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STUDY PROTOCOL

A Prospective Longitudinal Study on the Relationship Between Glucose Fluctuation and Cognitive Function in Type 2 Diabetes: PROPOSAL Study Protocol

Masaki Matsubara · Hisashi Makino · Kazuo Washida · Miki Matsuo · Ryo Koezuka · Yoko Ohata · Tamiko Tamanaha · Kyoko Honda-Kohmo · Michio Noguchi · Tsutomu Tomita · Cheol Son · Michikazu Nakai · Kunihiro Nishimura · Yoshihiro Miyamoto · Masafumi Ihara · Kiminori Hosoda

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ABSTRACT

Introduction: Although the risk of dementia among patients with type 2 diabetes mellitus (T2DM) is double that of those without T2DM, the mechanism remains to be elucidated and the glycemic goal to prevent progression of cognitive impairment is unclear. Results from cross-sectional studies suggest that glucose fluctuations are associated with impairment of cognitive function among T2DM patients. Therefore, the aim of the longitudinal study described here is to evaluate the relationships between glucose fluctuation indexes assessed by continuous glucose monitoring (CGM) and cognitive function among elderly patients with T2DM.

Methods: This will be a prospective, single-center, 2-year longitudinal study in which a total of 100 elderly patients with T2DM showing mild cognitive impairment (MCI) will be enrolled. Glucose fluctuations, assessed using the FreeStyle Libre Pro continuous glucose monitoring system (Abbott Laboratories), and results of cognitive tests, namely the Montreal Cognitive Assessment (MoCA) and Alzheimer's Disease Assessment Scale (ADAS), will be evaluated at baseline, 1-year visit and 2-year visit. The primary endpoint is the relationships between indexes of glucose fluctuation and change in MoCA and ADAS scores. Secondary endpoints are the relationships between the indexes of glucose fluctuation or cognitive scores and the following: indexes representing intracranial lesions obtained by magnetic resonance imaging and angiography of the head; Geriatric Depression Scale score; Apathy Scale score; carotid intima-media thickness assessed by echography; inflammatory markers; fasting glucose; glycated hemoglobin; blood pressure; and the development of cardiovascular and renal events.

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M. Matsubara · H. Makino (✉) · M. Matsuo · R. Koezuka · Y. Ohata · T. Tamanaha · K. Honda-Kohmo · M. Noguchi · T. Tomita · C. Son · K. Hosoda
Division of Diabetes and Lipid Metabolism, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan
e-mail: makinoh@ncvc.go.jp

K. Washida · M. Ihara
Department of Neurology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

M. Nakai · Y. Miyamoto
Center for Cerebral and Cardiovascular Disease Information, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

K. Nishimura
Department of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

Planned Outcomes: The current study is scheduled for completion in June 2022. The results could lead to the elucidation of novel glycemic goals to prevent the progression of cognitive impairment and/or of relationships between glucose fluctuations and cognitive function among T2DM patients. The findings of the study will be reported in publications and conference presentations.
Trial Registration: University Hospital Medical Information Network Clinical Trial Registry (UMIN000038546).

Keywords: Continuous glucose monitoring; Dementia; Glucose fluctuation; Mild cognitive impairment; Type 2 diabetes mellitus

Key Summary Points

The risk of dementia doubles among patients with type 2 diabetes mellitus (T2DM). However, the mechanism remains to be elucidated.

Some cross-sectional studies have suggested that glucose fluctuations, assessed by continuous glucose monitoring (CGM), is associated with cognitive function impairment among patients with T2DM.

To the best of our knowledge, this proposed study is the first longitudinal study to elucidate the relationships between glucose fluctuations and cognitive function among elderly patients with T2DM.

Secondary endpoints will comprise the relationships between glucose fluctuations or cognitive scores and various parameters related to cerebrovascular imaging, cardiovascular and renal events, inflammation, fasting glucose, glycated hemoglobin and blood pressure.

It is anticipated that this study could clarify the relationships between glucose fluctuations and cognitive function among patients with T2DM. The results of this study could provide new glycemic control strategies for prevention of cognitive impairment.

DIGITAL FEATURES

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INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide. T2DM is a risk factor for cognitive impairment as well as for cardiovascular (CV) diseases. Meta-analyses have revealed that, compared to individuals without T2DM, those with T2DM have a relative risk of Alzheimer's disease and vascular dementia of approximately 1.5 and 2.5, respectively [1] and that the pooled odds ratio of risk of progression from mild cognitive impairment (MCI) to dementia is approximately 1.5 [2]. The etiology of cognitive impairment and dementia in patients with T2DM is considered to be multifactorial, including such factors as hypoglycemia induced by hypoglycemic therapy, chronic hyperglycemia, hyperinsulinemia, advanced glycation endproducts (AGEs) and cerebral micro- and macro-vascular disease [3, 4]. However, although severe hypoglycemic episodes among older patients with T2DM have been associated with an apparent risk of dementia [5, 6], the relationships between mild to moderate hypoglycemia and cognitive impairment and dementia remain to be elucidated.

In terms of glycemic control, to the best of our knowledge, a large randomized control trial (RCT) which assesses whether strict glycemic

control can prevent the progression of cognitive impairment or onset of dementia as a primary endpoint among patients with T2DM has not been published. The IDEATel Study was a randomized trial of telemedicine case management versus usual care in elderly persons with T2DM [7]. In addition to the primary endpoints, namely hemoglobin A1c (HbA1c), low-density lipoprotein (LDL) cholesterol and blood pressure levels, improved diabetes control appeared to mediate a reduction in global cognitive decline. In subgroup analyses comparing cognitive function between patients with T2DM (ACCORD-MIND RCT [8]) or type 1 diabetes mellitus (T1DM) (DCCT/EDIC RCT [9]) receiving intensive versus standard glycemic control measures, cognitive outcomes did not differ between subgroups in both studies. Consequently, the glycemic goal to prevent progression of cognitive impairment or onset of dementia remains unclear among patients with diabetes.

The results from two cross-sectional studies [10, 11] have led to suggestions that glucose fluctuations assessed by continuous glucose monitoring (CGM) may be associated with cognitive function impairment among older patients with T2DM [10, 11]. However, the mechanism remains unclear, and to the best of our knowledge no longitudinal study has been reported that aimed to elucidate the relationships between glucose fluctuations and cognitive function of patients with T2DM.

The FreeStyle Libre Pro CGM (FLP-CGM) system (Abbott Laboratories, Chicago, IL, USA) can evaluate glucose profiles for up to 14 days without calibration by self-monitoring of blood glucose (SMBG) levels. Although glucose levels in interstitial fluid are measured by FLP-CGM—and not blood glucose levels—this tool has been demonstrated to be accurate in comparison with capillary blood glucose results [12]. Thus, the clinical implementation of FLP-CGM is not difficult to understand given that the potential pain and burden of daily fingerstick calibrations need no longer be performed.

The proposed study is therefore longitudinal and aims to elucidate the relationships between glucose fluctuation indexes assessed using FLP-CGM and cognitive function among elderly patients with T2DM. In addition, the development of CV and renal events, changes in cerebral lesions, such as ischemia and microbleeds demonstrated by magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), intima-media thickness (IMT) in the carotid arteries and inflammatory markers will be observed throughout the study period.

METHODS

Study Design

The aim of this prospective, single-center, longitudinal study is to evaluate the association between glucose fluctuation assessed using CGM and cognitive function in patients with T2DM showing signs of MCI. The target number of enrolled patients is set at 100 subjects who regularly attend the outpatient diabetes clinic at National Cerebral and Cardiovascular Center in Japan. The observation period will be 2 years; the visit schedule and measurements are shown in Table 1.

The study protocol was approved by the institutional ethics committee of the National Cerebral and Cardiovascular Center (M30-110-3) and will be conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and with current Japanese legal regulations. Written informed consent has been or will be obtained from all participants.

Sample Selection

Since decline in cognitive function can be observed during the longitudinal period, eligible subjects will be elderly participants showing MCI, a patient population at high risk of dementia [13, 14]. Our hypothesis is that patients exposed to high glucose fluctuations, especially hypoglycemia, are prone to cognitive decline; thus, patients using anti-diabetic agents considered to be at an elevated risk of hypoglycemia will be included regardless of the level of glycemic control as assessed by HbA1c. The inclusion criteria are: (1) patients with T2DM treated at National Cerebral and

Table 1 Study schedule

	Baseline	1 year	2 year
Informed consent	○		
Patient characteristics	○		
Physical examination and vital signs	○	○	○
FLP-CGM	○	○	○
Cognitive tests (MoCA and ADAS)	○	○	○
GDS and Apathy Scale	○	○	○
MRI and MRA of the head	○		○
Blood chemistry	○	○	○
Inflammatory biomarkers (hs-CRP and IL-6)	○	○	○
Urine test	○	○	○
8-OHdG	○[a]	○[a]	○[a]
Carotid artery echography	○		○
Cardiovascular events	→		
Renal events	→		

Cardiovascular events include cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, hospitalization due to unstable angina pectoris or heart failure, or percutaneous coronary intervention therapy

Renal events include progression of diabetic kidney disease, initiation of renal replacement therapy or doubling of the serum creatinine level from baseline

FLP-CGM FreeStyle Libre Pro continuous glucose monitoring, *MoCA* Montreal Cognitive Assessment, *ADAS* Alzheimer's Disease Assessment Scale, *GDS* Geriatric Depression Scale, *MRI* magnetic resonance imaging, *MRA* magnetic resonance angiography, *hs-CRP* high sensitivity C-reactive protein, *IL-6* interleukin-6, *8-OHdG* 8-hydroxydeoxyguanosine

[a] Optional examination

Cardiovascular Center who can provide written informed consent; (2) age between 65 and 85 years, regardless of gender; (3) patients taking sulphonylurea, glinide and/or insulin, or patients showing HbA1c $\geq$ 7.0% who take other oral hypoglycemic agents and/or glucagon-like peptide 1 receptor agonists (GLP-1 RA); and (4) Montreal Cognitive Assessment (MoCA) score of between 17 and 25. The exclusion criteria are patients: (1) with T1DM; (2) undergoing renal replacement therapy; (3) receiving therapy for malignancy; (4) taking antidementia drugs or having underlying comorbidities affecting cognitive function (depression, thyroid dysfunction or deficiency of vitamin B1, B12 or folate); (5) with carotid-artery stenosis $\geq$ 80% of luminal area; and (6) judged as inappropriate by the clinical investigators.

We were unable to identify any published longitudinal studies with the aim to elucidate relationships between glucose fluctuations and cognitive function in patients with T2DM and, therefore, we calculated sample size based on previous cross-sectional studies [10, 11]. With a power of 90% and an α of 0.05, the required sample size is 76 patients. Assuming a 20% dropout rate, 91 patients should be registered. With a power of 95% and an α of 0.05, the required sample size is 92 patients, with 110 patients needed, assuming a 20% dropout.

Measurements

The attending physician will provide a reasonable and understandable explanation of the study to patients who meet the above-mentioned eligibility criteria. If the patients themselves, not proxies, agree to participate and provide written informed consent, they are entered into the study. The visit schedule is shown in Table 1. Briefly, patient characteristics (sex, age, duration of diabetes mellitus, comorbidities, work, marital status and living conditions) are to be obtained at baseline. Measurements of vital signs (height, body weight [body mass index], blood pressure, pulse rate), laboratory tests (blood chemistry, complete blood count and urine test), CGM (FreeStyle Libre Pro), cognitive tests (MoCA and Alzheimer's Disease Assessment Scale [ADAS]), questionnaires related to depression and volition (Geriatric Depression Scale [GDS], Apathy Scale) and inflammatory biomarkers measurements (serum high-sensitivity C-reactive protein [hs-CRP] and interleukin-6 [IL-6]) are scheduled for baseline and the 1- and 2-year visits. If possible, urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG), which is an oxidative stress marker, will also be measured at baseline and at the 1- and 2-year visits. MRI and MRA of the head and carotid artery echography will be obtained at baseline and at the 2-year visit. During the study period, CV events (CV death, nonfatal stroke, nonfatal myocardial infarction, hospitalization due to unstable angina pectoris or heart failure or percutaneous coronary intervention [PCI] therapy) and renal events (progression of diabetic kidney disease, initiation of renal replacement therapy or doubling of the serum creatinine level from baseline) will also be observed.

The FLP-CGM system is an interstitial glucose monitoring device, and its accuracy has been demonstrated compared with capillary blood glucose measurements [12]. The FLP sensor is disposable and is applied on to the back of the upper arm for up to 14 days. A unique feature of the sensor is that calibration is not required using SMBG. After the sensor is removed, the collected data can be downloaded and glucose profiles evaluated. In addition to the standard CGM metrics, namely mean glucose, percent coefficient of variation (%CV), time in range (TIR), among others [15], indexes of glycemic variability can also be calculated, such as high blood glucose index (HBGI), low blood glucose index (LBGI), mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD), and continuous overall net glycemic action (CONGA) [16].

The IMT of the common carotid arteries (CCA) will be assessed with a 7.5-MHz linear array probe and a LOGIQ E10 (GE Healthcare Japan Co. Ltd., Tokyo, Japan), using the B-mode ultrasound technique. With subjects in the supine position, IMT measurements are performed with the head facing the contralateral side. The IMT calculated on both sides will represent the distance between the intimal-

luminal interface and the medial-adventitial interface at the far wall of the carotid artery, measured 1 cm proximal to the bifurcation. In addition to maximum IMT (Max-IMT), peak systolic velocity (PSV), pulsatility index (PI), resistance index (RI) and percentage area stenosis, if present, of the CCA and the internal carotid arteries (ICA), will also be assessed.

Planned Outcomes

The primary endpoints will be the relationships between the indexes obtained from the CGM data described above, and the change in MoCA and ADAS scores. The secondary endpoints will be:

1. Development of CV events: cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, hospitalization due to unstable angina pectoris or heart failure, or PCI therapy.
2. Development of renal events: progression of diabetic kidney disease, initiation of renal replacement therapy or doubling of the serum creatinine level from baseline.
3. Changes in Brain Observer Micro Bleed Scale (BOMBS) [17], Fazekas scale [18], cerebral small vessel disease (SVD) score [19], perivascular spaces [20] and percentage stenosis of intracranial artery as assessed by the WASID method [21]. These parameters will be obtained by MRI and MRA of the head.
4. Changes in GDS and Apathy Scale scores.
5. Changes in carotid Max-IMT, IMT measured 1 cm proximal to bifurcation of both CCA, PSV, PI, RI and percentage area stenosis, if present, of bilateral CCA and ICA assessed by carotid artery echography.
6. Changes in hs-CRP and IL-6.
7. Changes in fasting glucose and HbA1c.
8. Changes in blood pressure.

Data Collection and Analysis

Multiple measurements (baseline, 1-and 2-year visits) will be obtained from CGM, including mean glucose, %CV, TIR, HBGI, LBGI, MAGE, MODD and CONGA, as well as MoCA and ADAS scores. For statistical modeling of the primary endpoint, multilevel mixed-effect regression will be applied. Regarding secondary endpoints, multilevel mixed-effect regression modeling will also be applied to evaluate the relationships between the indexes of glucose fluctuation or cognitive scores and the parameters evaluated as secondary endpoints, including BOMBS, Fazekas scale, SVD score, perivascular spaces, percentage stenosis of intracranial artery, GDS, Apathy Scale, IMT assessed by carotid artery echography, inflammatory markers (hs-CRP and IL-6), fasting glucose, HbA1c and blood pressure.

STRENGTHS AND LIMITATIONS

Type 2 diabetes mellitus has spread worldwide, and its prevalence increases with age [22]. If patients with T2DM also suffer from dementia, glycemic control could be worsened due to poor adherence to diet or medication. In addition, the socio-economic burden of elderly patients with diabetes cannot be overlooked, especially in Japan and Western countries, with super-aged societies [23]. Therefore, preventing or reducing the progression of cognitive dysfunction among individuals with diabetes is important.

While HbA1c is the gold standard for assessing glycemic control, the glycemic goal to prevent the progression of cognitive impairment or onset of dementia has not yet been elucidated among patients with diabetes [8, 9]. An association between glycemic variability and cognitive function has been suggested among older patients with T2DM, but only in cross-sectional studies [10, 11]. To the best of our knowledge, this study would therefore be the first longitudinal study to elucidate the relationships between glucose fluctuations and cognitive function among patients with T2DM. The results obtained from the study could help to establish a new glycemic index to prevent the onset of dementia and lead to novel therapeutic strategies. In addition, findings from MRI/MRA imaging and inflammatory markers will be evaluated to assess the mechanism of cognitive

impairment, since relationships between glucose fluctuations and atherosclerosis [24–26], which could cause vascular dementia, or an association between cognitive function and inflammation [3] have been suggested in patients with T2DM.

The rate of conversion from MCI to overt dementia has been reported to be 10–15% per year, compared to the rate of 1–2% in normal control (NC) subjects [13, 14]. Thus, older patients with MCI are eligible for the current study as persons with MCI will be at risk of cognitive decline during the 2-year observation period. In comparison with the Mini-Mental State Examination (MMSE), the MoCA is a brief and useful screening tool to detect MCI. Its cut-off point to discriminate patients with MCI from NC subjects is 25/26 [27], and that to discriminate between patients with MCI and those with dementia is set at 16/17 (based on a previous report [28]). In addition to the MoCA, this study will utilize the ADAS to assess cognitive function for the primary endpoint. The ADAS is a sensitive and reliable psychometric scale that consists of 11 items which evaluate various functions, such as memory, language and orientation [29]; it could detect a slight decline in cognitive function during the observation period.

This study also has potential limitations. The study has a single-center design, which may not fully represent the entire scope of disease in Japan. Secondly, the study period will run for 2 years, which may be insufficient to observe a decline in cognitive function for all subjects.

However, despite these limitations, it is anticipated that this study could clarify the relationships between glucose fluctuations and cognitive function among patients with T2DM and MCI. The results of this study could therefore provide new glycemic control strategies for the prevention of cognitive impairment.

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Authorship. All authors meet the criteria for authorship of the International Committee of Medical Journal Editors (ICMJE), take responsibility for the study integrity as a whole, and approve this version for publication.

Disclosures. Masaki Matsubara, Hisashi Makino, Kazuo Washida, Miki Matsuo, Ryo Koezuka, Yoko Ohata, Tamiko Tamanaha, Kyoko Honda-Kohmo, Michio Noguchi, Tsutomu Tomita, Cheol Son, Michikazu Nakai, Kunihiro Nishimura, Yoshihiro Miyamoto, Masafumi Ihara and Kiminori Hosoda have nothing to disclose.

Compliance with Ethics Guidelines. The study protocol was approved by the institutional ethics committee of the National Cerebral and Cardiovascular Center (M30-110-3) and will be conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and with current Japanese legal regulations. Written informed consent has been or will be obtained from all participants.

Data Availability. The analyzed data will be available from the corresponding author on reasonable request.

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