindray, China), ALT, Cr, Triglycerides (TG), Total Cholesterol (TC), High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), Thyroid Stimulating Hormone (TSH) were tested by an automatic biochemical analyzer (TBA-120FR, Toshiba, Japan), while hemoglobin A1c (HbA1c) was analyzed using a fully automated Glycohemoglobin analyzer based on HPLC (high-performance liquid chromatography) (HA-8180, ARKRAY, Japan). In our study, HbA1c measurements were conducted in accordance with the Diabetes Control and Complications Trial(DCCT) standardization protocol, and the detection system we used has been certified by the National Glycohemoglobin Standardization Program(NGSP).

Glycemic metrics

Subjects performed seven-point daily fingerstick capillary glucose values were determined(pre meals, 120 min post meals and at bedtime) with the Glupadblood glucose meter (GlupadPlus878, Sinomedisite, Beijing, China) within 72 h 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.

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 ≥ 24 and MoCA ≥ 26, CI group: MMSE ≥ 24 and MOCA < 26 (Fig. 1).

Statistical analysis

Mean ± 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.

Results

Characteristics of the study subjects

Among 274 participants,114(41.6%) subjects suffered from CI. 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).

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 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) .

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).

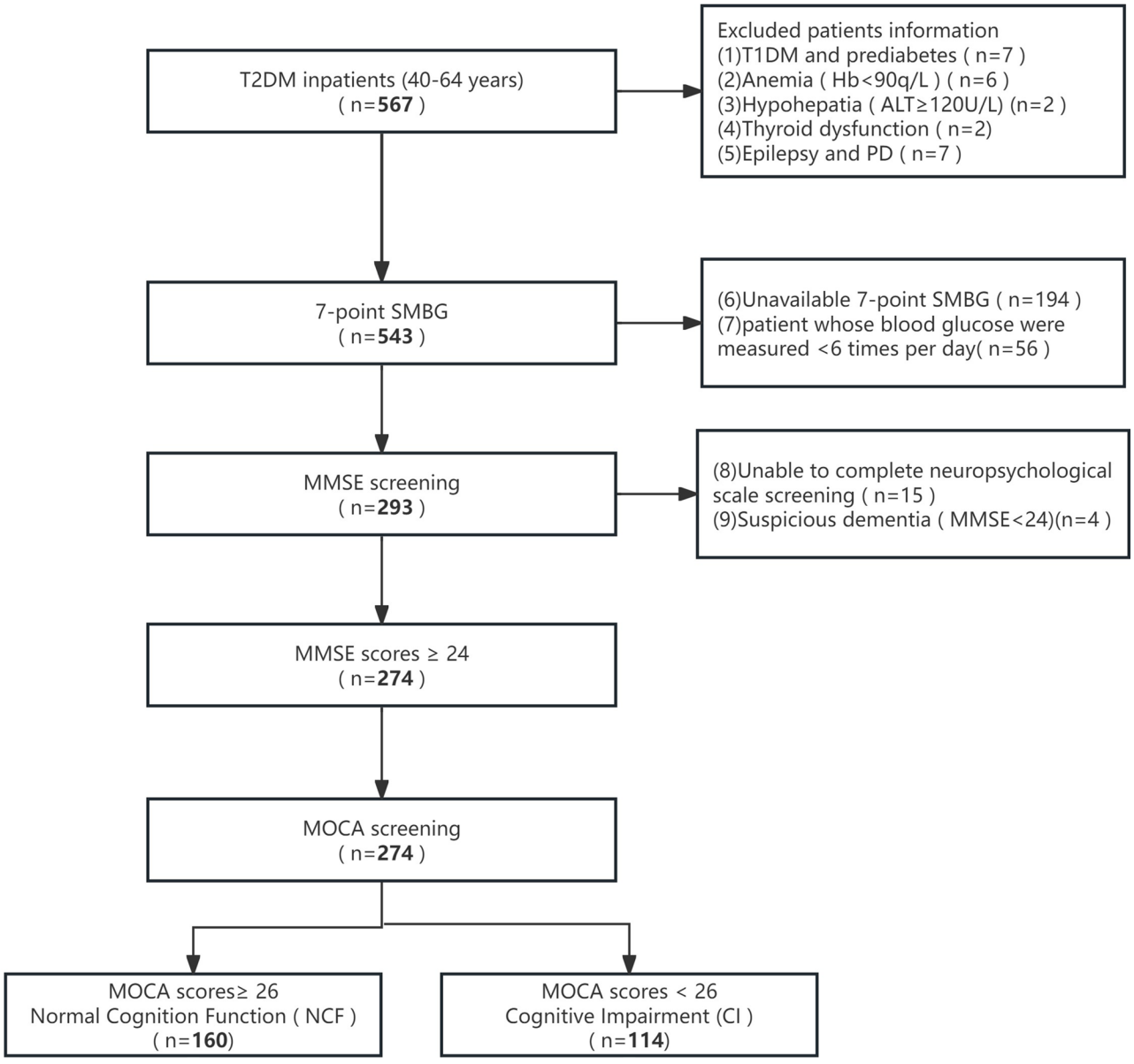

Fig. 1 Flow chart for screening subjects with inclusion and exclusion criteria

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 1 Baseline characteristics of participants by cognition status

Variables	All subjects (n = 274)	CI (n = 114)	NCF (n = 160)	P value
Male	124 (45.3%)	53 (46.5%)	71 (44.4%)	0.729
Age (years)	58.0 (54.0,62.0)	58.0 (55.0,62.0)	57.0 (54.0,61.0)	0.092
40–44(years)	8 (2.9%)	1 (0.9%)	7 (4.4%)	
45–59(years)	150 (54.7%)	58 (50.9%)	92 (57.5%)	
60–64(years)	116 (42.3%)	55 (48.2%)	61 (38.1%)	
Education(years)	12.0 (9.0,12.0)	9.0 (9.0,12.0)	12.0 (9.0,12.0)	**0.014**
Age at DM onset (years)	52.0 (45.0,57.0)	53.0 (46.0,57.5)	50.5 (44.0,56.0)	0.238
Ethnic Han	244 (89.1%)	104 (91.2%)	140 (87.5%)	0.330
Married	251 (91.6%)	96 (84.2%)	155 (96.9%)	**<0.001**
Sedentary lifestyle	66 (24.2%)	25 (21.9%)	41 (25.8%)	0.463
Diabetic diet control	163 (59.7%)	64 (56.1%)	99 (62.3%)	0.309
Use antidiabetic agents				
Insulin	135 (49.3%)	60 (52.6%)	75 (46.9%)	0.347
Insulin secretagogues	121 (44.2%)	51 (44.7%)	70 (43.8%)	0.871
Hypoglycemic events in last 3 months	59 (21.9%)	28 (25.0%)	31 (19.7%)	0.305
Diabetic microangiopathy	126 (46.2%)	56 (49.6%)	70 (43.8%)	0.103
CVD	54 (19.8%)	35 (31.0%)	19 (11.9%)	**<0.001**
Hypertension	173 (63.4%)	71 (62.8%)	102 (63.7%)	0.876
WBC(10^9/L)	5.9 (5.1, 7.2)	5.8 (5.1, 7.2)	5.9 (5.1, 7.1)	0.813
NLR	1.7 (1.3, 2.2)	1.6 (1.3, 2.1)	1.7 (1.4, 2.2)	0.412
RBC(10^{12}/L)	4.5 (4.2, 4.8)	4.5 (4.1, 4.8)	4.5 (4.2, 4.8)	0.908
Hb(g/L)	135.9 ± 14.9	136.3 ± 15.1	135.7 ± 14.8	0.753
ALT(U/L)	20.9 (14.2, 34.2)	31.4 (18.1, 53.6)	34.3 (21.8, 52.9)	0.181
Cr(μmol/L)	55.0 (46.8, 63.0)	63.0 (56.0, 67.7)	64.0 (53.0, 73.7)	0.358
TC(mmol/L)	5.0 (4.3, 5.6)	5.6 (5.0, 6.4)	5.7 (5.0, 6.5)	0.600
TG(mmol/L)	1.7 (1.2, 2.48)	2.6 (1.6, 4.5)	2.5 (1.7, 4.5)	0.953
LDL-C(mmol/L)	2.8 (2.5, 3.4)	3.4 (2.9, 3.9)	3.43 (2.9, 4.0)	0.871
HDL-C(mmol/L)	1.2 (1.1, 1.4)	1.4 (1.2, 1.6)	1.4 (1.2, 1.6)	0.424
TSH(μIU/mL)	2.8 (1.9, 4.4)	2.8 (1.8, 4.5)	2.8 (2.0, 4.2)	0.839

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 2 Comparison of TIR and other glycemic metrics between different cognitive status

Variables	All subjects (n = 274)	CI (n = 114)	NCF (n = 160)	P value
TIR(%)	33.3 (14.3, 57.1)	28.6 (14.3, 50.0)	42.9 (14.3, 66.7)	**0.004**
TAR(%)	66.7 (42.9, 85.7)	71.4 (48.2, 85.7)	57.1 (33.3, 85.1)	**0.008**
SD(mmol/L)	2.83 (2.10, 3.63)	2.94 (2.14, 3.73)	2.80 (2.08, 3.59)	0.199
CV(%)	23.1 (18.7, 29.2)	22.9 (18.4, 29.3)	23.3 (18.8, 29.2)	0.841
HbAlc(%)	9.0 (7.8, 10.8)	8.8 (7.7, 10.6)	9.2 (7.9, 10.9)	0.296
TIR>70%	44 (16.1%)	11 (9.6%)	33 (20.6%)	**0.015**

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

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% 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 association of HbA1c with the risk of CI in our study ($p>0.05$ in all models) (Table 3).

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.

Discussion

To the best of our knowledge, this is the first study that investigates the association between TIR obtained from BGM and CI in T2DM patients. 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

Table 3 Association of TIR and other glycemic metrics with cognitive impairment in patients with T2DM

	OR per increase of	Unadjusted	Model 1	Model 2	Model 3	Model 4
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
TIR	10%	0.88 (0.81–0.96)[#]	0.85 (0.77–0.93)[#]	0.84 (0.76–0.92)[#]	0.84 (0.76–0.93)[#]	0.83 (0.75–0.92)[#]
TAR	10%	1.12 (1.03–1.22)[#]	1.16 (1.06–1.28)[#]	1.18 (1.07–1.29)[#]	1.17 (1.06–1.29)[#]	1.19 (1.08–1.31)[#]
HbA1c	1%	0.93 (0.82–1.05)	0.95 (0.84–1.08)	0.95 (0.84–1.09)	0.92 (0.80–1.06)	0.95 (0.84–1.09)

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

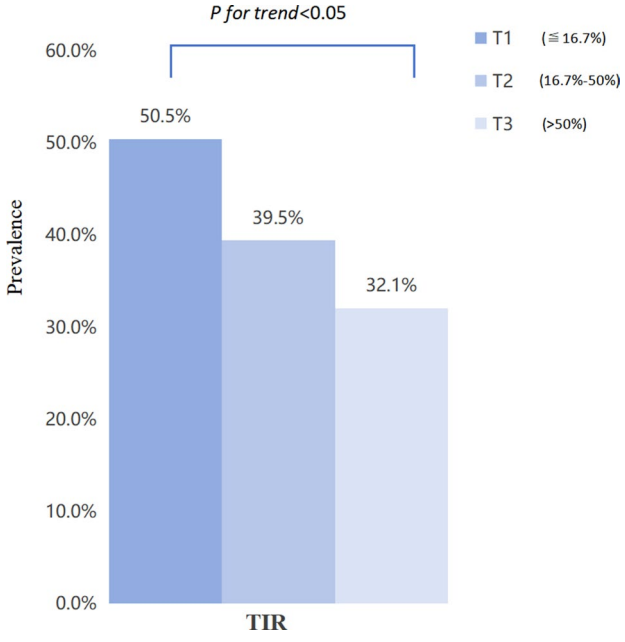

Fig. 2 Prevalence of cognitive impairment as a function of TIR tertiles

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 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. In the English longitudinal study of aging comprising 5189 participants (mean age 65.6±9.4 years), 22.9% (1190) of whom were prediabetes and 8.6% (446) of whom were diabetic. After followed up 8.1(2.8) years, there was an association between HbA1c levels and cognitive decline [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

Table 4 Association between tertiles of TIR and cognitive impairment

Tertiles of TIR	No.	unadjusted	Model 1	Model 2	Model 3	Model 4
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
T1(≤17%)	107	1.00 (ref)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
T2(17–50%)	86	0.64(0.36–1.14)	0.61(0.33–1.11)	0.59(0.32–1.10)	0.59(0.32–1.11)	0.52(0.27–1.01)
T3(>50%)	81	0.46(0.25–0.85)[*]	0.34(0.18–0.66)[#]	0.32(0.16–0.62)[#]	0.33(0.17–0.67)[#]	0.29(0.14–0.58)[#]
P for trend		0.011	0.001	0.001	0.002	<0.001

[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 tertiles of TIR

*p value<0.05,[#]p value<0.01

Table 5 Protective effect on cognitive function for TIR in T2DM adults

	Unadjusted	Model 1	Model 2	Model 3	Model 4
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
TIR(≤70%)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
TIR(>70%)	0.41(0.20–0.85)	0.31(0.14–0.69)	0.25(0.11–0.57)	0.25(0.10–0.60)	0.25(0.11–0.57)

[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 value<0.01 for each model

educational level [36]. In contrast, no association of HbA1c with the risk of CI was found when HbA1c was considered as a continuous variable in a meta-analysis of 144 prospective studies [37]. And HbA1c wasn't a prediction of 10 year dementia risk in individuals with T2DM patients in a diabetes and aging study [38]. No association of HbA1c with the risk of CI was found when HbA1c was considered as a continuous variable in a meta-analysis of 144 prospective studies [37]. In our study, there was no association of HbA1c with the risk of CI in T2DM patients. And, a HbA1c goal of <7% could't reduce the risk of cognitive impairment in middle-aged T2DM (Supplementary Table 2). 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 [19]. It has been shown that blood glucose fluctuations are associated with cognitive dysfunction [18, 39–43]. Hypoglycemia has been proven to be associated with cognitive impairment [9]. 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]. 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, 44]. 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 middle-aged 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. The possible reasons is that higher TIR for a patient means spending more time within the target glucose range (3.9–10.0 mmol/L) and less time above or below it, resulting in fewer instances of hypoglycemia or hyperglycemia. Glucose fluctuations measured by CGM were associated with cognitive decline among older T2DM patients in two cross-sectional studies [45, 46]. Blood glucose fluctuation can damage the function of endothelial cells, aggravate chronic inflammation and increases the risk of diabetic complications [46]. Recently, GV metrics have aroused extensive attention as independent predictors of diabetes complication [47], including SD, CV and Mean Amplitude of Glycemic Excursions (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 middle-aged T2DM. In our study, achieving a HbA1c goal of <7% could't reduce the risk of CI in middle-aged T2DM (Supplementary Table 2). One possible reason is that HbA1c reflects the average blood glucose level over the past three months and provides no indication of hypoglycemia or glycemic fluctuation. Hypoglycemia has been proven to be associated with cognitive impairment [9]. Hyperglycemia probably affect cognitive function by damaging vascular endothelium and blood-brain barrier, demyelination and axonal loss, or aggravation of oxidative stress [48].

There were several limitations of this study. Firstly, this is a cross-sectional study, so we cannot determine the causal relationship between TIR and the development of CI. On the other hand, Compared to CGM data, seven-point BGM data can only partially assess intra-individual and inter-individual glucose variability. Additionally, the data is collected only during the daytime, excluding the nighttime period. Therefore, the calculation of TIR and other metrics may underestimate nighttime glucose levels and reduce the chance of detecting hypoglycemia. 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. However, BGM is flexible, convenient, easy to operate, relatively economical and has a high feasibility and good correlation with CGM [20]. Previous studies have shown that TIR measured by CGM and BGM are similar [49, 50], 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. Further research is needed to explore the relationship between CGM-measured TIR and CI.

Conclusion

In conclusion, we provide evidence that TIR, as a supplemental metric of HbA1c for glycemic management is probably associated with CI in middle-aged T2DM patients. Moreover, from a therapeutic perspective, we found that achieving the TIR goal probably had protective effects 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.

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.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01772-5.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We thank all those who participated in this study and the Department of Endocrinology in Tianjin Union Medical for giving us the opportunity to conduct this study.

Author contributions

J-NL, C-JL contributed to the concept and design of the study. The statistical analysis and manuscript preparation as well as revision were performed by Y-TL and Y-LL. The extraction, collection and management of data were contributed by H-NQ, J-BL, FW, Y-SL and L-FX, W-RJ, C-YL. NH edited and revised the final manuscript. All authors read and approved the submitted version of the manuscript.

Funding

This study was supported by Natural Science Foundation of Tianjin City under Grant [J.N.L, number 18ZXDBSY00120] and the Science and Technology Project of Tianjin Municipal Health Commission [J.N.L, number ZD20006]. Note, the funders were not involved in any way in the design, data analysis or organization of this article.

Data availability

All data generated or analysed during this study are included in this published article (and its supplementary information files).

Declarations

Ethical approval and consent to participate

The studies involving human participants were reviewed and approved by Institutional Review Board of Tianjin Union Medical Center, Nankai University affiliated hospital. Patients/participants signed written informed consent to participate in this study.

Clinical trial number

Not applicable.

Copyright Statement

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Tianjin Medical University, Tianjin, China
[2]Department of Endocrinology, Tianjin Union Medical Center, Nankai University Affiliated Hospital, Tianjin, China
[3]Department of Neurology, Tianjin Union Medical Center, Tianjin, China
[4]School of Global Health, Chinese Center for Tropical Diseases Research, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[5]Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, New York, US
[6]School of Medicine, Nankai University, Tianjin, China
[7]Department of Endocrinology, Health Management Center, Tianjin Union Medical Center, Tianjin, China

Received: 9 September 2023 / Accepted: 31 October 2024
Published online: 08 November 2024

References

1. Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *NEUROLOGY* 2018, 90(3).
2. Rawlings AM, Sharrett AR, Schneider ALC, Coresh J, Albert M, Couper D, Griswold M, Gottesman RF, Wagenknecht LE, Windham BG, et al. Diabetes in Midlife and cognitive change over 20 years. ANN INTERN MED. 2014;161(11):785.
3. Dyer AH, McKenna L, Gamage G, Bourke NM, Killane I, Widdowson M, Woods CP, Gibney J, Reilly R, O Neill D et al. Cognitive performance in midlife type 2 diabetes: results from the ENBIND study. Diabet MED 2021, 38(6).
4. Ojo O, Brooke J. Evaluating the Association between Diabetes, Cognitive decline and Dementia. Int J Environ Res Public Health. 2015;12(7):8281–94.
5. Rawlings AM, Sharrett AR, Albert MS, Coresh J, Windham BG, Power MC, Knopman DS, Walker K, Burgard S, Mosley TH, et al. The Association of late-life diabetes status and hyperglycemia with incident mild cognitive impairment and dementia: the ARIC Study. Diabetes Care. 2019;37(6):1248.
6. Mukai N, Ohara T, Hata J, Hirakawa Y, Yoshida D, Kishimoto H, Koga M, Nakamura U, Kitazono T, Kiyohara Y, et al. Alternative measures of hyperglycemia and risk of Alzheimer's Disease in the community: the Hisayama Study. J CLIN ENDOCR METAB. 2017;102(8):3002–10.
7. Mullins RJ, Diehl TC, Chia CW, Kapogiannis D. Insulin resistance as a link between amyloid-Beta and tau pathologies in Alzheimer's Disease. FRONT AGING NEUROSCI 2017, 9.
8. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang H, Ahima RS, Craft S, Gandy S, Buettner C, Stoeckel LE, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. NAT REV NEUROL. 2018;14(3):168–81.

9. Lee AK, Rawlings AM, Lee CJ, Gross AL, Huang ES, Sharrett AR, Coresh J, Selvin E. Severe hypoglycaemia, mild cognitive impairment, dementia and brain volumes in older adults with type 2 diabetes: the atherosclerosis risk in communities (ARIC) cohort study. Diabetologia. 2018;61(9):1956–65.
10. Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, Seaquist ER, Ismail-Beigi F, Sullivan MD, Lovato LC, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes. Diabetes Care. 2012;35(4):787–93.
11. Cryer PE. Hypoglycemia, functional brain failure, and brain death. J CLIN INVEST. 2007;117(4):868–70.
12. Valenza S, Paciaroni L, Paolini S, Bonfigli AR, Di Rosa M, Rabini RA, Tortato E, Pelliccioni P, Pelliccioni G. Mild cognitive impairment subtypes and type 2 diabetes in Elderly subjects. J CLIN MED. 2020;9(7):2055.
13. Intensive blood-glucose. Control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–53.
14. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. NEW ENGL J MED. 1993;329(14):977–86.
15. Tuligenga RHM, Dugravot AM, Tabák AGM, Elbaz AM, Brunner EJP, Kivimäki MP, Singh-Manoux AD. Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: a post-hoc analysis of the Whitehall II cohort study. Lancet Diabets Endocrionol. 2014;2(3):228–35.
16. Zheng F, Yan L, Yang Z, Zhong B, Xie W. HbA1c, diabetes and cognitive decline: the English Longitudinal Study of Ageing. *DIABETOLOGIA* 2018, 61(4):839–848.
17. Yuan ZHONG, And X, And YZHANG, Ya MIAO. And: the relationship between glucose excursion and cognitive function in aged type 2 diabetes patients. Biomedical & Environmental Sciences; 2012.
18. Xia W, Luo Y, Chen Y, Chen H, Ma J, Yin X. Glucose fluctuations are linked to disrupted Brain Functional Architecture and Cognitive Impairment. J Alzheimers Dis. 2020;74(2):603–13.
19. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, et al. Clinical targets for continuous glucose Monitoring Data Interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593–603.
20. Hsu C, Chen Y, Sheu WHH. Glycemic variability and diabetes retinopathy: a missing link. J DIABETES COMPLICAT. 2015;29(2):302–6.
21. Advani A. Positioning time in range in diabetes management. Diabetologia. 2020;63(2):242–52.
22. Avari P, Uduku C, George D, Herrero P, Reddy M, Oliver N. Differences for Percentage Times in Glycemic Range between continuous glucose monitoring and Capillary Blood glucose monitoring in adults with type 1 diabetes: analysis of the REPLACE-BG dataset. DIABETES TECHNOL THE. 2020;22(3):222–7.
23. Kröger J, Reichel A, Siegmund T, Ziegler R. Clinical recommendations for the Use of the ambulatory glucose Profile in Diabetes Care. J Diabetes Sci Technol. 2020;14(3):586–94.
24. Livingstone R, Boyle JG, Petrie JR. How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with type 1 diabetes? Diabet MED. 2020;37(4):513–21.
25. Messer LH, Berget C, Vigers T, Pyle L, Geno C, Wadwa RP, Driscoll KA, Forlenza GP. Real world hybrid closed-loop discontinuation: predictors and perceptions of youth discontinuing the 670G system in the first 6 months. PEDIATR DIABETES. 2019;21(2):319–27.
26. Vigersky RA, McMahon C. The relationship of Hemoglobin A1C to Time-in-range in patients with diabetes. DIABETES TECHNOL THE. 2019;21(2):81–5.
27. Beck RW, Bergenstal RM, Cheng P, Kollman C, Carlson AL, Johnson ML, Rodbard D. The relationships between Time in Range, Hyperglycemia Metrics, and HbA1c. J Diabetes Sci Technol. 2019;13(4):614–26.
28. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, Lu W, Zhu W, Bao Y, Vigersky RA et al. Association of Time in Range, as assessed by continuous glucose monitoring, with Diabetic Retinopathy in Type 2 diabetes. Diabetes Care 2018, 41(11).
29. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, Close KL. Validation of Time in Range as an Outcome measure for diabetes clinical trials. Diabetes Care. 2019;42(3):400–5.
30. Sheng X, Xiong G, Yu P, Liu J. The correlation between Time in Range and Diabetic Microvascular complications utilizing Information Management platform. INT J ENDOCRINOL. 2020;2020:1–7.
31. Huang ZX, Zhang HH, Huang Y, Ye SL, Ma YN, Xin YH, Chen XQ, Zhao S. Association of time in range with postoperative wound healing in patients with diabetic foot ulcers. INT WOUND J. 2022;19(6):1309–18.
32. Fang XG, Shao XJ, Ma WG, He FY, Chen XQ, Li Y. Correlation between time in range and diabetic foot. Chin J DIABETES. 2022;14(07):650–5.
33. Lu J, Ma X, Shen Y, Wu Q, Wang R, Zhang L, Mo Y, Lu W, Zhu W, Bao Y, et al. Time in Range is Associated with Carotid Intima-Media thickness in type 2 diabetes. DIABETES TECHNOL THE. 2020;22(2):72–8.
34. American DA. Standards of medical care in diabetes–2013. Diabetes Care. 2013;36(Suppl 1):S11–66.
35. Barbiellini AC, Fayosse A, Dumurgier J, Machado-Fragua MD, Tabak AG, van Sloten T, Kivimaki M, Dugravot A, Sabia S, Singh-Manoux A. Association between Age at Diabetes Onset and subsequent risk of Dementia. JAMA-J AM MED ASSOC. 2021;325(16):1640–9.
36. Gao Y, Xiao Y, Miao R, Zhao J, Cui M, Huang G, Fei M. The prevalence of mild cognitive impairment with type 2 diabetes mellitus among elderly people in China: a cross-sectional study. ARCH GERONTOL GERIAT 2016.
37. Xue M, Xu W, Ou Y, Cao X, Tan M, Tan L, Yu J. Diabetes mellitus and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 144 prospective studies. AGEING RES REV. 2019;55:100944.
38. Exalto LG, Biessels GJ, Karter AJ, Huang ES, Katon WJ, Minkoff JR, Whitmer RA. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. LANCET DIABETES ENDO. 2013;1(3):183.
39. Rizzo MR, Marfella R, Barbieri M, Boccardi V, Vestini F, Lettieri B, Canonico S, Paolisso G. Relationships between Daily Acute glucose fluctuations and cognitive performance among aged type 2 Diabetic patients. Diabetes Care. 2010;33(10):2169–74.
40. ZHONG Y, ZHANG XY, MIAO Y, ZHU JH, YAN H, WANG BY, HU JINJ, JIA WP. The relationship between glucose excursion and cognitive function in aged type 2 diabetes patients. BIOMED ENVIRON SCI. 2012;25(1):1–7.
41. Rawlings AM, Sharrett AR, Mosley TH, Ballew SH, Deal JA, Selvin E. Glucose peaks and the risk of Dementia and 20-Year cognitive decline. Diabetes Care 2017, 40(7).
42. Zheng B, Su B, Price G, Tzoulaki I, Ahmadi-Abhari S, Middleton L. Glycemic Control, Diabetic complications, and risk of dementia in patients with diabetes: results from a large U.K. Cohort Study. Diabetes Care. 2021;44(7):1556–63.
43. Cox D, Gonder-Frederick L, Mccall A, Kovatchev B, Clarke W. The effects of glucose fluctuation on cognitive function and QOL: the functional costs of hypoglycaemia and hyperglycaemia among adults with type 1 or type 2 diabetes. Int J Clin Pract Suppl. 2002;129(129):20–6.
44. Yapanis M, James S, Craig ME, O'Neal D, Ekinci EI. Complications of Diabetes and Metrics of Glycemic Management Derived from continuous glucose monitoring. J Clin Endocrinol Metab 2022, 107(6).
45. Cui X, Abduljalil A, Manor BD, Peng CK, Novak V. Multi-scale glycemic variability: a link to gray matter atrophy and cognitive decline in type 2 diabetes. PLoS ONE. 2014;9(1):e86284.
46. Skrha J, Soupal J, Skrha JJ, Prazny M. Glucose variability, HbA1c and microvascular complications. REV ENDOCR METAB DIS. 2016;17(1):103–10.
47. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin a 1c –Independent risk factor for Diabetic complications. JAMA J Am Med Association. 2006;295(14):1707–8.
48. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. NAT REV ENDOCRINOL. 2018;14(10):591–604.
49. Group TDRI. Eight-point glucose testing versus the continuous glucose monitoring system in evaluation of glycemic control in type 1 diabetes. J CLIN ENDOCR METAB. 2005;6:3387–91.
50. Beck RW, Calhoun P, Kollman C. Use of continuous glucose monitoring as an Outcome measure in clinical trials. DIABETES TECHNOL THE. 2012;14(10):877–82.

Publisher's note