RESEARCH

Open Access

Relationship between key continuous glucose monitoring-derived metrics and specific cognitive domains in patients with type 2 diabetes mellitus

Shanshan Dong[1†], Lina Wang[1†], Chenxu Zhao[1], Rui Zhang[2,3,4], Zhaoyu Gao[2,3,4], Lei Jiang[2,3,4], Yingying Guo[1], Huimin Zhou[1,3,4*] and Shunjiang Xu[2,3,4*]

Abstract

Background Continuous glucose monitoring (CGM)-derived time in range (TIR) is closely associated with micro- and macrovascular complications in type 2 diabetes mellitus (T2DM). This study was performed to investigate the relationship between key CGM-derived metrics and specific cognitive domains in patients with T2DM.

Methods Outpatients with T2DM who were otherwise healthy were recruited for this study. A battery of neuropsychological tests was performed to evaluate cognitive function, including memory, executive functioning, visuospatial ability, attention, and language. Participants wore a blinded flash continuous glucose monitoring (FGM) system for 72 h. The key FGM-derived metrics were calculated, including TIR, time below range (TBR), time above range (TAR), glucose coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE). Furthermore, the glycemia risk index (GRI) was also calculated by the GRI formula. Binary logistic regression was used to assess risk factors for TBR, and we further analysed the associations between neuropsychological test results and key FGM-derived metrics with multiple linear regressions.

Results A total of 96 outpatients with T2DM were recruited for this study, with 45.8% experiencing hypoglycemia (TBR$^{< 3.9 \text{ mmol/L}}$). Spearman analysis results revealed that a higher TBR$^{< 3.9 \text{ mmol/L}}$ was correlated with worse performance on the Trail Making Test A (TMTA), Clock Drawing Test (CDT), and cued recall scores ($P < 0.05$). Logistic regression analysis results indicated that the TMTA (OR = 1.010, $P = 0.036$) and CDT (OR = 0.429, $P = 0.016$) scores were significant factors influencing the occurrence of TBR$^{< 3.9 \text{ mmol/L}}$. Multiple linear regressions further demonstrated that TBR$^{< 3.9 \text{ mmol/L}}$ (β = -0.214, $P = 0.033$), TAR$^{> 13.9 \text{ mmol/L}}$ (β = -0.216, $P = 0.030$) and TAR$^{10.1-13.9 \text{ mmol/L}}$ (β = 0.206, $P = 0.042$) were significantly

---

†Shanshan Dong and Lina Wang these authors have contributed equally to this work.

*Correspondence:
Huimin Zhou
zhouhuimindoctor@163.com
Shunjiang Xu
xushunjiang@hebmu.edu.cn
Full list of author information is available at the end of the article

correlated with cued recall scores after adjusting for confounding factors. However, TIR, GRI, CV and MAGE showed no significant correlation with the results of neuropsychological tests ($P > 0.05$).

Conclusions A higher $TBR^{< 3.9\ mmol/L}$ and $TAR^{> 13.9\ mmol/L}$ were associated with worse cognitive functions (memory, visuospatial ability, and executive functioning). Conversely, a higher TAR of 10.1–13.9 mmol/L was associated with better memory performance in memory tasks.

Keywords Time below range (TBR), Time in range (TIR), Time above range (TAR), Type 2 diabetes mellitus (T2DM), Cognitive impairment

Background

According to the International Diabetes Federation 2021 report, the number of people affected with diabetes worldwide is 536.6 million, which is estimated to reach 783.2 million in 2045 [1]. Over 90% of people with diabetes have type 2 diabetes mellitus (T2DM) [2, 3]. People with T2DM are at risk of life-threatening acute and chronic complications, especially central nervous system damage, which can cause functional and structural changes in the brain that lead to cognitive impairment and behavioral deficits [4]. Chronic hyperglycemia, recurrent hypoglycemic episodes, and glycemic excursions have been implicated as potential causative factors of cognitive impairment [5–7]. Therefore, continuous glucose monitoring (CGM) has evolved as an essential part of diabetes management for diabetic patients with cognitive impairment. With the development of CGM technology, flash continuous glucose monitoring (FGM) systems have increased in popularity in recent years because of the highly detailed information and enhanced accuracy they provide. The key FGM-derived metrics enable quantitative evaluation of the quality of short-term glycemic control, including time in range (TIR), time below range (TBR), time above range (TAR), glucose coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE) [8]. However, as a single metric, TIR does not indicate whether the out-of-range readings are too low or too high; therefore, several researchers have proposed a new evaluation index of blood glucose the glycemia risk index (GRI) [9]. The GRI is based on weighted combinations of TBR (the hypoglycemia component) and TAR (the hyperglycemia component) [9]. As such, we believe that key FGM-derived metrics and GRI could provide more direct, comprehensive, and complete information on blood glucose levels.

Human cognitive function is a complex construct composed of seven key cognitive domains: learning and memory, visuospatial ability, executive functioning, language, complex attention, perceptual-motor function, and social cognition [10]. Cognitive impairment refers to the impairment of one or more of these cognitive domains [10]. Recently, it was shown that glucose variability is associated with disruption of executive functioning, attention and language ability [11].

Glucose variability increases the production of reactive oxygen species (ROS) [12]. Overproduction of ROS can cause oxidative stress, which leads to neuronal damage and apoptosis [13]. Thus, glucose variability induces the activation of oxidative stress, which may be a major contributor to the development of cognitive impairment [12–14]. Previous studies have shown that TIR, TBR, MAGE, and severe hypoglycemia are associated with cognitive impairment [11, 14–17]. However, there is a lack of understanding regarding the specific relationships between TBR/TAR/TIR/GRI and different cognitive domains in patients with T2DM. In this study, we conducted a cross-sectional analysis to explore the relationship between key FGM-derived metrics and specific cognitive domains in patients with T2DM to prevent the occurrence and development of cognitive impairment.

Research design and methods

Participants

Outpatients with T2DM who were otherwise healthy were recruited from the First Hospital of Hebei Medical University. This study recruited outpatients who met the following inclusion criteria: (1) age between 40 and 80 years old; (2) patients with T2DM who met the 1999 World Health Organization (WHO) diagnostic criteria for diabetes mellitus [18] and had been on a stable glucose-lowering regimen for the past 3 months. The exclusion criteria included (1) diabetic ketoacidosis, hyperglycemic-hyperosmolar state or severe hypoglycemia and recurrent episodes of hypoglycemia within the past 3 months, thyropathy, parathyropathy or other endocrinopathies; (2) major medical illness, such as severe anemia, serious heart disease, liver, and kidney dysfunction or other systemic diseases; (3) acute infection; (4) malignant tumors and autoimmune diseases; (5) severe neurological or psychiatric diseases, alcoholism or abuse of psychotropic medicines; and (6) large infarcts, infection, tumor, or multifocal gray matter and/or white matter lesions observed on magnetic resonance imaging (MRI).

Clinical and biochemical measurements

Patient information on age, sex, diabetes duration, education, and prescription medications, such as

Dong *et al. BMC Neurology*   (2023) 23:200

Page 3 of 12

glucose-lowering drugs, was collected by doctors. Each patient underwent a physical examination that included measurements of height, weight, and blood pressure. Blood samples were drawn by an experienced nurse after a 10-h overnight fast. Total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were determined by applying standard enzymatic methods using a biochemical analyzer (US Beckman AU5800 automatic chemistry analyzer, Beckman Coulter, America). Fasting plasma glucose (FPG) levels were assayed by using the glucose hexokinase method. Hemoglobin A1c (HbA1c) was measured by using high-performance liquid chromatography with a Hemoglobin A1c analyzer (Afinion 2 HbA1c, Abbott Diagnostics Technologies AS, Norway).

Neuropsychological assessment
Several neuropsychological tests, including the Mini-Mental State Examination (MMSE) [19], Montreal Cognitive Assessment (MoCA) [20], Digit Span Test forward (DST forward) and backward (DST backward) [21], Trail Making Test A and B (TMTA and TMTB) [22], Boston Naming Test (BNT) [23], self-assessment of depression [24], Clock Drawing Test (CDT) [25, 26], Verbal Fluency Test (VFT) [27] and Auditory Verbal Learning Test (AVLT) [28], were performed to evaluate cognitive function, such as memory, executive functioning, visuospatial ability, attention and language. The AVLT included immediate memory total scores and scores on 20-min delayed recall, cued recall, and long-delayed recognition.

FGM parameters
Each patient wore a blinded FGM system (FreeStyle Libre H; Abbott Diabetes Care, Witney, UK) for 72 h [29, 30]. The glucose data were automatically recorded and saved every 15 min, and finger blood correction was exempted. The sensor of the FGM system was inserted on Day 0. After 72 h of monitoring, the data were downloaded to a computer and analysed. Key FGM-derived metrics were calculated. These metrics included the following: (1) TIR: % of readings and time in the range of 3.9–10.0 mmol/L. (2) TBR: % of readings and time at <3.9 mmol/L (TBR$^{<3.9}$ $^{mmol/L}$). According to the value of TBR$^{<3.9 mmol/L}$, the participants were divided into two groups based on absence or presence of hypoglycemia (with or without hypoglycemia). Furthermore, the TBR values were classified as level 1 hypoglycemia (% of readings and time in the range of 3.0-3.8 mmol/L (TBR$^{3.0–3.8 mmol/L}$)) and level 2 hypoglycemia (% of readings and time at <3.0 mmol/L (TBR$^{<3.0}$ $^{mmol/L}$)). Nocturnal asymptomatic hypoglycemia (NAH) was defined as T2DM patients with glucose levels<3.9 mmol/L without the typical symptoms of hypoglycemia occurring between 0:00 am and 6:00 am [29]. (3) TAR: % of readings and time at >10.0 mmol/L. The TAR

values were further classified as level 1 hyperglycemia (% of readings and time in the range of 10.1–13.9 mmol/L (TAR$^{10.1–13.9}$ $^{mmol/L}$)) and level 2 hyperglycemia (% of readings and time at >13.9 mmol/L (TAR$^{>13.9 mmol/L}$)) [8]. (4) CV and MAGE. GRI was calculated through the GRI formula. '.

Statistical analysis
Statistical analyses were carried out with the IBM SPSS 25.0 software package (IBM Corp., Armonk, N.Y., USA). Continuous variables with a normal distribution are presented as the mean±SD, and those not conforming to a normal distribution are expressed as the interquartile range [M (QL, QU)]. For continuous variables with normal or skewed distributions, Student's t test, one-way ANOVA or the Mann−Whitney U test were used for comparisons between groups. The χ2-test was used for categorical variables. Spearman analysis was used to analyse the relationships between glucose metrics and neuropsychological test results. Binary logistic regression was used to analyse the associations between TBR and neuropsychological test results. Multilinear regression analysis was used to analyse the correlations between neuropsychological test results and FPG, key FGM-derived metrics and GRI.

Results
Characteristics of the study participants
A total of 96 outpatients with T2DM were recruited for this study. Participant characteristics are shown in Table 1. The mean age of the 96 patients was 61.40±7.84 years, 59.38% (n=57) of the patients were male and 40.62% (n=39) were female, the duration of diabetes was 13.05±7.81 years, HbA1c was 7.85% (7.20%, 8.70%), and CV% was 26.50% (23.65%, 33.00%). A total of 45.8% of patients with T2DM had hypoglycemia (TBR$^{<3.9 mmol/L}$). Among them, 23 patients (23.96%) had NAH. There were no significant differences in sex, age, duration of disease, education, blood pressure, BMI or blood lipid levels between the groups with and without hypoglycemia (*P*>0.05). Compared with T2DM patients without hypoglycemia, T2DM patients with hypoglycemia showed increased TIR and CV values (*P*<0.01) and lower HbA1c, FPG, TAR$^{10.1–13.9 mmol/L}$, TAR$^{>13.9 mmol/L}$, and mean glucose (MG) values (all *P*<0.01). T2DM patients with hypoglycemia exhibited significantly worse performance on the TMTA and CDT (all *P*<0.05) (Table 2). Moreover, compared with T2DM patients without hypoglycemia, T2DM patients with level 1 hypoglycemia (TBR$^{3.0–3.8 mmol/L}$) exhibited significantly worse performance on the TMTA and CDT (all *P*<0.05), as shown in Supplementary Table S1.

Dong *et al. BMC Neurology*   (2023) 23:200

Page 4 of 12

Table 1 Characteristics of study participants

Variable	Total (*n* = 96)	Without hypoglycemia (*n* = 52)	With hypoglycemia (*n* = 44)	*P* values
Male, n (%)	57 (59.38)	27 (51.92)	30 (68.18)	0.106
Age (years)	61.40 ± 7.84	61.06 ± 8.57	61.80 ± 6.96	0.648
Education: junior college degree or above, n (%)	41 (42.71)	20 (38.46)	21 (47.73)	0.087
Diabetes duration (years)	13.05 ± 7.81	13.00 ± 7.69	13.11 ± 8.03	0.944
SBP (mmHg)	133.89 ± 13.88	133.88 ± 14.37	133.89 ± 13.44	1.000
DBP (mmHg)	80.68 ± 9.07	81.15 ± 8.61	80.11 ± 9.66	0.578
BMI (kg/m^2)	26.11 ± 3.91	26.64 ± 4.15	25.48 ± 3.56	0.150
Total cholesterol (mmol/L)	4.84 ± 1.09	4.90 ± 1.12	4.76 ± 1.06	0.510
Triglycerides (mmol/L)	1.39 (0.98, 2.19)	1.68 (0.93, 2.46)	1.31 (1.01, 1.85)	0.184
HDL (mmol/L)	1.18 (1.03, 1.39)	1.19 (1.04, 1.40)	1.16 (1.01, 1.32)	0.476
LDL (mmol/L)	3.00 ± 0.79	3.03 ± 0.76	2.97 ± 0.83	0.753
HbA1c (%)	7.85 (7.20, 8.70)	8.15 (7.43, 9.08)	7.45 (6.70, 8.18)	< 0.001
FPG (mmol/L)	8.50 (7.13, 10.47)	8.83 (7.69, 11.58)	7.91 (6.21, 9.44)	0.005
TIR (%)	61.66 ± 27.76	52.34 ± 31.25	72.68 ± 17.73	< 0.001
TAR$^{10.1-13.9 \text{ mmol/L}}$ (%)	20.50 (11.26, 33.27)	29.30 (16.75, 41.75)	16.08 (6.00, 21.05)	< 0.001
TAR$^{> 13.9 \text{ mmol/L}}$ (%)	2.91 (0.00, 18.00)	8.60 (0.09, 28.86)	1.05 (0.00, 6.81)	0.002
SD (mmol/L)	2.60 ± 0.84	2.59 ± 0.73	2.61 ± 0.96	0.883
GRI	34.32 (20.00, 64.60)	39.75 (18.18, 83.30)	29.38 (20.98, 47.03)	0.158
MG (mmol/L)	9.27 ± 2.76	10.50 ± 2.88	7.81 ± 1.71	< 0.001
CV (%)	26.50 (23.65, 33.00)	24.77 (21.61, 27.02)	32.15 (26.85, 37.50)	< 0.001
MAGE (mmol/L)	5.66 (4.21, 7.00)	5.80 (4.36, 6.81)	5.24 (3.98, 7.66)	0.903
Use antidiabetes agents				
Insulin, n (%)	47 (48.96)	27 (51.92)	20 (45.45)	0.528
Sulfonylurea, n (%)	19 (19.79)	11 (21.15)	8 (18.18)	0.716
Biguanides, n (%)	67 (69.79)	38 (73.08)	29 (65.91)	0.446
α-glucosidase inhibitors, n (%)	51 (53.13)	27 (51.92)	24 (54.55)	0.798
Dipeptidyl peptidase 4 inhibitors, n (%)	10 (10.42)	6 (11.54)	4 (9.09)	0.696
Glucagon-like peptide 1 receptor agonists, n (%)	10 (10.42)	4 (7.69)	6 (13.64)	0.342
Sodium–glucose cotransporter 2 inhibitors, n (%)	5 (5.21)	3 (5.77)	2 (4.55)	0.788

Data are presented as means ± standard deviations or medians (interquartile ranges) for continuous variables, and numbers (percentages) for categorical variables. A two-tailed value of *P* < 0.05 was considered as statistically significant.

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; TIR, time in range; TAR, time above range; SD, standard deviation; GRI, glycemia risk index; MG, mean glucose; CV, coefficient of variation; MAGE, mean amplitude of glycemic excursions

Associations between TBR$^{< 3.9 \text{ mmol/L}}$ and neuropsychological test results

The correlation analysis of TBR$^{< 3.9 \text{ mmol/L}}$ with neuropsychological test results was performed with Spearman's analysis. TBR$^{< 3.9 \text{ mmol/L}}$ was positively correlated with TMTA scores (*P* < 0.01) and negatively correlated with cued recall and CDT scores (*P* < 0.05) (Fig. 1). Binary logistic regression analysis was carried out to further analyse the association between TBR and neuropsychological test results. The binary dependent variables were TBR$^{< 3.9 \text{ mmol/L}}$ (T2DM patients with glucose levels < 3.9 mmol/L were coded as 1, and T2DM patients without glucose levels < 3.9 mmol/L were coded as 0), and the independent variables included age, duration of disease, education, BMI, and neuropsychological test results (scores on MMSE, MoCA, CDT, TMTA and cued recall). The results revealed that TMTA (OR = 1.010, *P* = 0.036) and CDT (OR = 0.429, *P* = 0.016) scores were independent influencing factors for the occurrence of TBR$^{< 3.9 \text{ mmol/L}}$ (Fig. 2). After adjusting for age, sex, diabetes duration, education, and BMI, significant associations existed between CDT scores (OR = 0.379, *P* = 0.008) and TBR$^{< 3.9 \text{ mmol/L}}$. There was still a significant correlation after further adjustment for scores on the TMTA (*P* < 0.05) (Table 3).

Dong *et al. BMC Neurology*   (2023) 23:200

Page 5 of 12

Table 2 Neuropsychological test information in all patients

Variable	Without hypoglycemia ($n=52$)	With hypoglycemia ($n=44$)	P values
MMSE	28.00 (27.00, 29.00)	28.00 (26.00, 29.00)	0.418
MoCA	23.37 ± 2.69	22.70 ± 3.35	0.286
Immediate memory total scores	23.81 ± 5.07	22.34 ± 5.16	0.165
20-min delayed recall	8.33 ± 2.20	7.64 ± 3.09	0.206
Cued recall	10.50 (9.00, 11.75)	10.00 (8.00, 11.00)	0.118
Long delayed recognition	12.00 (11.00, 13.75)	12.00 (10.00, 14.00)	0.965
DST forward	7.00 (6.00, 8.00)	6.00 (6.00, 8.00)	0.114
DST backward	4.00 (4.00, 5.00)	4.00 (3.00, 5.00)	0.503
TMTA	38.43 (32.43, 60.25)	62.79 (38.16, 150.00)	0.010
TMTB	88.00 (57.93, 300.00)	300.00 (72.37, 300.00)	0.053
BNT	23.50 (22.00, 27.00)	24.00 (21.00, 26.00)	0.799
CDT	3.00 (2.00, 3.00)	2.00 (1.25, 3.00)	0.028
VFT	18.00 (15.00, 20.00)	17.00 (14.00, 21.00)	0.507
Depression scale	51.88 (47.50, 57.50)	52.50 (47.50, 56.25)	0.997
Negative emotion	86.50 (76.00, 95.00)	87.50 (76.75, 92.75)	0.953

Data are presented as means±standard deviations or medians (interquartile ranges) for continuous variables. A two-tailed value of *P*<0.05 was considered as statistically significant.

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; DST, Digit Span Test; TMT, Trail Making Test; BNT, Boston Naming Test; CDT, Clock Drawing Test; VFT, Verbal Fluency Test

Associations between FPG and neuropsychological test results

FPG was negatively correlated with scores on DST forward, BNT, delayed recall, and cued recall (*P*<0.01 or *P*<0.05) (Fig. 3).

Associations between cued recall scores and key FGM-derived metrics

After adjusting for age, sex, diabetes duration, education, and BMI, FPG (β = -0.307, *P*=0.003), TBR$^{<3.9 \text{ mmol/L}}$ (β = -0.214, *P*=0.033), TAR$^{>13.9 \text{ mmol/L}}$ (β = -0.216, *P*=0.030) and TAR$^{10.1-13.9 \text{ mmol/L}}$ (β=0.206, *P*=0.042) were significantly correlated with cued recall scores, and there was still a significant correlation after adjustment for depression scale scores (*P*<0.05). After adjusting for FPG, the correlation of TAR$^{>13.9 \text{ mmol/L}}$ (β = -0.031, *P*=0.818) disappeared, but TBR$^{<3.9 \text{ mmol/L}}$ (β = -0.327, *P*=0.001) and TAR$^{10.1-13.9 \text{ mmol/L}}$ (β=0.343, *P*=0.001) were even more significantly correlated with cued recall scores (Table 4).

Associations between TIR/GRI/CV/MAGE and neuropsychological test results

Multiple linear regression was used to investigate the associations between TIR/GRI/CV/MAGE and neuropsychological test results, and the results revealed that TIR, GRI, CV and MAGE had no correlation with

neuropsychological test results (*P*>0.05) (Supplementary Table S2).

All of the participants were stratified according to tertiles of TIR (TIR<57%; 57% ≤ TIR<79%; TIR≥79%). In patients with the same incidence of TBR$^{<3.9 \text{ mmol/L}}$, compared with T2DM patients with 57% ≤ TIR<79%, T2DM patients with TIR≥79% exhibited significantly better performance on the BNT (*P*=0.020), and there was no difference in other neuropsychological test results (*P*>0.05) (Supplementary Table S3).

Discussion

The present study demonstrated that a higher TBR$^{<3.9 \text{ mmol/L}}$ was associated with worse cognitive performance, especially with memory, visuospatial ability and executive functioning. A higher TAR$^{>13.9 \text{ mmol/L}}$ was associated with worse memory performance. Conversely, a higher TAR$^{10.1-13.9 \text{ mmol/L}}$ was associated with better memory performance in outpatients with T2DM.

Previous studies have indicated that both severe hypoglycemia and recurrent episodes of hypoglycemia were related to cognitive impairment in patients with T2DM [31, 32]. In another study, it was demonstrated that TBR was negatively correlated with MoCA scores [15]. However, our study found no correlation between TBR$^{<3.9 \text{ mmol/L}}$ and MoCA scores. This disparity in results may be due to differences in the study population, as the patients in our study were relatively younger (mean age: 61.40 years) than those in the previous study (mean age: 70.35 years) [15]. Several studies reported that diabetes-associated cognitive impairment could occur in adolescents and young adults with T2DM [33, 34], while other studies are inconsistent with this view [35].

Our study revealed that a higher TBR$^{<3.9 \text{ mmol/L}}$ was correlated with worse performance on TMTA, CDT and cued recall. Therefore, TBR$^{<3.9 \text{ mmol/L}}$ was found to be associated with cognitive impairment, particularly memory dysfunction, deficits in visuospatial ability, and impaired executive functioning in younger patients with T2DM, which is consistent with previous studies [17].

In addition, FGM provided an improved opportunity to capture NAH events, and we found that 23.96% of patients with T2DM experienced NAH. NAH was associated with neurological damage, which was consistent with previous studies [36]. The occurrence of NAH in patients might be related to disorders of rapid eye movement (REM) sleep phases and the suppression of counterregulatory hormone responses to hypoglycemia during REM sleep [37].

Furthermore, we conducted a comparison of TMTA and CDT performance between T2DM patients with level 1 hypoglycemia (TBR$^{3.0-3.8 \text{ mmol/L}}$) and T2DM patients without hypoglycemia. Our findings revealed that T2DM patients with level 1 hypoglycemia (TBR$^{3.0-3.8}$
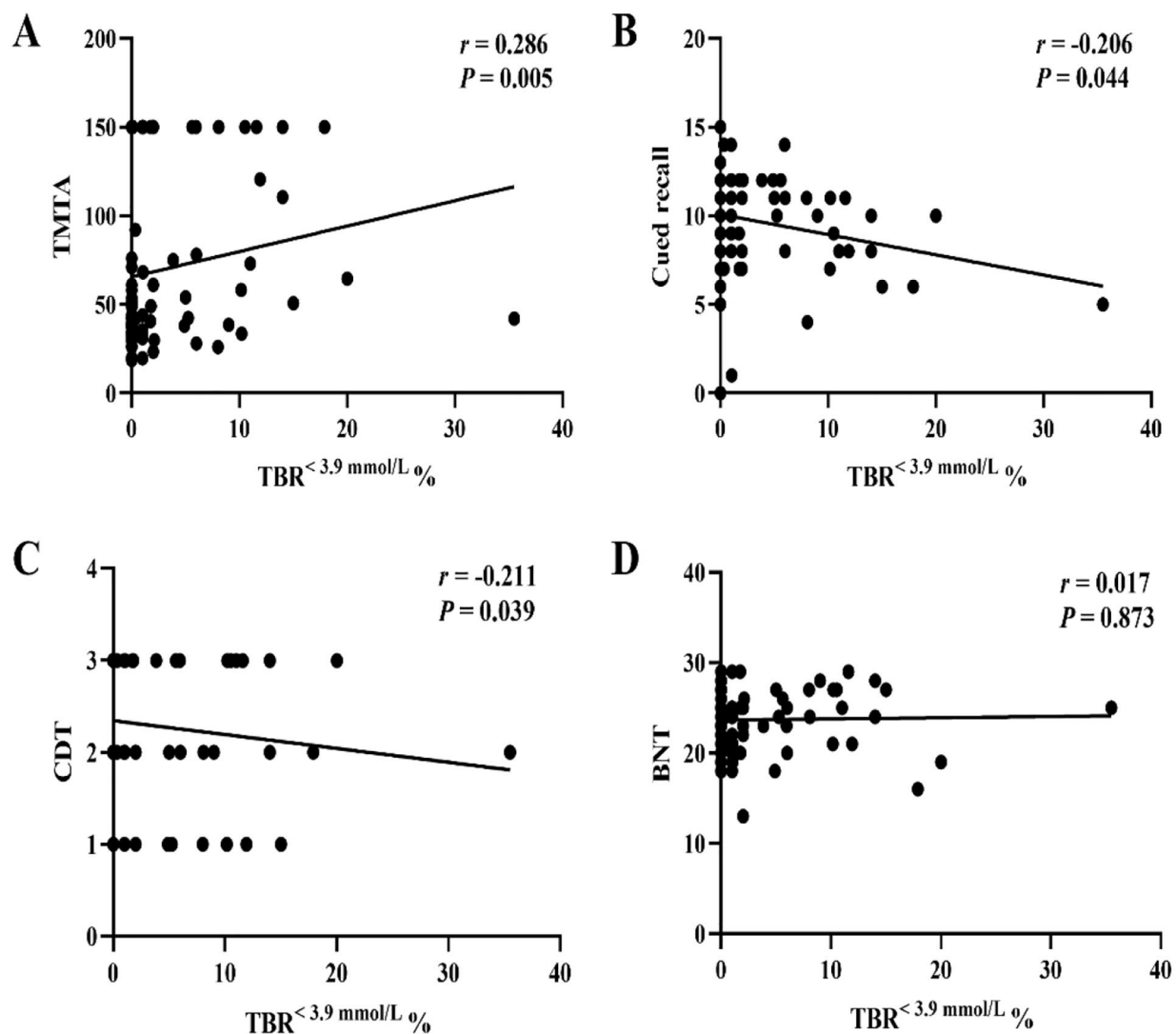
Fig. 1 Correlation of TBR$^{<3.9 \text{ mmol/L}}$ and neuropsychological test results. **A**, Correlation between TBR$^{<3.9 \text{ mmol/L}}$ and TMTA scores. **B**, Correlation between TBR$^{<3.9 \text{ mmol/L}}$ and cued recall scores. **C**, Correlation between TBR$^{<3.9 \text{ mmol/L}}$ and CDT scores. **D**, Correlation between TBR$^{<3.9 \text{ mmol/L}}$ and BNT scores. TMTA, Trail Making Test A; BNT, Boston Naming Test; CDT, Clock Drawing Test; TBR, time below range

$^{\text{mmol/L}}$) exhibited significantly worse performance on the TMTA and CDT, which indicates that nonsevere hypoglycemia is associated with cognitive impairment, specifically deficits in visuospatial ability and impaired executive functioning. However, we did not observe any significant association between TBR$^{<3.9 \text{ mmol/L}}$ and cognitive performance in the global cognition, language, and attention domains.

Previous studies have demonstrated a bidirectional association between severe hypoglycemia and cognitive impairment in individuals with T2DM. Severe hypoglycemia can contribute to a decline in cognitive function, and cognitive impairment may increase the risk of severe hypoglycemia [38]. Our findings were consistent with numerous studies on T2DM, indicating that TBR$^{<3.9}$

$^{\text{mmol/L}}$ was associated with disruption in memory, executive functioning, and visuospatial ability. Furthermore, we found that deficits in executive functioning and visuospatial ability may lead to the occurrence of TBR$^{<3.9 \text{ mmol/L}}$, and the impairment of visuospatial ability was a more important factor for the occurrence of TBR$^{<3.9 \text{ mmol/L}}$. Therefore, our study has shown a bidirectional association between TBR$^{<3.9 \text{ mmol/L}}$ and cognitive impairment.

Hypoglycemic episodes can have detrimental effects on the brain, including neuronal death in the hippocampus and cerebral cortex, as well as increased consumption of alternate respiratory substrates, such as ketone bodies, glycogen and monocarboxylate, in the brain, leading to mitochondrial dysfunction and brain function damage [39, 40]. Moreover, patients with cognitive impairment
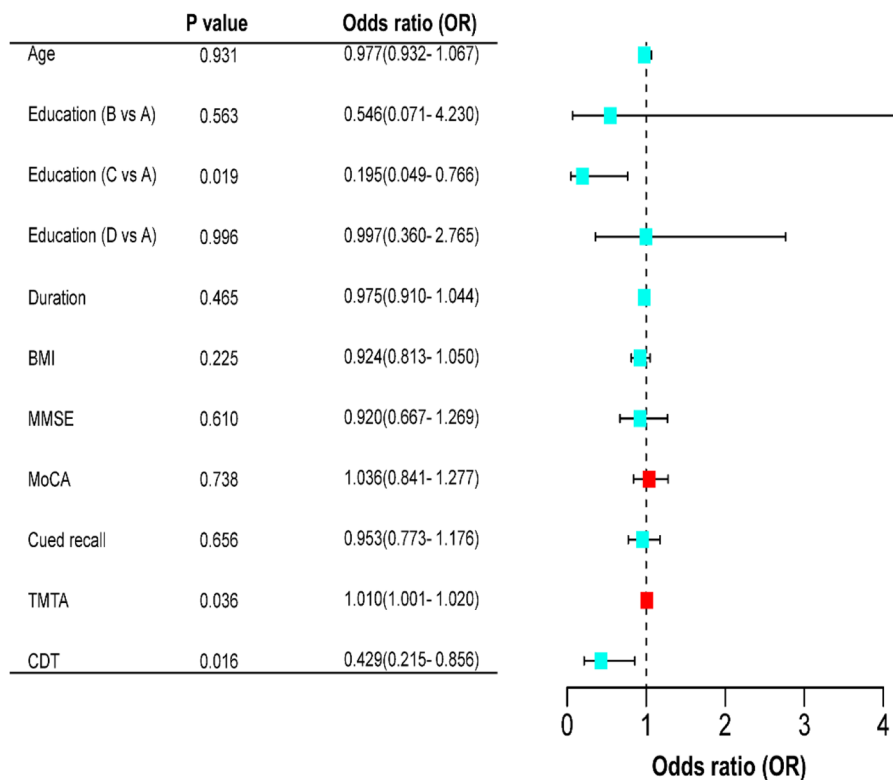
	P value	Odds ratio (OR)
Age	0.931	0.977(0.932- 1.067)
Education (B vs A)	0.563	0.546(0.071- 4.230)
Education (C vs A)	0.019	0.195(0.049- 0.766)
Education (D vs A)	0.996	0.997(0.360- 2.765)
Duration	0.465	0.975(0.910- 1.044)
BMI	0.225	0.924(0.813- 1.050)
MMSE	0.610	0.920(0.667- 1.269)
MoCA	0.738	1.036(0.841- 1.277)
Cued recall	0.656	0.953(0.773- 1.176)
TMTA	0.036	1.010(1.001- 1.020)
CDT	0.016	0.429(0.215- 0.856)

Fig. 2 Logistic regression analysis of risk factors for the development of T2DM combined with $TBR^{<3.9\ mmol/L}$. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; TMTA, Trail Making Test A; CDT, Clock Drawing Test; TBR, time below range. Education, A: primary school; B: junior middle school; C: senior high school; D: junior college degree

Table 3 Association between CDT scores and $TBR^{<3.9\ mmol/L}$ after controlling for confounding factors

Models	$TBR^{<3.9\ mmol/L}$		
	OR	95% CI	*P* values
Model 1			
CDT	0.379	(0.185–0.778)	0.008
Model 2			
CDT	0.385	(0.186–0.800)	0.011
TMTA	1.010	(0.999–1.021)	0.071

Model 1 was adjusted for age, sex, duration of disease, education and BMI.

Model 2 includes all variables in Model 1 plus TMTA.

TMTA, Trail Making Test A; CDT, Clock Drawing Test

may have a decreased ability to sense hypoglycemia, resulting in repeated episodes of hypoglycemia. In addition, patients with cognitive dysfunction may have a higher risk of hypoglycemia due to reduced capacity for self-care and the potential for overdose of glucose-lowering medications. This bidirectional association highlights the importance of managing hypoglycemia in patients with T2DM to prevent further cognitive decline.

In our study, we also investigated the association between hyperglycemia and cognitive performance using TAR and FPG as metrics of hyperglycemia. Previous studies have consistently shown a strong correlation between hyperglycemia and cognitive impairment [16, 41]. Our findings revealed that a higher $TAR^{10.1-13.9\ mmol/L}$ was associated with better memory performance. Even after adjusting for various confounding factors, $TAR^{10.1-13.9\ mmol/L}$ remained one of the main factors affecting memory. Therefore, we speculate that maintaining blood glucose levels within the range of 10.1–13.9 mmol/L may potentially slow the decline in memory and impede the occurrence and development of cognitive impairment. Notably, our study is the first to reveal that a higher $TAR^{10.1-13.9\ mmol/L}$ was associated with better cognitive function. Therefore, we recommended that glycemic control target values should be relaxed for T2DM patients with cognitive impairment.

However, it is important to note that another study demonstrated that a higher $TAR^{>10.0\ mmol/L}$ was associated with a lower performance in executive functioning and working memory [16]. Our results are in line with these findings. We found that a higher $TAR^{>13.9\ mmol/L}$ was correlated with worse memory performance in younger patients with T2DM. Additionally, previous studies have suggested that elevated FPG could increase the risk of dementia [42]. In our study, we observed that
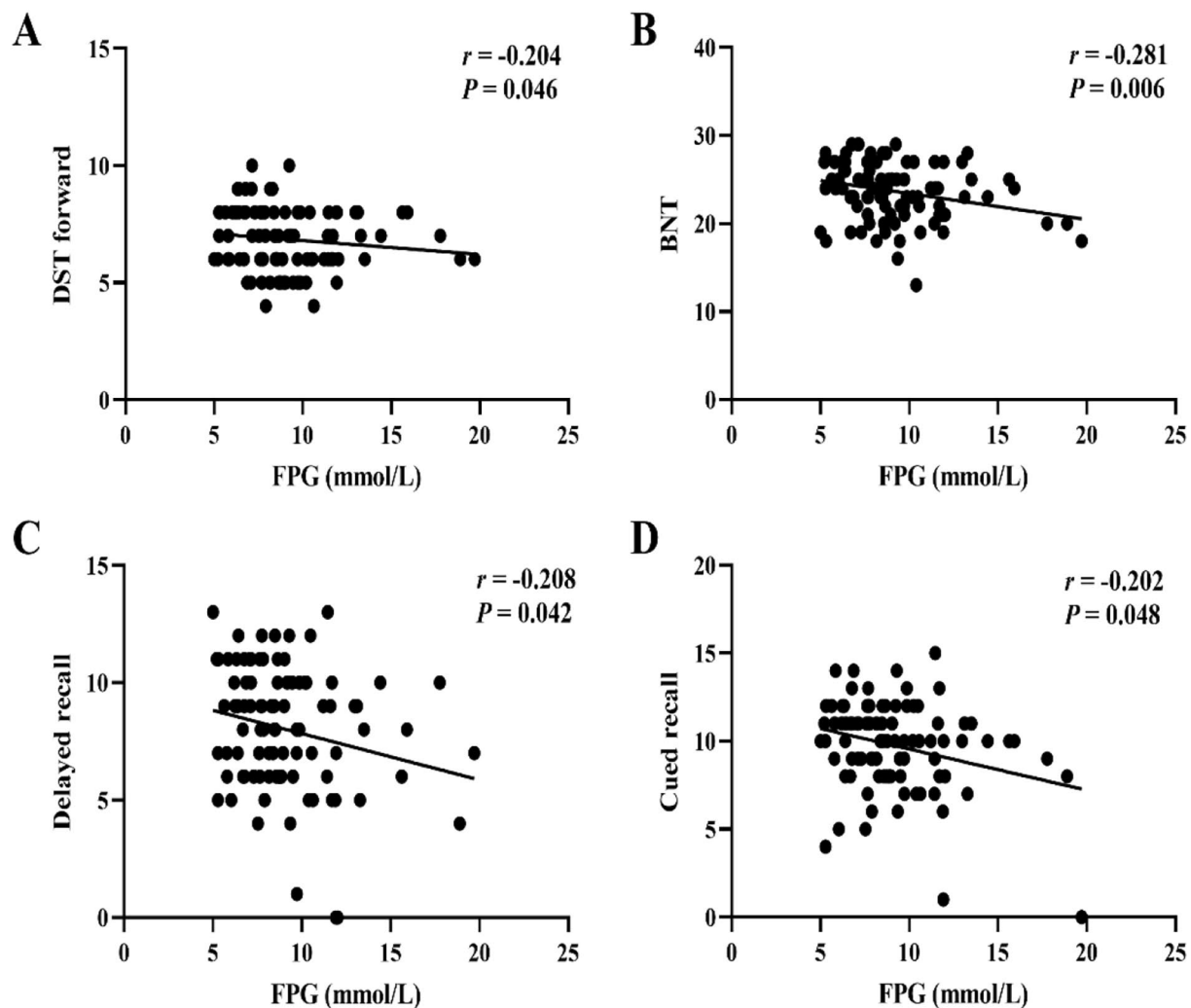
Fig. 3 Correlation of FPG and neuropsychological test results. **A**, Correlation between FPG and DST forward scores. **B**, Correlation between FPG and BNT scores. **C**, Correlation between FPG and delayed recall scores. **D**, Correlation between FPG and cued recall scores. DST, Digit Span Test; BNT, Boston Naming Test; FPG, fasting plasma glucose

higher FPG levels were associated with worse memory, attention and language abilities. Even after adjusting for various confounding factors, FPG remained one of the main factors affecting memory.

As such, our findings suggest that a higher TAR$^{>13.9 \text{ mmol/L}}$ and FPG levels were associated with worse cognitive function in younger patients with T2DM. The underlying mechanism for the association between very high-glucose hyperglycemia (TAR$^{>13.9 \text{ mmol/L}}$) and cognition remains unknown. Acute high-glucose hyperglycemia may lead to cellular hypoxia and intracellular hyperosmosis in cerebral neurons, resulting in neuronal damage [43]. Chronic high-glucose hyperglycemia can cause the accumulation of advanced glycation end products, ROS, and proinflammatory cytokines that induce neuronal damage [44]. Additionally, T2DM patients with

cognitive dysfunction may have a higher risk of hyperglycemia due to forgetting to take glucose-lowering medications, although hyperglycemia may also be caused by a combination of excessive food intake and lack of exercise.

TIR is closely associated with micro- and macrovascular complications and mortality in patients with T2DM [30, 45–47]. Several studies have reported that TIR is closely related to cognitive dysfunction [15, 16]. However, in contrast to a previous study, our findings did not reveal a relationship between TIR and global cognition or specific cognitive domains. The discrepancies in our findings may be attributable to various reasons, including the age and ethnicity of participants and the duration of FGM. Another potential factor contributing to the inconsistent outcome could be the high incidence of TBR$^{<3.9 \text{ mmol/L}}$, which was observed in 45.8% of patients.

Dong *et al. BMC Neurology*   (2023) 23:200

Page 9 of 12

Table 4 Association between cued recall scores and FPG/TBR/TAR/TIR/GRI after controlling for confounding factors

	β	95% CI	P values
Model 1			
FPG	-0.307	(-0.441 - -0.092)	0.003
Model 2			
TBR$^{<3.9\ mmol/L}$ (%)	-0.214	(-0.186 - -0.008)	0.033
TAR$^{>13.9\ mmol/L}$ (%)	-0.216	(-0.053 - -0.003)	0.030
TAR$^{10.1-13.9\ mmol/L}$ (%)	0.206	(0.001–0.067)	0.042
TIR (%)	0.086	(-0.011–0.026)	0.399
GRI	-0.154	(-0.030–0.004)	0.129
Model 3			
TBR$^{<3.9\ mmol/L}$ (%)	-0.327	(-0.234 - -0.062)	0.001
TAR$^{>13.9\ mmol/L}$ (%)	-0.031	(-0.038–0.030)	0.818
TAR$^{10.1-13.9\ mmol/L}$ (%)	0.343	(0.025–0.089)	0.001
Model 4			
TBR$^{<3.9\ mmol/L}$ (%)	-0.212	(-0.186 - -0.006)	0.036
TAR$^{>13.9\ mmol/L}$ (%)	-0.218	(-0.054 - -0.003)	0.030
TAR$^{10.1-13.9\ mmol/L}$ (%)	0.203	(0.001–0.067)	0.046

Model 1 was adjusted for age, sex, duration of disease, education and BMI.

Model 2 was adjusted for age, sex, duration of disease, education and BMI.

Model 3 includes all variables in model 2 plus FPG.

Model 4 includes all variables in model 2 plus depression scale.

FPG, fasting plasma glucose; TIR, time in range; TAR, time above range; TBR, time below range

GRI, glycemia risk index

Interestingly, patients with higher TIR had better language ability at the same incidence of TBR$^{<3.9\ mmol/L}$. Therefore, when adjusting the glucose-lowering regimen for patients with T2DM, the DATAA (Download Data, Assess Safety, Time in Range, Areas to Improve, Action Plan) model should be adopted in interpreting the FGM data in elderly patients and those with cognitive impairment [48], and the first priority in this approach should be to reduce TBR to target levels, followed by addressing TIR. Moreover, implementing individualized glucose-lowering treatment regimens may lead to improvements in language ability and help prevent the occurrence and progression of cognitive impairment.

The GRI is a composite metric for evaluating glycemic control by utilizing the percentages of hyperglycemia and hypoglycemia based on CGM data. The lower the GRI is, the better the quality of glycemic control [9]. However, in our study, we did not observe an association between the GRI and specific cognitive domains, which may be attributed to the limitations of the GRI. The GRI cannot independently reflect the composition of hyperglycemia and hypoglycemia groups, and it may not predict the occurrence of cognitive impairment in patients with T2DM.

Several studies have suggested that cognitive dysfunction in patients with T2DM may be associated with glucose variability [11, 14]. However, a cross-sectional study in Japan found no association between CV and cognitive performance [16]. A CV% target ≤ 36% was defined as stable glucose, and a CV% target > 36% was defined as unstable glucose [49]. In the current study, we found that the CV% was 26.50% (23.65%, 33.00%), indicating stable blood glucose levels. As a result, there was no significant relationship between CV and global cognition or specific cognitive domains in the study population, which is consistent with the Japanese study. Previous studies have shown that MAGE correlated negatively with MMSE [14]. However, in our study, we did not find any association between MAGE and cognitive performance. One possible explanation for this discrepancy is the age difference between the two studies. The patients in our study were much younger (mean age: 61.40 years) than those in the other study (mean age: 78 years). Overall, our findings suggest that glucose variability may not significantly impact cognitive function in younger patients with T2DM.

This study had several limitations. The cross-sectional design did not allow us to explore the relationship between the key FGM-derived metrics and the development of cognitive impairment. The present study also had a small sample size, and expansion of the sample volume and follow-up observation studies on patients are necessary. In the future, we will collect more clinical samples in groups of different age stages, and participants will wear a blinded FGM system for 14 days.

Conclusions

Through the study of the relationship between key FGM-derived metrics and specific cognitive domains, we found that a higher TBR$^{<3.9\ mmol/L}$ was associated with worse cognition (memory dysfunction, deficits in visuospatial ability, and impaired executive functioning). At the same incidence of TBR$^{<3.9\ mmol/L}$, the patients with a higher TIR exhibited better performance on language ability. In addition, we found that a higher TAR$^{10.1-13.9\ mmol/L}$ was associated with better memory performance, whereas a higher TAR$^{>13.9\ mmol/L}$ was correlated with worse memory performance. Therefore, it is important to be relaxed when setting glycemic targets for T2DM patients with cognitive impairment, with a strong focus on reducing TBR$^{<3.9\ mmol/L}$ and preventing high-glucose hyperglycemia (TAR$^{>13.9\ mmol/L}$).

Dong *et al. BMC Neurology*   (2023) 23:200

Page 10 of 12

Abbreviations

CGM	Continuous glucose monitoring
T2DM	Type 2 diabetes mellitus
FGM	Flash continuous glucose monitoring
TIR	Time in range
TBR	Time below range
TAR	Time above range
GRI	Glycemia risk index
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
FPG	Fasting plasma glucose
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
DST forward	Digit Span Test forward
DST backward	Digit Span Test backward
TMTA	Trail Making Test A
TMTB	Trail Making Test B
BNT	Boston Naming Test
CDT	Clock Drawing Test
VFT	Verbal Fluency Test
AVLT	Auditory Verbal Learning Test
NAH	Nocturnal asymptomatic hypoglycemia
REM	Rapid eye movement
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
BMI	Body mass index
HbA1c	Hemoglobin A1c
SD	Standard deviation
MG	Mean glucose
CV	Coefficient of variation
MAGE	Mean amplitude of glycemic excursions
ROS	reactive oxygen species.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-023-03242-2.

Supplementary Material 1

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee of the First Hospital of Hebei Medical University (approval number: 20210502) and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant. No potentially identifiable human images or data are presented in this study. This study was registered on 15 September 2021, with the registration number ChiCTR2100051164.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest.

Author details

[1]Department of Endocrinology and Metabolism, The First Hospital of Hebei Medical University, No.89, Donggang Road, Shijiazhuang 050031, P. R. China
[2]Central Laboratory, The First Hospital of Hebei Medical University, Shijiazhuang 050031, P. R. China
[3]Hebei International Joint Research Center for Brain Science, Shijiazhuang 050031, P. R. China
[4]Hebei Key Laboratory of Brain Science and Psychiatric-Psychologic Disease, Shijiazhuang 050031, P. R. China

References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119. https://doi.org/10.1016/j.diabres.2021.109119.
2. Koyani CN, Trummer C, Shrestha N, Scheruebel S, Bourgeois B, Plastira I, et al. Saxagliptin but not Sitagliptin inhibits CaMKII and PKC via DPP9 inhibition in Cardiomyocytes. Front Physiol. 2018;9:1622. https://doi.org/10.3389/fphys.2018.01622.
3. Chia CW, Egan JM, Ferrucci L. Age-related changes in glucose metabolism, hyperglycemia, and Cardiovascular Risk. Circ Res. 2018;123 7:886–904. https://doi.org/10.1161/CIRCRESAHA.118.312806.
4. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. Lancet Neurol. 2008;7 2:184 – 90. https://doi.org/10.1016/S1474-4422(08)70021-8.
5. Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, et al. Glucose levels and risk of dementia. N Engl J Med. 2013;369 6:540–8. https://doi.org/10.1056/NEJMoa1215740.
6. Gao R, Ren L, Zhou Y, Wang L, Xie Y, Zhang M, et al. Recurrent non-severe hypoglycemia aggravates cognitive decline in diabetes and induces mitochondrial dysfunction in cultured astrocytes. Mol Cell Endocrinol. 2021;526:111192. https://doi.org/10.1016/j.mce.2021.111192.
7. Yang J, Zhao Z, Yuan H, Ma X, Li Y, Wang H, et al. The mechanisms of glycemic variability accelerate diabetic central neuropathy and diabetic peripheral neuropathy in diabetic rats. Biochem Biophys Res Commun. 2019;510 1:35–41. https://doi.org/10.1016/j.bbrc.2018.12.179.
8. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, 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. https://doi.org/10.2337/dci19-0028.
9. Klonoff DC, Wang J, Rodbard D, Kohn MA, Li C, Liepmann D, et al. A glycemia risk index (GRI) of hypoglycemia and hyperglycemia for continuous glucose monitoring validated by clinician ratings. J Diabetes Sci Technol. 2022;19322968221085273. https://doi.org/10.1177/19322968221085273.
10. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. Classifying neurocognitive disorders: the DSM-5 approach. Nat Rev Neurol. 2014;10 11:634–42. https://doi.org/10.1038/nrneurol.2014.181.
11. Xia W, Luo Y, Chen YC, 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. https://doi.org/10.3233/JAD-191217.
12. Ohara M, Fukui T, Ouchi M, Watanabe K, Suzuki T, Yamamoto S, et al. Relationship between daily and day-to-day glycemic variability and increased

oxidative stress in type 2 diabetes. Diabetes Res Clin Pract. 2016;122:62–70. https://doi.org/10.1016/j.diabres.2016.09.025.

13. Hoyos CM, Stephen C, Turner A, Ireland C, Naismith SL, Duffy SL. Brain oxidative stress and cognitive function in older adults with diabetes and pre-diabetes who are at risk for dementia. Diabetes Res Clin Pract. 2022;184:109178. https://doi.org/10.1016/j.diabres.2021.109178.

14. Rizzo MR, Marfella R, Barbieri M, Boccardi V, Vestini F, Lettieri B, et al. Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. Diabetes Care. 2010;33 10:2169–74. https://doi.org/10.2337/dc10-0389.

15. Shang J, Lyu Y, An R, Yuan H. Relationship between mild cognitive impairment and time in the range of blood glucose targets and time below the target range in elderly patients with type 2 diabetes by a cognitive assessment. Chin J Endocrinol Metab. 2020;36(9):789–893.

16. Sugimoto T, Tokuda H, Miura H, Kawashima S, Ando T, Kuroda Y, et al. Cross-sectional association of metrics derived from continuous glucose monitoring with cognitive performance in older adults with type 2 diabetes. Diabetes Obes Metab. 2023;25(1):222–8. https://doi.org/10.1111/dom.14866.

17. Lacy ME, Gilsanz P, Eng C, Beeri MS, Karter AJ, Whitmer RA. Severe hypoglycemia and cognitive function in older adults with type 1 diabetes: the study of longevity in diabetes (SOLID). Diabetes Care. 2020;43 3:541–8. https://doi.org/10.2337/dc19-0906.

18. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539–53. https://doi.org/10.1002/(SICI)1096-9136(199807)15:7%3C539::AID-DIA668%3E3.0.CO;2-S.

19. Wang B, Guo QH, Chen MR, Zhao QH, Zhou Y, Hong Z. The clinical characteristics of 2,789 consecutive patients in a memory clinic in China. J Clin Neurosci. 2011;18 11:1473–7. https://doi.org/10.1016/j.jocn.2011.05.003.

20. Lu J, Li D, Li F, Zhou A, Wang F, Zuo X, et al. Montreal cognitive assessment in detecting cognitive impairment in chinese elderly individuals: a population-based study. J Geriatr Psychiatry Neurol. 2011;24 4:184–90. https://doi.org/10.1177/0891988711422528.

21. Leung JL, Lee GT, Lam YH, Chan RC, Wu JY. The use of the Digit Span Test in screening for cognitive impairment in acute medical inpatients. Int Psychogeriatr. 2011;23 10:1569–74. https://doi.org/10.1017/S1041610211000792.

22. Wei M, Shi J, Li T, Ni J, Zhang X, Li Y, et al. Diagnostic accuracy of the Chinese Version of the trail-making test for Screening Cognitive Impairment. J Am Geriatr Soc. 2018;66(1):92–9. https://doi.org/10.1111/jgs.15135.

23. Cheung RW, Cheung MC, Chan AS. Confrontation naming in chinese patients with left, right or bilateral brain damage. J Int Neuropsychol Soc. 2004;10 1:46–53. https://doi.org/10.1017/S1355617704101069.

24. Feng Q, Zhang QL, Du Y, Ye YL, He QQ. Associations of physical activity, screen time with depression, anxiety and sleep quality among chinese college freshmen. PLoS ONE. 2014;9 6:e100914. https://doi.org/10.1371/journal.pone.0100914.

25. Hazan E, Frankenburg F, Brenkel M, Shulman K. The test of time: a history of clock drawing. Int J Geriatr Psychiatry. 2018;33(1):e22–e30. https://doi.org/10.1002/gps.4731.

26. Kaplan E. The process approach to neuropsychological assessment of psychiatric patients. J Neuropsychiatry Clin Neurosci. 1990;2 1:72–87. https://doi.org/10.1176/jnp.2.1.72.

27. Cheng Y, Jin Y, Unverzagt FW, Su L, Yang L, Ma F, et al. The relationship between cholesterol and cognitive function is homocysteine-dependent. Clin Interv Aging. 2014;9:1823–9. https://doi.org/10.2147/CIA.S64766.

28. Zhao Q, Guo Q, Liang X, Chen M, Zhou Y, Ding D, et al. Auditory verbal learning test is Superior to Rey-Osterrieth Complex figure memory for Predicting mild cognitive impairment to Alzheimer's Disease. Curr Alzheimer Res. 2015;12 6:520–6. https://doi.org/10.2174/1567205012666150530202729.

29. Wang S, Tan Z, Wu T, Shen Q, Huang P, Wang L, et al. Largest amplitude of glycemic excursion calculating from self-monitoring blood glucose predicted the Episodes of Nocturnal Asymptomatic Hypoglycemia detecting by continuous glucose monitoring in outpatients with type 2 diabetes. Front Endocrinol (Lausanne). 2022;13:858912. https://doi.org/10.3389/fendo.2022.858912.

30. Lu J, Wang C, Shen Y, Chen L, Zhang L, Cai J, et al. Time in Range in Relation to all-cause and Cardiovascular Mortality in patients with type 2 diabetes: a prospective cohort study. Diabetes Care. 2021;44(2):549–55. https://doi.org/10.2337/dc20-1862.

31. Han E, Han KD, Lee BW, Kang ES, Cha BS, Ko SH, et al. Severe hypoglycemia increases dementia risk and related mortality: a Nationwide,

32. McCrimmon RJ. Consequences of recurrent hypoglycaemia on brain function in diabetes. Diabetologia. 2021;64 5:971–7. https://doi.org/10.1007/s00125-020-05369-0.

33. Brady CC, Vannest JJ, Dolan LM, Kadis DS, Lee GR, Holland SK, et al. Obese adolescents with type 2 diabetes perform worse than controls on cognitive and behavioral assessments. Pediatr Diabetes. 2017;18 4:297–303. https://doi.org/10.1111/pedi.12383.

34. Heath CA, Mercer SW, Guthrie B. Vascular comorbidities in younger people with dementia: a cross-sectional population-based study of 616 245 middle-aged people in Scotland. J Neurol Neurosurg Psychiatry. 2015;86 9:959–64. https://doi.org/10.1136/jnnp-2014-309033.

35. Kadohara K, Sato I, Kawakami K. Diabetes mellitus and risk of early-onset Alzheimer's disease: a population-based case-control study. Eur J Neurol. 2017;24 7:944–9. https://doi.org/10.1111/ene.13312.

36. Jauch-Chara K, Hallschmid M, Gais S, Schmid SM, Oltmanns KM, Colmorgen C, et al. Hypoglycemia during sleep impairs consolidation of declarative memory in type 1 diabetic and healthy humans. Diabetes Care. 2007;30:8. https://doi.org/10.2337/dc07-0067.

37. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. Diabetes. 2005;54 12:3592–601. https://doi.org/10.2337/diabetes.54.12.3592.

38. Mattishent K, Loke YK. Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. Diabetes Obes Metab. 2016;18(2):135–41. https://doi.org/10.1111/dom.12587.

39. Rehni AK, Dave KR. Impact of hypoglycemia on Brain Metabolism during Diabetes. Mol Neurobiol. 2018;55 12:9075–88. https://doi.org/10.1007/s12035-018-1044-6.

40. Zhou Y, Huang L, Zheng W, An J, Zhan Z, Wang L, et al. Recurrent nonsevere hypoglycemia exacerbates imbalance of mitochondrial homeostasis leading to synapse injury and cognitive deficit in diabetes. Am J Physiol Endocrinol Metab. 2018;315(5):E973–E86. https://doi.org/10.1152/ajpendo.00133.2018.

41. Rawlings AM, Sharrett AR, Albert MS, Coresh J, Windham BG, Power MC, et al. The Association of late-life diabetes status and hyperglycemia with incident mild cognitive impairment and dementia: the ARIC Study. Diabetes Care. 2019;42 7:1248–54. https://doi.org/10.2337/dc19-0120.

42. Wang F, Luo J, Ding D, Zhao Q, Guo Q, Liang X, et al. Elevated fasting blood glucose level increases the risk of cognitive decline among older adults with diabetes Mellitus: the Shanghai Aging Study. J Alzheimers Dis. 2019;67 4:1255–65. https://doi.org/10.3233/JAD-180662.

43. Malone JI, Hanna S, Saporta S, Mervis RF, Park CR, Chong L, et al. Hyperglycemia not hypoglycemia alters neuronal dendrites and impairs spatial memory. Pediatr Diabetes. 2008;9 6:531–9. https://doi.org/10.1111/j.1399-5448.2008.00431.x.

44. Valente T, Gella A, Fernandez-Busquets X, Unzeta M, Durany N. Immuno-histochemical analysis of human brain suggests pathological synergism of Alzheimer's disease and diabetes mellitus. Neurobiol Dis. 2010;37 1:67–76. https://doi.org/10.1016/j.nbd.2009.09.008.

45. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, et al. Association of Time in Range, as assessed by continuous glucose monitoring, with Diabetic Retinopathy in Type 2 diabetes. Diabetes Care. 2018;41 11:2370–6. https://doi.org/10.2337/dc18-1131.

46. Li F, Zhang Y, Li H, Lu J, Jiang L, Vigersky RA, et al. TIR generated by continuous glucose monitoring is associated with peripheral nerve function in type 2 diabetes. Diabetes Res Clin Pract. 2020;166:108289. https://doi.org/10.1016/j.diabres.2020.108289.

47. Li J, Li Y, Ma W, Liu Y, Yin X, Xie C, et al. Association of Time in Range levels with lower extremity arterial disease in patients with type 2 diabetes. Diabetes Metab Syndr. 2020;14 6:2081–5. https://doi.org/10.1016/j.dsx.2020.09.028.

48. Isaacs D, Cox C, Schwab K, Oser TK, Rinker J, Mason MJ, et al. Technology Integration: the role of the Diabetes Care and Education specialist in practice. Diabetes Educ. 2020;46(4):323–34. https://doi.org/10.1177/0145721720935123.

49. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 6. Glycemic targets: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):97–S110. https://doi.org/10.2337/dc23-S006.

Publisher's Note