Continuous glucose monitoring can disclose glucose fluctuation in advanced Parkinsonian syndromes

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Abstract

Continuous glucose monitoring (CGM) is a method to examine glucose concentration in subcutaneous interstitial fluid sequentially. CGM can disclose glucose fluctuation (GF), which can be unrecognized in routine blood tests. A limited number of studies suggest advanced Parkinsonian syndromes (PS) is at risk of GF, however, the report of CGM in PS is scarce. We performed CGM for 72 h in 11 nondiabetic patients with advanced PS. The etiology was Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, or dementia with Lewy bodies. All participants were bedridden, elderly (≥65 year-old), and receiving enteral nutrition. The retrospective data was obtained after the removal of CGM device. In the glucose concentration, 9 (81.8%) participants showed nocturnal decline (≤70 mg/dL; 4 of them reached recordable limit of 40 mg/dL), and 6 (54.5%) participants showed remarkable elevation (≥200 mg/dL) postprandially. In the majority, these abnormalities were difficult to predict from routine blood tests. Standard deviation and mean of sequential glucose concentration were higher than those in precedent reports of young or middle-aged healthy controls. CGM in nondiabetic and elderly patients with advanced PS can disclose GF, with features of nocturnal decline and/or postprandial remarkable elevation of glucose concentration. Owing to limitations such as small sample size, heterogeneity of etiology, and retrospectivity of CGM data, further investigations are required.

Introduction

To deliver carbohydrate in daily practice is a clinical concern because glucose fluctuation (GF), *i.e.*, unstable concentration of glucose, can lead to adverse events such as cardiovascular or cerebral complications.[1,2] However, the Harris-Benedict equation (HBE) and its variant formulas, including simplified method of delivering 25-30 kcal/kg body weight (BW) per day, cannot completely fill the exact demand of energy, and comorbid disorders can affect glucose tolerance.[3] In neurological disorders, patients with muscular wasting can be prone to fasting-induced hypoglycemia.[4] Moreover, Parkinson's disease (PD) and multiple system atrophy (MSA) can lead to GF by central and/or peripheral causes of dysautonomia; however, continuous monitoring of glucose dynamics in Parkinsonian syndromes (PS) is limited.[5,6] Therefore, it shall be beneficial to examine the presence and pattern of GF in patients with PS as the vulnerable population, since previous studies did not clarify these points or compare glucose profiles of patients with PS to healthy controls. Continuous glucose monitoring (CGM) is a method of evaluating continuously the concentration of interstitial glucose (IG) for several days or weeks, and it can record asymptomatic elevation and/or decline in IG which can be overlooked in conventional methods, such as hemoglobin A1c (HbA1c), spot percutaneous blood glucose measurement, and help to know the duration and sequence (*i.e.*, on fasting or postprandial) of low or high IG and to know the mean and standard deviation (SD) of IG.[7] Recently, CGM has been utilized to detect GF in pediatric patients under enteral feeding, with potential contribution of muscular wasting or dumping syndrome.[8,9] Therefore, we performed this study to examine glucose profiles by CGM in patients with PS under enteral nutrition because fixed and stabilized administration can help us know what is occurring in daily practice.

Materials and Methods

We recruited patients from May 2016 to March 2018. Inclusion criteria were as follows: i) clinical diagnosis of PD, Parkinsonian subtype of probable MSA, probable progressive supranuclear palsy, or probable dementia with Lewy bodies (DLB) in each diagnostic criteria; ii) bedridden state; iii) enteral feeding by gastrostomy or nasogastric tube three times per day; iv) administration of CZ-Hi, a semidigestive nutrient with energy resources of 60% from carbohydrate, 20% from protein, and 20% from fat (Clinico Co. Ltd., Tokyo, Japan), without any oral intake; and v) normal HbA1c (4.6-5.7% as the referential value) and no history of glucose intolerance or diabetes mellitus.[10-13] The exclusion criteria were: i) comorbid diseases or prescriptions that could influence glucose dynamics (*e.g.*, infection and prednisolone); ii) mechanical ventilation; iii) young age at disease onset (<40 year-old) or family history of PS; and iv) presence of remarkable involuntary movements (*e.g.*, levodopa-induced dyskinesia) to increase energy expenditure. This study was approved by the Ethical Committee of Hyogo-Chuo National Hospital, Sanda City, Japan (approval number: 28-06). The patients or their representative family members provided informed consent. To evaluate presence of muscular wasting, the participants underwent dual-energy X-ray absorptiometry by PRODIGY (GE Healthcare Japan Co. Ltd., Tokyo, Japan) to obtain skeletal muscle index (SMI). SMI ≤7.0 for male and ≤5.4 for female were defined as pathological.[14] Daily energy intake (EI) was determined by the following strategy: starting from 25 to 30 kcal/kg BW considering HBE, adjust the EI to stabilize the BW within ±1 kg/3

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months. Nutrient administration started at around 5:00, 11:00, and 17:00 at the administrative rate of 200 kcal/h. In CGM, iPro2 (Medtronic Japan Co., Ltd., Tokyo, Japan) was placed in the paraumbilical subcutaneous tissue at 15:00 to record concentration of IG, having certain lag for initial recording. The mean IG was recorded in every 5 minutes for 72 h. The recordable range of IG was 40-400 mg/dL. The device only shows retrospective data after the removal of the sensor. Plasma glucose (PG) in fingerstick blood was examined 13 times during the CGM (measured once at the start of the recording and then four times per day) to evaluate correlation in the mean absolute difference (MAD). Normality of continuous variables was examined by Shapiro-Wilk test. Median [interquartile range (IQR)] and mean±standard deviation (SD) were used to present clinical data (*e.g.*, SMI) and CGM data, respectively. The correlation between IG and PG was examined by Pearson analysis. We used Excel Toukei Software (version 2018; SSRI Co. Ltd., Tokyo, Japan) for statistical analysis. The level of statistical significance was defined as two-tailed, P<0.05. All data were presented as mean±SD. The result of CGM was interpreted by the following viewpoints: i) presence and duration of low glucose (LG) and high glucose (HG), ii) mean of the measured IG in 72 h (MG), and iii) presence of glycemic variability (GV), which was examined by the SD of IG. The presence of LG, severe LG, HG, and severe HG was defined as one or more recordings of the value during 72 h with the cutoff value of ≤70, ≤50, ≥140, and ≥200 mg/dL, respectively, according to guideline of American Diabetes Association and previous CGM studies in young or middle-aged healthy Asians.[15-18] Duration of time with LG >11.7 % and HG >17.1 %, MG >119.0 mg/dL, and SD of IG >25.2 mg/dL was defined as pathologic from the 95th percentile of healthy people.[17,18] To examine potential discrepancy from plasma HbA1c, estimated HbA1c was obtained from MG in CGM by a conversion formula reported previously.[19]

Results

Eleven patients were enrolled. The age was 80 [5.5] year-old, male (M): female (F) ratio was 7:4, the diagnosis was PD (N= 3), MSA (N= 2), PSP (N= 2), and DLB (N=4), and BMI was 16.2 [3.4] kg/m^2 (Table 1). Except case 9, whose contracture of limb prevented undergoing absorptiometry although the muscular wasting was apparent in inspection, SMI of participants filled the criteria of pathological muscular wasting. Nutritional administration was performed by nasogastric tube in 3 participants (cases 3, 7, and 8) and by gastrostomy in the remaining 8 participants. Daily EI was 1000 [100] kcal, *i.e.*, 24.0 [5.7] kcal/BW. Excluding age and daily EI, normality of clinical data was not confirmed (P>0.05). The result of CGM in any patient showed normality (P<0.05). In total recordings, IG was 120.2±34.0 mg/dL, while PG 121.6±35.1 mg/dL (r=0.85, P<0.001), and MAD was 20.5%. This fulfills the criteria of optimal accuracy of CGM (r>0.79, MAD≤28%).[17] 9 participants (81.8%) experienced LG, and 4 of them experienced severe LG reaching lower recordable limit of 40 mg/dL (Table 2). The timing of LG was mostly nocturnal, occurring between 21:00 and 5:00. The presence and duration of LG had interday variability even in the same patients. In their medical records, cases 1, 3, 7, 9, and 11, in whom CGM recorded LG, never experienced hypoglycemia in routine blood tests. When comparing our results to referential studies, time with LG did not exceed the referential range (≤11.7 %), however, duration of each event with severe LG was longer (range: 55-365 *vs* 5-30 min.).[17] Both HG (prevalence: 100%) and severe HG (prevalence: 54.5%) mostly occurred in postprandial time, *i.e.* from the start of feeding until 3 h after the end of nutritional administration. 6 (54.5%) participants had high MG (>119 mg/dL), and 9 (82.8%) participants had GV (SD>25.2 mg/dL).[17,18] The glucose profile of case 8 is shown to present these abnormalities in CGM (Figure 1). Estimated HbA1c was higher than plasma HbA1c in all cases (5.9 [0.55] *vs* 5.2 [0.15]%).

Table 1. Clinical features of the patients.

Case number	1	2	3	4	5	6	7	8	9	10	11	Median [IQR]
Age (year-old) and sexuality	80M	81M	71M	67M	80M	77F	83F	82M	83F	83F	77M	80 [5.5]
Diagnosis	MSA	PSP	PD	DLB	PSP	DLB	MSA	DLB	PD	PD	DLB	
BMI (kg/m^2)	16.3	15.3	13.2	14.3	17.3	18.7	24.6	15.0	18.7	14.2	16.2	16.2 [3.4]
SMI (kg/m^2)	5.0	3.8	3.7	4.8	4.9	4.4	4.6	4.1	NA	3.6	5.5	4.5 [1.0]
Energy intake (kcal/day)	1200	1200	900	1000	1000	1000	800	1000	1000	1200	1000	1000 [100]
Energy intake (kcal/day/kg BW)	32.7	28.1	23.6	29.2	24.0	22.0	16.4	24.4	22.3	34.8	23.6	24.0 [5.7]

IQR, interquartile range; M, male; F, female; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; PD, Parkinson's disease; DLB, dementia with Lewy bodies; BMI, body mass index; SMI, Skeletal muscle index; NA, not available; BW, body weight.

Table 2. Results of continuous glucose monitoring.

Case number	1	2	3	4	5	6	7	8	9	10	11	Median [IQR]
Mean glucose (mg/dL)	108.1	108.0	114.6	113.0	116.4	121.4	125.0	127.1	131.5	131.6	137.2	121.4 [15.5]
Standard deviation (mg/dL)	32.1	30.7	24.7	23.0	28.0	38.0	30.6	34.0	32.1	52.6	44.6	32.1 [6.7]
Minimal glucose (mg/dL)	≤40	≤40	64	73	73	62	60	≤40	68	54	≤40	Undetermined
Time with LG (%)	10.9	10.0	3.2	0.0	0.0	1.9	3.7	6.0	0.7	7.5	6.1	3.7 [5.5]
Time with severe LG (%)	8.4	5.2	0.0	0.0	0.0	0.0	0.0	2.5	0.0	0.0	3.7	0.0 [3.1]
Maximal glucose (mg/dL)	185	194	183	185	208	263	185	317	238	286	233	208 [65.5]
Time with HG (%)	18.1	16.0	19.3	15.7	20. 4	26.9	36.6	50.3	37.5	38.1	45.2	26.9 [19.1]
Time with severe HG (%)	0.0	0.0	0.0	0.0	1.6	4.9	0.0	28.0	2.2	13.0	10.3	1.6 [7.6]
Estimated/plasma HbA1c (%)	5.4/5.0	5.4/5.2	5.6/5.0	5.6/5.2	5.7/5.5	5.9/5.1	6.0/5.3	6.1/5.2	6.2/5.4	6.2/5.3	6.4/5.2	5.9 [0.55]/5.2 [0.15]

IQR, interquartile range; LG, low glucose; HG, high glucose; HbA1c, hemoglobin A1c. The minimal glucose of case 1, 2, 8, and 11 reached lower recordable limit of 40 mg/dL.

Discussion and Conclusions

We presented the result of CGM in advanced PS under enteral nutrition. The core finding was GF, which was featured by nocturnal LG and postprandial severe HG, although the nutrition was considered clinically adequate. Our results suggested impaired homeostasis in glucose concentration from the higher prevalence of LG (82.8 *vs* 41%), severe LG (36.4 *vs* 5.5%), HG (100 *vs* 60%), and severe HG (54.5 *vs* 1.8%) and longer recovery time from each event of severe LG (55-365 *vs* 5-30 min) than those in referential studies.[17,18] In addition, the majority of the participant had high MG and GV. The time within normal range of glucose concentration (71-139 mg/dL) in total recordings of CGM was shorter than referential data (approximately 70 *vs* 93%).[17] The present study also suggested that CGM had the potential to detect conventionally unrecognized LG and/or HG, since severe LG in neuroglycopenic level (≤50 mg/dL) and severe HG in diabetic level (≥200 mg/dL) were difficult to expect from routine blood tests.[2,16] In addition, estimated HbA1c by CGM was higher than plasma HbA1c, potentially owing to shortened lifespan of red blood cell by aging to make plasma HbA1c less accurate.[16] Several mechanisms can be hypothesized to cause GF. First, PS can impair the autonomic function by neuronal damage, although the severity can be different in each disorder and individual.[6] Second, since muscular wasting was observed in all patients, impaired gluconeogenesis from muscular glycogen can contribute to GF.[4] Third, high MG, long time with HG and high SD could originate from aging, although the contribution of aging towards LG and sexual difference towards any CGM abnormality is still not established.[17,18] Fourth, high prevalence and long duration of HG might originate from subclinical glucose intolerance which was unrecognized by plasma HbA1c and potentially long administration of nutrients (200 kcal/h). Lastly, dumping syndrome could be a contributor, although LG was not reproducibly observed in postprandial time.[19] The present study has several limitations. Our sample size was suboptimal for thorough analysis, hence the influence of PS, aging, sexuality, EI, and muscular wasting was not determined. Moreover, examination in age-matched disease controls is absent, and the background disorders of PS were heterogeneous. Since our device for CGM was not real time, we could not perform blood test during LG and HG, not only to know simultaneous PG but also to know the mechanism of LG and HG by simultaneous testing of contributors for glucose control such as insulin. The possibility of error in measurement shall be considered because CGM is less accurate in the range of LG.[20] To determine EI, more accurate method than HBE, such as indirect calorimetry, was not available in our institution.[3] In addition, the clinical significance of GF, *e.g.*, cardiovascular and cerebral complications, was not examined. In conclusion, CGM can disclose conventionally unrecognized GF, featured by nocturnal LG and/or postprandial severe HG, in elderly patients with advanced PS under enteral nutrition. To our knowledge, this is the first study to show continuous change of glucose level in advanced PS under enteral nutrition. However, owing to limitations such as small sample size, heterogeneity of etiology, and retrospectivity of CGM data, further investigations are required.

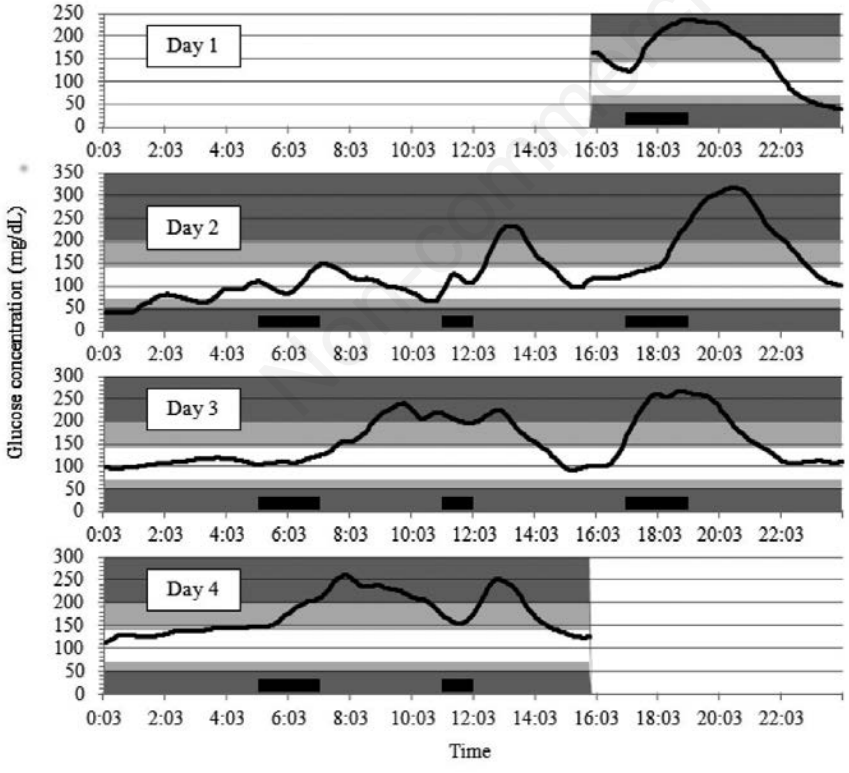

Figure 1. Result of CGM in case 8. Glucose fluctuation, featured by nocturnal decline and postprandial elevation of glucose concentration, was observed in examination for 72 hours. The recording started at 16:03 on day 1. Black bands represent feeding time of enteral nutrition. Abnormal level of glucose was noted by bands in light gray (51-70 mg/dL or 140-199 mg/dL) as mild abnormalities and dark gray (≤50 mg/dL or ≥200 mg/dL) as severe abnormalities.

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