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Ambulatory glucose profile in diabetes-related dementia

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Aim: Diabetes-related dementia (DrD), a dementia subgroup associated with specific diabetes mellitus (DM)-related metabolic abnormalities rather than Alzheimer's disease (AD) pathology or cerebrovascular disease, is characterized by less well-controlled glycemia. We investigated the glucose level, variability and stability, and risk of hypoglycemia in DrD to determine characteristic ambulatory glucose profiles (AGP).

Methods: We obtained AGP for 14 days of 40 patients with AD associated with DM and 19 patients with DrD using a novel sensor-based flash glucose monitoring system (FreeStyle Libre Pro).

Results: Despite similar mean glucose and estimated A_{1c} values, the DrD group showed significantly greater glucose variability and higher percentage of time spent in hypoglycemia than the AD associated with DM group. Glucose level and variability correlated significantly and negatively with Mini-Mental State Examination in DrD, but not in AD associated with DM The estimated A_{1c} levels calculated from the 14 days of AGP data significantly correlated with the HbA_{1c} levels measured within 2 months of the insertion of the sensor.

Conclusions: DrD has a distinctively different AGP from that of AD associated with DM. Glucose variability and hypoglycemia are more involved in the pathophysiology of DrD than in that of AD associated with DM. The AGP analysis using the flash glucose monitoring system might provide useful information undetected by HbA_{1c} values. **Geriatr Gerontol Int 2019; ••: ••–••.**

Keywords: Alzheimer's disease, ambulatory glucose profile, diabetes-related dementia, flash glucose monitoring, glucose variability.

Introduction

It is well known that type 2 diabetes mellitus (DM) increases the risk for cognitive decline and dementia, such as in Alzheimer's disease (AD) and vascular dementia (VaD).[1,2] In addition, there might be a dementia subgroup associated with specific DM-related metabolic abnormalities rather than AD pathology or cerebrovascular disease.

We propose a new clinical entity of a dementia subgroup, referred to as "diabetes-related dementia," which is clinically different from the characteristics of AD and VaD.[3–6] Although DrD might underlie heterogeneous neuropathological conditions, glycemic controls can improve some domains of cognitive function, such as attention and executive functions determined by the Trail-Making Test Part A and B, in individuals with DrD. Therefore, this dementia subgroup can be considered as a controllable or modifiable dementia.

In late 2016, a novel sensor-based flash glucose monitoring system was introduced in Japan.[7] Use of the device allows recording daily glucose profiles for up to 14 days. As DrD is characterized by less well-controlled glycemia, this system might provide information to characterize the glucose level, glucose variability and stability, and risk of hypoglycemia in each individual. In the present study, we analyzed daily glucose profiles, specifically ambulatory glucose profiles (AGP), in individuals with DrD using a flash glucose monitoring system, and determined differences in AGP between DrD and AD associated with DM.

Methods

Participants

As described in our previous studies, there are patients with dementia associated with less well-controlled glycemia in our Memory Clinic at Tokyo Medical University Hospital, Tokyo, Japan.[3,4] Some of them showed neither significant medial temporal lobe atrophy on magnetic resonance imaging (MRI) nor parietotemporal hypoperfusion on single-photon emission computed tomography (SPECT), which are characteristic features of AD. In addition, they showed no definite cerebrovascular disease lesions on MRI that would be responsible for cognitive impairment or dementia. Among them, there was a dementia subgroup with characteristics predominantly associated with DM-related metabolic abnormalities, referred to as DrD. Patients with clinically diagnosed DrD were enrolled in the present study.

Our proposed guidelines for the clinical diagnosis of DrD are as follows:[5]

1. **Type 2 DM**: long duration and less well-controlled glycemia
2. **Dementia**: impaired attention and executive functions, but less impaired memory, slow progression of cognitive decline
3. **Brain MRI**: no evidence of cerebrovascular lesions, generalized cortical atrophy, but less severe medial temporal lobe atrophy
4. **Perfusion SPECT**: no significantly decreased hypoperfusion in the parietotemporal and posterior cingulate cortices
5. **Cerebrospinal analysis**: no significantly increased phosphorylated tau and normal β-amyloid 42
6. **Exclusion of other dementing causes** (e.g. thyroid disease, vitamin B_1, B_{12} deficiency, head trauma, chronic alcoholism, cerebrovascular disease and other types of dementia)

Based on the above guidelines, we enrolled 20 outpatients with DrD. As a control group, we enrolled at random 42 outpatients with probable AD associated with DM (AD[+DM] group). The patients with AD had to meet the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition criteria.[8] All patients underwent general physical examinations, clinical neurological examinations,

laboratory tests and brain imaging studies (MRI and SPECT) to exclude other potential causes of dementia. SPECT studies showed a significant hypoperfusion in the parietotemporal and posterior cingulate cortices in all patients with AD[+DM], but not in those with DrD. We carried out cerebrospinal fluid analysis in 14 patients with AD[+DM] and 12 patients with DrD. Just three out of 12 patients with DrD showed abnormal p-tau levels (high levels exceeding the normal value), while no patients showed abnormal Aβ42 levels (low levels below the normal value).

DM was defined as having undergone treatment for diabetes or non-fasting plasma glucose level of 200 mg/dL or a fasting plasma glucose level of 126 mg/dL.[9] Cognitive function was assessed using the Mini-Mental State Examination (MMSE).[10] We determined the prevalence of major chronic diseases among participants using the Charlson Comorbidity Index score.[11] We excluded individuals with severe dementia (MMSE score <12/30), malignancies, severe cardiac or pulmonary diseases, liver cirrhosis and severe kidney diseases. Although some patients reported self-monitoring of blood glucose (SMBG) levels on a regular basis in the study, we did not compare SMBG and AGP findings because of missing data.

The ethics committee of Tokyo Medical University approved the study protocol. All participants gave written informed consent before participating in this study.

Measurements of daily glucose profiles

A novel sensor-based flash glucose monitoring system (FreeStyle Libre Pro; Abbott Diabetes Care, Tokyo, Japan) was introduced with AGP reporting in late 2016 in Japan.[6] This system consists of three separate elements, namely, the sensor, the reader and the interpretive software. Then, this system determined 80–140 mg/dL as normoglycemia, >140 mg/dL as hyperglycemia and <80 mg/dL as hypoglycemia. The sensor stores interstitial fluid glucose levels every 15 min for up to 14 days. This sensor is calibrated at the time of manufacturing and does not require recalibration. After reading 14 days of data stored on a memory chip within the sensor disc and displaying on a PC for reviewing using the software, we could easily understand the AGP in each participant, including levels of glycemia, glucose variability and stability, and the duration of normo-, hyper- and hypoglycemia. The technology of this device was described in detail in another manuscript.[7]

Figure 1 shows a representative AGP of a participant with DrD. AGP provides both graphic and quantitative characterizations of diurnal glucose patterns, including averaged daily blood glucose, averaged blood glucose every 2 h and estimated A_{1c}. The percentage of time within, above and below the target range (80–140 mg/dL) is shown.

Using averaged daily blood glucose levels, we measured the standard deviation of blood glucose levels (SD), coefficients of variance (CV) for the blood glucose levels (CV% = SD/mean × 100), difference between minimum and maximum glucose levels (Δ difference), and mean amplitude of glycemic excursions (MAGE). In addition, averaged percentage of time spent in normoglycemia, hyperglycemia and hypoglycemia, were calculated and compared between the two groups.

Statistical analysis

Values were expressed as the mean ± SD. Statistical analysis was carried out using Student's *t*-test, Mann–Whitney *U*-test and the χ^2-test. Group comparison was analyzed by adjusting for the disease duration and insulin treatment. Correlations between glycemic measurements and MMSE scores, and between estimated A_{1c} levels and HbA_{1c} levels were calculated using Spearman's rank correlation test and Pearson's correlation test. Furthermore, correlations between MAGE or SD and MMSE were calculated using multivariate analysis after adjusting the mean glucose and HbA1c. *P* values <0.05 were considered statistically significant.

Results

Demographic characteristics

There were no participants who changed the treatment for DM within the 14 days. Except for three unavailable data points (2 in AD[+DM] and 1 in DrD) because of early removal, the remaining 40 patients with AD[+DM] and 19 patients with DrD were analyzed. Table 1 shows demographic characteristics of the AD[+DM] group and the DrD group. There were no significant differences in age, sex, duration of dementia, education, MMSE scores and Charlson Comorbidity Index scores between the groups. Although there were no significant differences in HbA_{1c} levels between the two groups, the DrD group showed significantly longer duration of DM and higher frequency of insulin therapy than the AD[+DM] group. BMI was significantly higher in the DrD group than in the AD[+DM] group.

Comparison of glycemic measurements

Table 2 shows differences in glycemic measurements between the AD[+DM] group and the DrD group. Although there were similar mean glucose and estimated A_{1c} values, the profiles clearly showed distinctive patterns. The DrD group showed significantly higher SD, CV and MAGE than the AD group. The Δ difference was higher in the DrD group than in the AD[+DM] group, but no significant difference was found. Figure 2 shows differences in the percentage of time spent in normo-, hyper- and hypoglycemia between AD[+DM] and DrD (37.4 ± 22.0 *vs* 35.2 ± 21.7, 59.4 ± 23.9 *vs* 55.4 ± 27.1, 2.6 ± 4.2 *vs* 9.4 ± 12.8, respectively). The DrD group showed a significantly higher

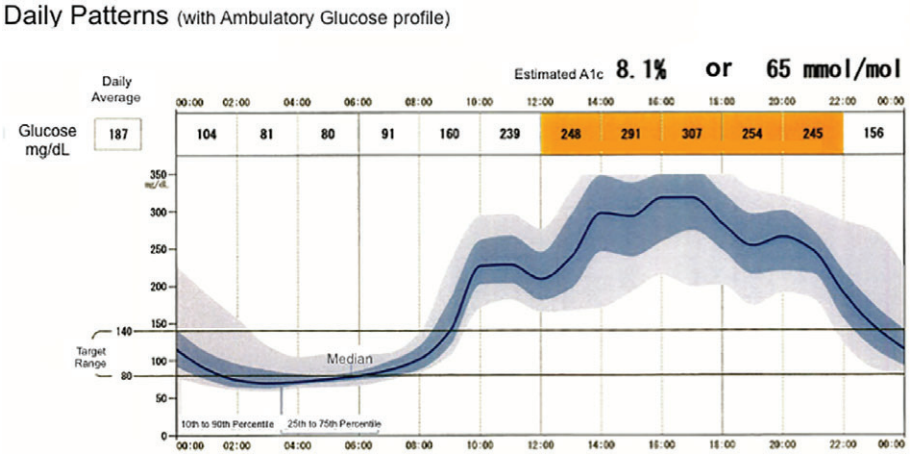

Figure 1 Ambulatory glucose profile of a patient with diabetes-related dementia.

Table 1 Demographic characteristics of Alzheimer's disease and diabetes-related dementia

	AD[+DM]	DrD
No. patients	40	19
Age (years)	82.1 ± 6.0	81.9 ± 5.0
Sex (male/female)	19/21	8/11
Duration of dementia (years)	3.5 ± 1.1	3.5 ± 1.3
Education (years)	12.9 ± 2.7	12.3 ± 2.6
MMSE score	20.0 ± 3.3	19.8 ± 3.4
HbA1c (%)	7.9 ± 1.5	8.0 ± 1.4
Duration of diabetes (years)	16.3 ± 9.9	25.0 ± 8.5 **
Treatment of diabetes		
Insulin	13	12
OHA	27	7 *
DPP4 inhibitors	12	6 *
Biguanide	9	3 *
Sulfonylureas	7	0 *
SGLT2 inhibitor	4	0 *
Alpha glucosidase inhibitors	2	0 *
Pioglitazone	2	0 *
Charlson Comorbidity Index score	2.2 ± 0.4	2.4 ± 0.5
BMI (kg/m^2)	23.2 ± 3.7	26.4 ± 2.8 **
No. patients underwent lumbar puncture	14	12
No. patients with decline of CSF $A\beta_{42}$	6/14	3/12
No. patients with elevation of CSF p-tau	10/14	0/12

*P < 0.05, **P < 0.01. $A\beta_{42}$, β-amyloid 42; AD[+DM], Alzheimer's disease associated with diabetes; BMI, body mass index; CSF, cerebrospinal fluid; DPP4 inhibitors, dipeptidyl peptidase-4 inhibitors; DrD, diabetes-related dementia; HbA1c, hemoglobin A1c; MMSE, Mini-Mental State Examination; OHA, oral hypoglycemic agents; SGLT2 inhibitor, sodium–glucose cotransporter-2 inhibitors.

Table 2 Comparison of glycemic measurements (adjusting the disease duration and insulin treatment)

	AD[+DM]	DrD
Mean glucose (mg/dL)	172.9 ± 49.0	175.9 ± 55.5
Estimated A1c	7.6 ± 1.7	7.8 ± 1.9
SD (mg/dL)	37.4 ± 16.9	49.3 ± 25.8 *
CV (%)	0.21 ± 0.07	0.28 ± 0.10 **
Δ Difference (mg/dL)	106.5 ± 48.5	130.5 ± 54.8
MAGE (mg/dL)	124.5 ± 35.7	159.3 ± 45.7 **

*P < 0.05, **P < 0.01. AD[+DM], Alzheimer's disease associated with diabetes; CV, coefficient of variation; DrD, diabetes-related dementia; MAGE, mean amplitude of glycemic excursions; SD, standard deviation.

percentage of time spent in hypoglycemia than the AD[+DM] group, but no significant differences in percentage of time spent in normoglycemia and hyperglycemia were found. After reviewing 14 days of data, two patients with DrD and one patient with AD[+DM] needed to make therapy dose adjustments, because they showed moderate hypoglycemia <70 mg/dL in the early morning.

Correlations between glycemic measurements and MMSE

MMSE scores correlated significantly and negatively with mean glucose, estimated $A_{1c,}$ SD, MAGE and percentage of time in hyperglycemia in the DrD group, but did not significantly correlate with any glycemic measurements in the AD[+DM] group (Table 3).

Correlation between estimated A_{1c} and laboratory HbA_{1c}

The estimated A_{1c} levels calculated from the 14 days of AGP data significantly correlated with the HbA_{1c} levels measured within 2 months of the insertion of the sensor (r^2 = 0.655, P < 0.0001).

Discussion

We found a distinctive difference in AGP between AD[+DM] and DrD. The DrD group showed significantly greater glucose variability indicated by higher SD, CV and MAGE, and a higher percentage of time spent in hypoglycemia than the AD[+DM] group, despite similar mean glucose and estimated A_{1c} values. In addition, MMSE scores correlated significantly and negatively with glucose level, estimated A_{1c} and some indexes, as assessed by glucose variability in the DrD group, but not in the AD[+DM] group. The AGP might provide useful and important information, including glucose variability and hypoglycemia, undetectable by HbA_{1c} measurement.

There is growing evidence that DM carries greater risks of cognitive decline and dementia compared with healthy individuals.[12,13] Studies have reported that hyperglycemia, hypoglycemic episodes, postprandial glucose excursions and glucose variability might contribute to cognitive impairment and brain atrophy in individuals with DM.[14–18] In addition to cerebrovascular diseases, several mechanisms, such as impaired neuronal insulin signaling, inflammation, mitochondrial dysfunction and oxidative stress, β-amyloid accumulation, and tau phosphorylation, have been proposed for neuronal damage associated with DM.[19,20] However, underlying neuropathological conditions in DrD remain unclear. Although our preliminary PET study showed variable amyloid and tau accumulation patterns in participants with DrD, the positive rate of amyloid was low (39%), whereas the positive rate of tau was very high (89%) (unpubl. data). Some studies showed that DM might promote neurodegeneration independent of an AD dementia diagnosis, and its effect might be driven by tau phosphorylation.[21,22] Recently, Li *et al.* stated that tau-related neurofibrillary tangles instead of β-amyloid plaques are more likely to be the pathological biomarkers for DM-related dementia.[20] These studies are consistent with our PET findings showing that DrD might be associated predominantly with tau pathology, in addition to non-amyloid/non-tau neuronal damage as a result of glucose toxicity.

DrD is clinically characterized by less well-controlled glycemia. The present findings suggest that glucose variability and hypoglycemia are characteristics of AGP in DrD. In addition to long-standing hyperglycemia, a few studies have shown the association between individual glycemic variability and cognitive function.[14–18] High glucose variability, including short-term and long-term glucose fluctuations, might affect cognitive function mediated by oxidative stress or inflammatory processes. Oxidative stress caused by free radicals damages the endothelial cells in the blood vessels of the central nervous system, and plays a role in the pathogenesis of microvascular diseases and neuronal degeneration.[14,15] The nervous system might be particularly vulnerable to glycemic variability.[23] Our previous study showed that inflammatory cytokines and oxidative stress are associated with development of dementia and progression of cognitive decline in patients with DrD, but not in those with AD[+DM].[24,25] The present findings suggest that glucose variability is also associated with cognitive impairment in DrD.

Hypoglycemia, particularly with severe hypoglycemic episodes, is associated with a greater risk of dementia.[17] The mechanisms implicated in neuronal damage as a result of hypoglycemia are not completely understood, but many factors have been identified including excitotoxicity, oxidative stress and mitochondrial dysfunction.[26] A recent experimental study suggests that hypoglycemia induces activation of GSK-3β and leads to hyperphosphorylation of tau, supporting our PET findings.[27] Our AGP analysis showed that recurrent hypoglycemia, even if mild,

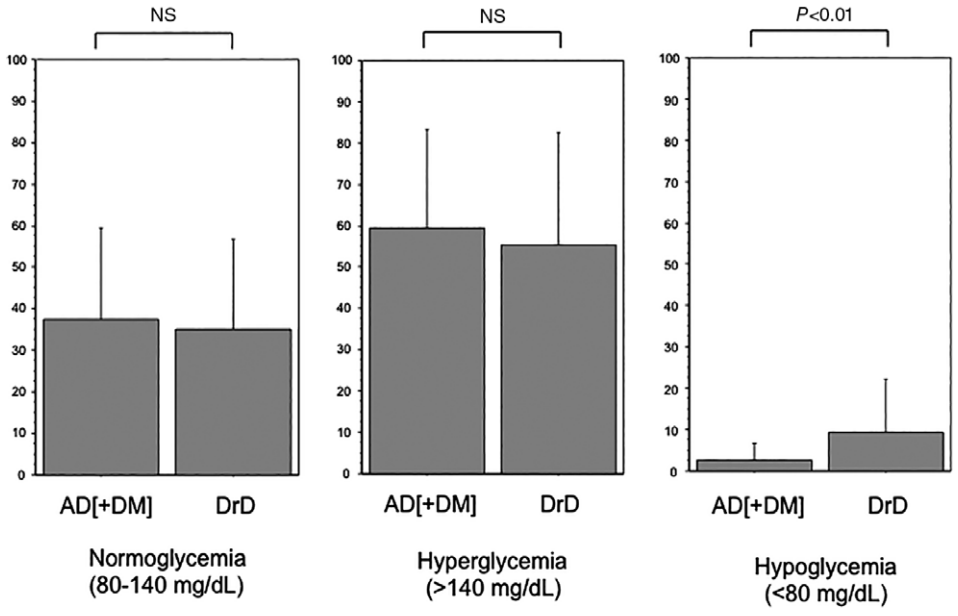

Figure 2 Averaged percentage of time spent in normo-, hyper- and hypoglycemia. AD[+DM], Alzheimer's disease associated with diabetes; DrD, diabetes-related dementia; NS, not significant.

Table 3 Correlations between glycemic measurements and Mini-Mental State Examination

	AD[+DM]	DrD
Mean glucose (mg/dL)	−0.219	−0.543 *
Estimated A1c (%)	−0.209	−0.531 *
CV (%)	−0.023	−0.267
Δ Difference (mg/dL)	−0.127	−0.407
Percentage of time in normal glycemia (%)	0.267	0.404
" " " "hyperglycemia (%)	−0.251	−0.495 *
" " " "hypoglycemia (%)	0.106	−0.186
Multivariate analysis between MAGE or SD and MMSE(adjusting the mean glucose and HbA1c)		
SD (mg/dL)(adjusting the mean glucose and HbA1c)	0.052	−0.104 *
MAGE (mg/dL)(adjusting the mean glucose and HbA1c)	−0.016	−0.029 *

*$P < 0.05$. AD[+DM], Alzheimer's disease associated with diabetes; CV, coefficient of variation; DrD, diabetes-related dementia; MAGE, mean amplitude of glycemic excursions; SD, standard deviation.

might lead to neuronal damage, and be associated with several aspects of cognitive dysfunction, including attention and executive functions. However, the present results showed that duration of hypoglycemia is significantly longer, but MMSE score is correlated with hyperglycemia in DrD. The certain mechanism of explanation of this discrepancy was unclear. It is certain that hypoglycemia, which is the one of the most important characteristics of DrD, was associated with the onset of dementia. However, we have to keep in mind that onset, severity and progression of dementia are different things. From the present study, there was the possibility that onset of dementia was associated with hypoglycemia; in contrast, the severity and progression of dementia were associated with hyperglycemia in DrD. However, this was a cross-sectional study, and further longitudinal studies are required to confirm this mechanism.

Conventional SMBG adherence rates were reported to be as low as 44% for adults with type 1 diabetes, and 24% for adults with type 2 diabetes.[28] The rate appears to be lower in older patients with dementia than in those without. In the present study, 14 days of AGP data were obtained from 59 out of 62 participants (95%) without any adverse effects. The blinded CGM device is highly acceptable, even in individuals with dementia. In addition, this system can help to detect hypoglycemia in the early morning that would enable the patient to make dose adjustments. A randomized controlled study demonstrated that sensor-based flash glucose testing showed a 38% reduction in time spent in hypoglycemia compared with SMBG in type 1 diabetes patients.[29] In the present study, dose adjustment was carried out for two patients with DrD and for one patient with AD[+DM] by physicians after reviewing 14 days of AGP data because of moderate hypoglycemia. Estimated A_{1c} values highly correlated with laboratory HbA_{1c} values, although there were different timings of the assay.

The present study had some limitations. First, this study had a cross-sectional design, and therefore it is difficult to draw causal relationships. However, as relationships between glucose variability, hypoglycemia and cognitive function have been described in previous studies, we also found that glucose level and variability correlated significantly with cognitive function as assessed by the MMSE in DrD.[14–18] The present findings indicate that therapy aimed at controlling glycemic variability, in addition to hyperglycemia, might be beneficial for improving or maintaining cognitive function in patients with DrD. Second, microvascular and macrovascular diabetic complications were not evaluated in the present study. Although the Charlson Comorbidity Index scores were similar, participants with DrD showing glycemic variability and hypoglycemia could likely have several systemic complications, which might be confounding factors for cognitive function. Third, there have been only a few reports regarding clinical experience and usability of this factory-calibrated flash glucose monitoring system.[7,29,30] Although interstitial glucose measurements made with a factory-calibrated flash glucose monitoring system were found to be accurate compared with capillary blood glucose, the accuracy and stability over 14 days should be examined under several different conditions.[30]

In conclusion, we found that DrD shows a distinctly different AGP from AD associated with DM. There might be the possibility that glucose variability and hypoglycemia are more involved in the pathophysiology of DrD rather than that of AD associated with DM. The AGP analysis using this novel sensor-based flash glucose monitoring system might provide useful and important information to improve the overall glycemic profile of patients with DrD.

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Disclosure statement

The authors declare no conflict of interest.

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