Original Article

The Relationship between Glucose Excursion and Cognitive Function in Aged Type 2 Diabetes Patients*

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Abstract

Objective Evidence suggests that type 2 diabetes (T2DM) is associated with an increased risk of dementia and that glucose variability is an independent risk factor for diabetic complications. This study investigated the relationship between glucose excursion and cognitive function in aged T2DM patients.

Methods A total of 248 aged T2DM patients wore a continuous glucose monitoring system (CGMS) for 3 days in order to evaluate glucose excursion, including mean amplitude of glycemic excursions (MAGE) and mean of daily difference (MODD). All subjects were evaluated with a number of accepted cognitive function tests, including the mini-mental status examination (MMSE). The relationship between MAGE and MODD and performance on these cognitive tests was assessed.

Results The MAGE and MMSE score were negatively correlated, likewise with the correlation between MODD and MMSE. Liner multivariate regression analysis showed that MAGE and MODD were also negatively related to MMSE independent of age, sex, glycemic control, hypertension, smoking, or coronary heart disease history.

Conclusion Glucose excursion is related to cognitive function in aged T2DM patients. Elevated glucose excursion decreased the MMSE score, which reflects general cognitive function. Thus, therapy aimed at controlling glucose excursion may be beneficial for maintaining cognitive function in aged T2DM patients.

Key words: Glucose excursion; Continuous glucose monitoring system; Diabetes mellitus; Aged

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INTRODUCTION

It is well documented that maintaining tight glycemic control is critical for preventing diabetes complications[1-3]. Moreover, it is known that overall glycemic control, as reflected by glycosylated hemoglobin A1c (HbA1c) levels, acts as a surrogate maker for the risk of diabetes complications. However, from a more practical point of view, glycemic disorders can be described as being the function of two components: the duration and magnitude of chronic sustained hyperglycemia (as reflected by HbA1c levels) and acute glucose fluctuations. Recent findings indicate that acute glycemic fluctuations might also act as a risk factor for diabetes complications[4]. A recent review

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concluded that glucose variability, in combination with HbA1c, maybe a more reliable indicator of blood glucose control and provide greater insight into the risk of long-term diabetes complications than mean HbA1c alone[5]. A lightweight, portable, minimally-invasive continuous glucose monitoring system (CGMS), was recently developed, and represents a new approach to studying the influence of glycemic fluctuation in real life[6-7]. The system is characterized by the ability to monitor serum glucose levels on a continuous basis. Furthermore, the system continuously measures subcutaneous tissue interstitial glucose levels, and records values (on average) every 5 min.

A number of clinical and epidemiological studies have provided direct evidence to show that patients with type 2 diabetes (T2DM) are at an increased risk of developing dementia and AD[8-10]. Indeed, individuals with diabetes are 1.5 times more likely to experience cognitive decline and frank dementia than individuals without diabetes[11]. Further, T2DM often leads to cardiovascular complications and other morbidities, meaning that many T2DM patients succumb to their diabetes or the associated complications before the onset of AD, usually when the patients are in their 70 s. However, with advances in the therapeutic regimens for diabetes, T2DM patients are increasingly living longer, meaning that the number of T2DM patients with concomitant AD will likely increase.

It is likely that T2DM leads to cognitive dysfunction and alterations in the brain signals necessary for cognitive function. The mechanisms underlying the impact of diabetes on the brain are currently unknown, but are likely to be multifactorial. A number of studies have shown that HbA1c is an independent risk factor for the decline in cognitive performance in patients with T2DM. However, very little research has explored the role of glucose exursion on cognitive decline. Given that the brain is dependent on a continuous supply of glucose as its principal energy source and that acute changes in blood glucose can alter regional cerebral blood flow and cause osmotic changes in cerebral neurons, it is plausible that glucose excursion may also affect cognitive function. Thus, the purpose of this study was to investigate the relationship between glucose excursion and cognitive function in a cohort of aged type 2 diabetes patients.

RESEARCH DESIGN AND METHODS

Patient Selection

From January 2008 to May 2010, diabetic patients from the Department of Geriatrics, Shanghai Jiaotong University Affiliated Sixth People's Hospital were recruited into the study. Inclusion criteria included: (1) that the patients were aged ⩾65 years, (2) that the patients were without cerebral stroke history (which would be further proved by brain CT or MRI scan) and that their Hachinski Ischemic Score (HIS) score was ⩽4, (3) they had no non-AD dementia history, such as Parkinson disease, frontotemporal dementia, normal pressure hydrocephalus, epilepsy, brain trauma, brain tumor, intracranial infection, or (4) no depression history and a whose Hamilton Rating Scale for Depression (HAMD) score of <7, (5) no other psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria, (6) no drug or alcohol abuse or dependence in the last two years, (7) were free (within the last month) from any medications that influence brain function, (8) had no clinically significant or unstable medical illnesses, severe diabetes complications (e.g., diabetic ketoacidosis, hyperglycemic, hyperosmolar nonketotic syndrome), or any other disorders affecting glucose metabolism, and (9) were in a stable condition, whereby their individual treatment protocols had not be adjusted for at least the last 3 months.

A total of 284 patients were screened, of which 248 patients (193 males and 55 females) aged 65 to 85 years with T2DM were recruited into the study. All patients provided written, informed consent allowing for inclusion into the study, which was approved by the Shanghai Jiaotong University affiliated Sixth People's Hospital.

Study Protocol

Glucose Monitoring The CGMS sensor (Medtronic MiniMed) was inserted by the same investigator on day 0 and removed midmorning on day 3. Data were downloaded from the system and the patients' glucose profiles were evaluated based on the data collected on days 1 and 2. A minimum of four self-monitoring blood glucose samples were entered into the monitor for calibration; event markers were also entered into the monitor. The patients were also required to keep detailed written records of insulin administration, food intake, exercise and hypoglycemic symptoms. For optimal accuracy, the

following cutoff criteria were adhered to: (1) when the difference in the blood glucose (BG) values of the meter reading were ⩾5.6 mmol/L, mean absolute deviation ⩽28%, and correlation coefficient ⩾0.79, and (2) when the difference in the BG values of meter readings was <5.6 mmol/L and the mean absolute differences were ⩽18%. The patients were asked not to change their daily habits, particularly insulin administration. All patients received dietary instructions according to uniform criteria as the CGMS device was implemented. While the CGMS device was implanted, the patients' were maintained on a total calorific intake (obtained through three daily meals) amounting to 30 kcal/kg/day, and consisting of 50% carbohydrate, 15% protein, and 35% fat. The calorific distribution between breakfast, lunch and dinner was 20%, 40%, and 40%, respectively. Meal time is relatively constant, 6:30-7:30 A.M. for breakfast, 11:30 A.M. - 12:30 P.M. for lunch, and 5:30-6:30 P.M. for dinner. Data were downloaded at the end of the 72 h period, and analyzed using the MiniMed Solutions software. Insertion sites were inspected for evidence of inflammation or infection.

Glucose Excursion Parameter The 24 h mean blood glucose (MBG) levels were calculated based on the 288 readings obtained by the CGMS over each of the 24 h periods. Several approaches were used to quantify the amplitude of glycemic swings: standard deviation of blood glucose levels (SD), difference between minimum and maximum glucose levels (LAGE), and mean amplitude of glycemic excursions (MAGE). The MAGE was designed to quantify major glycemic swings, and exclude minor ones, and was used to assess intra-day blood glucose variability. Only increases of more than one standard deviation of the mean glycemic values were taken into account. The MAGE calculations were obtained by measuring the arithmetic mean of the differences between consecutive peaks and nadirs; measurements in the peak-to-nadir or nadir-to-peak direction were determined by the first qualifying excursion[12]. Finally, the mean of daily differences (MODD) was used to assess day-to-day glycemic variability and calculated based on the absolute difference between the paired continuous glucose monitoring values obtained during two successive days[13]. All of the above parameters were based on the mean values taken on days 1 and 2.

Biochemical Measurements The HbA1c levels were measured by high-performance liquid chromatography (Arkary, Japan), using a non-diabetic normal range of 4.9%-5.8%. Plasma glucose concentrations were determined by the glucose oxidase method (Automatic Biochemistry Analyzer, Beckman). Capillary glucose concentrations were measured by a Roche glucotrend 2 BG meter.

Cognitive Testing All participants completed a series battery of cognitive rating scale tests, including the mini-mental state examination (MMSE), clinical dementia rating (CDR), global deterioration scale (GDS), and clock drawing test (CDT). Functional status was evaluated using the Activities of Daily Living Scale (ADL). All of the tests were completed on day 1 or day 2, and during the period where the patients were monitored by the CGMS. To ensure that participants were not hypoglycemic at the time of cognitive testing, the tests were administered after breakfast, and a capillary glucose levels were measured before testing. Tests were administered and scored by certified technicians. The MMSE is a screening tool for detecting changes in cognitive skills, which can identify changes in cognitive function for elderly individuals without dementia, and may identify individuals in the prodromal phase of dementia. Patients receive a score from 0 to 30, with higher scores indicating a better performance on the test.

Measures of Confounding Variables and Covariates We adjusted the analyses for several factors that may confound the association between glycemic status measures and cognitive function, including (1) education, (2) diabetes duration, (3) hypertension history, (4) coronary heart disease history, and (5) smoking history.

Data Analysis

The CGM parameters were analyzed using the CGMS software, version 3.0. Descriptive data were expressed as a mean±standard deviation. *t*-tests were used to compare the measurement data. The ratios of count data were compared with χ^2 tests. The relationships between variables were assessed using a Pearson's correlation coefficient. In the first instance, multiple regression models were used to explore the influence of different variables on cognition performance, including age, sex, diabetes duration, FPG, PPG, MBG, and HbA1c. Subsequent analysis included the aforementioned parameters in addition to the following variables: hypertension history, coronary heart disease history, and smoking history. Statistical significance was set at the $P<0.05$ level. Analyses were performed using SPSS System (version 16.0).

RESULTS

Clinical Characteristics

All of the patients tolerated the CGMS for the duration of the study. None complained of discomfort, or experienced inflammation or allergic changes at the embedding sites. As noted in Table 1, the 248 participants had mean age of 80.2 years, mean education year of 12.95, mean diabetes duration of 15.5, mean HbA1c of 7.06%. A total of 193 were male. Of this group, 153 reported existing hypertension, 147 reported coronary heart disease, and 95 reported a history of smoking.

The glucose excursion parameters are showed in Table 1. The MAGE obtained from the CGMS over the 24 h in the 248 patients was 58.02 mg/dL, with a MODD of 27.59 mg/dL. Cognitive function test scores are also showed in Table 1, whereby the mean MMSE score was 25.11.

Table 1. Clinical Characteristics of the Type 2 Diabetes Patients Recruited into the Study

Variable	Result
n	248
Age (years)	80.2±5.6
Sex (Male/Female)	193/55
Education (years)	12.95±4.12
Diabetes duration (years)	15.50±5.62
Hypertension (yes/no)	153/95
Coronary heart disease (yes/no)	147/101
Smoking history (yes/no)	95/153
Fasting plasma glucose (mg/dL)	115.73±48.42
Postprandial plasma glucose(mg/dL)	171.57±69.08
HbA1c (%)	7.06±2.09
MBG (mg/dL)	138.20±33.92
LAGE (mg/dL)	118.37±54.44
SD (mg/dL)	28.59±12.68
MAGE (mg/dL)	58.02±26.26
MODD (mg/dL)	27.59±14.88
MMSE score	25.11±6.06
ADL score	29.24±14.31
CDR score	0.59±0.48
GDS score	2.62±1.0
CDT score	3.08±1.24

Note. ADL, activities of daily living scale; CDR, clinical dementia rating; CDT, clock drawing test; GDS, global deterioration scale; LAGE, large amplitude of glycemia excursion; MAGE, Mean amplitude of glycemia excursion; MBG, mean blood glucose; MODD, mean of daily difference, SD, standard deviation of the mean blood glucose; MMSE, mini-mental state examination.

As 77.8% of the patients were male, the patients were then divided into two groups according gender. With the exception of smoking history, there was no difference between the two groups, for variables such as the glycemia exclusion parameters or cognitive test scores (Table 2).

Table 2. Comparison of Clinical Characteristics between the Male and Female Type 2 Diabetes Patients

Variable	Male	Female	$t(\chi^2)$	*P*
n	193	55		
Age (years)	79.85±5.76	81.58±4.83	-1.876	0.094
Education (years)	12.94±4.20	12.98±3.88	-0.059	0.953
Diabetes duration (years)	14.38±5.91	13.91±4.59	-0.390	0.697
Hypertension (yes/no)	161/32	46/9	0.001	0.990
Coronary heart disease (yes/no)	126/67	32/23	1.078	0.300
Smoking history (yes/no)	98/95	9/46	20.67	<0.001
Fasting plasma glucose (mg/dL)	117.11±50.79	111.17±39.67	0.767	0.444
Postprandial plasma glucose (mg/dL)	175.61±71.20	157.98±60.21	1.440	0.152
HbA1c (%)	7.10±2.19	6.91±1.68	0.419	0.676
MBG (mg/dL)	138.67±33.78	136.54±34.66	0.410	0.682
LAGE (mg/dL)	118.15±56.03	119.11±49.41	-0.105	0.916
SD (mg/dL)	28.74±13.34	28.11±10.28	0.298	0.766
MAGE (mg/dL)	58.52±27.48	56.36±21.96	0.495	0.621
MODD (mg/dL)	27.52±15.36	27.81±13.20	-0.119	0.905
MMSE score	25.09±6.11	25.18±5.97	-0.101	0.920
ADL score	29.82±5.45	27.15±8.93	1.418	0.159
CDR score	0.60±0.20	0.5±0.3	1.238	0.218
GDS score	2.60±1.07	2.72±0.84	-0.622	0.535
CDT score	3.13±1.26	2.89±1.15	1.183	0.238

Note. ADL, activities of daily living scale; CDR, clinical dementia rating; CDT, clock drawing test; GDS, global deterioration scale; LAGE, large amplitude of glycemia excursion; MAGE, Mean amplitude of glycemia excursion; MBG, mean blood glucose; MODD, mean of daily difference, SD, standard deviation of the mean blood glucose; MMSE, mini-mental state examination.

The Correlation between Glucose Excursion and Cognitive Function Test Scores

There was a negative correlation between MAGE and the MMSE (r=-0.308, P<0.001). Similarly, MODD was also negatively correlated with the

MMSE scores (r=-0.226, P=0.001). Following partial correlation analyses, adjusted for age, education and diabetes duration, the MAGE was still negatively correlated with MMSE (r=-0.221, P<0.006), and equally the correlation between MODD and MMSE remained negative (r=-0.175, P=0.022).

A negative correlation was also observed between SD and MMSE (r=-0.326, P<0.001), the LAGE and MMSE (r=-0.191, P=0.003). When adjusted for age, education and diabetes duration this relationship persisted (r=-0.213, P=0.008; r=-0.153, P=0.035).

The association between the level of MAGE or MODD and the scores of CDT, GSD, CDR, and ADL were all statistically significant. After being adjusted for age, education, and diabetes duration, this relationship remained significant (data not shown); however, in all cases the relationship was weak, and the r values were low.

Linear Multivariate Regression Analysis of Glucose Excursion and Cognitive Function Test Scores

As noted in Table 3, a statistically significant association between a higher MAGE and lower MMSE score was observed in both of the models. Linear multivariate regression analysis showed that MAGE had an independent effect on MMSE (β=-0.391, P=0.001). The linear multivariate regression model included age, sex, diabetes duration, diabetes control, hypertension history, coronary heart disease history, and smoking history. The MODD was also associated with MMSE, independent of all of the parameters noted above (β=-0.364, P=0.003, Table 4).

Table 3. Linear Multivariate Regression Analysis of MAGE and MMSE

variable	MMSE				
	B	Std. Error	β	t	P Value
Model 1					
Age	-0.196	0.083	-0.222	-2.370	0.020
Sex	1.287	1.154	0.111	1.115	0.268
Diabetes Duration	-0.048	0.090	-0.076	-0.531	0.597
HbA1C	0.544	0.301	0.247	1.807	0.075
MBG	-0.258	0.295	-0.107	-0.877	0.383
FPG	-0.054	0.279	-0.029	-0.194	0.847
PPG	-0.109	0.141	-0.094	-0.771	0.443
MAGE	-1.179	0.337	-0.397	-3.504	0.001
Model 2					
Age	-0.181	0.086	-0.205	-2.104	0.039
Sex	.916	1.281	0.079	0.715	0.477
Diabetes Duration	-0.056	0.092	-0.090	-0.615	0.540
HbA1C	0.567	0.306	0.257	1.851	0.068
MBG	-0.254	0.301	-0.105	-0.844	0.401
FPG	-0.074	0.285	-0.040	-0.261	0.795
PPG	-0.126	0.144	-0.108	-0.870	0.387
Hypertension	0.312	1.143	0.028	0.273	0.785
Smoking history	-0.662	1.046	-0.068	-0.633	0.529
Coronary heart disease	-0.632	1.009	-0.064	-0.627	0.533
MAGE	-0.064	0.019	-0.391	-3.394	0.001

Note. R^2=0.308 (Model 1); R^2=0.315 (Model 2). MBG, mean blood glucose; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; MAGE, mean amplitude of glycemia excursion; MODD, mean of daily difference.

Table 4. Linear Multivariate Regression Analysis of MODD and MMSE

Variable	MMSE				
	B	Std. Error	β	t	P value
Model 1					
Age	-0.222	0.080	-0.255	-2.755	0.007
Sex	0.481	0.293	0.237	1.644	0.104
Diabetes duration	-0.102	0.222	-0.066	-0.462	0.645
HbA1C	-0.382	0.330	-0.144	-1.156	0.251
MBG	0.038	0.082	0.063	0.461	0.646
FPG	-0.015	0.121	-0.013	-0.123	0.902
PPG	0.731	1.085	0.066	0.673	0.502
MODD	-2.049	0.684	-0.359	-2.995	0.004
Model 2					
Age	-0.216	0.083	-0.249	-2.593	0.011
Sex	0.509	1.201	0.046	0.424	0.673
Diabetes duration	0.033	0.083	0.054	0.394	0.694
HbA1C	0.500	0.298	0.247	1.680	0.096
MBG	-0.364	0.338	-0.137	-1.077	0.284
FPG	-0.117	0.225	-0.076	-0.520	0.605
PPG	-0.023	0.125	-0.020	-0.183	0.855
Hypertension	0.808	1.094	0.072	0.739	0.462
Smoking history	-0.375	0.988	-0.040	-0.379	0.706
Coronary heart disease	-0.500	0.919	-0.053	-0.544	0.588
MODD	-2.078	0.693	-0.364	-2.998	0.003

Note. R^2=0.231 (Model 1); R^2=0.238 (Model 2). MBG, mean blood glucose; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; MAGE, mean amplitude of glycemia excursion; MODD, mean of daily difference.

DISCUSSION

Aged T2DM patients are more likely to have moderate cognitive deficits and neurophysiologic and structural changes in the brain. The analysis of 248 individuals with established T2DM presented herein demonstrated a clear inverse relationship between cognitive function and the degree of glucose excursion, as measured by the MAGE and MODD. The relationship between the MAGE or MODD level, and cognition was attenuated after adjustment for other factors associated with cognitive function, but remained significant.

As populations age, the prevalence of AD is increasing and AD is increasingly becoming a major public health issue due to its high caregiver burden, and due to the high personal and financial costs of care. According to the organization, Alzheimer's Disease International, there are approximately 24.3 million people with dementia today, with 4.6 million new cases of dementia being diagnosed per year[14]. As a progressive neurological disorder, AD is characterized by a deterioration in cognitive ability, an impaired ability to perform daily activities, in addition to other behavioral and psychiatric signs and symptoms. With respect to the underlying etiology of AD, it is likely that multiple mechanisms contribute to the neurodegeneration observed in AD. Since the initial Rotterdam study suggesting that patients with T2DM are at an increased risk of developing dementia and AD[15], a number of clinical and epidemiological studies have provided further direct evidence to strengthen the link between T2DM and AD. For instance, there is evidence to suggest that insulin resistance plays a role in cognitive impairment in individuals with type 2 diabetes, while others have Gone so far as to refer to AD as type 3 diabetes, in order to emphasize the potential endocrine links between these diseases[16-17].

In the main, lowering glucose concentrations is of pivotal importance in the treatment of diabetes, with proven beneficial effects on microvascular and macrovascular outcomes. The currently available markers for glycemic control, such as HbA1c and fructosamine (FA), only reflect average glucose levels, potentially missing out important hyperglycemia excursions that may be balanced out by hypoglycemia. Patients with similar HbA1c levels and mean glucose values can have markedly different daily glucose excursions. In the Diabetes Control and Complications Trial, two subgroups of participants (an intensive control group and the conventional group) characterized by a HbA1c of 9% for the study duration, had their risk of retinopathy evaluated. It was found that participants in the intensive control group had their risk of retinopathy reduced by >50% compared with the conventional group, even though these two subgroups of patients had the same HbA1c levels. Such a difference may have been due to lower intra-day glucose variability in the intensive control group[18].

Several CGMS have recently become available. These systems offer the advantage being able to detect glucose variability in more detail than conventional self-monitoring methods of blood glucose monitoring. Moreover, blood glucose concentrations obtained by GCMS compare favorably, and correlate well with subcutaneous adipose tissue glucose concentrations. There is also a physiologic lag between blood and interstitial space glucose of approximately 5 to 10 min, and this lag is accentuated when glucose levels are undergoing rapid change[19-21]. The different measures used in this study, including SD, LAGE, MAGE, and MODD can be used to characterize glucose variability in T2DM patients; however, the MAGE index remains the gold standard for evaluating the intra-day glucose excursion[22].

Recently, Rizzo et al.[23] showed that MAGE observed over a daily period was associated with impaired cognitive functioning independent of HbA1c, FPG, and PPG among aged T2DM patients (r=0.83, P<0.001). Although our study reached the same conclusion, the association between MAGE and MMSE was weaker, possibly because our participants had lower glucose excursion (58.02±26.26 mg/dL *vs* 71±19 mg/dL) and better glucose control.

The effect of glucose excursion is strongly related to oxidative stress both in vitro[24], and in animal, and human studies. Moreover, work by Monnier et al, shows that diabetes is associated with a doubling of urinary isoprostanes, which has the particular effect of increasing glycemic variability[25]. Although the mechanisms by which glucose excursion affects cognitive function are not clear, they may also be related to oxidative stress. Work by Abbatecola et al. also demonstrated that exaggerated postprandial glucose excursions are associated with disturbances in both global executive and attention functioning[26]. Thus it is possible that a tight control of postprandial glucose may prevent cognitive decline in elder diabetic individuals and we hope to investigate whether lowering glucose excursion could slow down

cognitive decline in elder diabetic patients.

In summary, the present study demonstrated a negative relationship between glucose excursion and cognitive function in aged T2DM patients. The results of this study further support the view that glucose variability should be one of the targets of treatment for the glycemic disorders encountered in T2DM patients. The results of the study also suggest that therapy aimed at controlling glucose excursion in T2DM patients may also be beneficial in maintaining cognitive function.

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