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CASE REPORT

A case of insulinoma-induced hypoglycemia managed by Dexcom G4 Platinum

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Abstract

This report details the case of a 41-year-old woman who was diagnosed with insulinoma. As the patient developed severe life-threatening hypoglycemia, we introduced Dexcom G4 Platinum (DG4P), a modern continuous glucose-monitoring system (CGM). The algorithm of the sensor glucose (SG) values of CGM is based on patients with diabetes; therefore, we evaluated the accuracy of DG4P in this patient. The mean absolute relative differences and absolute differences between SG of DG4P and self-monitoring of blood sugar values were 10.8%±8.3% and 6.8±5.7 mg/dL, respectively, in the hypoglycemic region, which verifies DG4P's accuracy. DG4P was found to be useful for monitoring hypoglycemia not only in patients with diabetes but also in those with insulinoma.

INTRODUCTION

Insulinoma is a functional neuroendocrine tumor (NET) characterized by insulin overproduction that leads to hypoglycemia (Maggio *et al.* 2020). In epidemiological studies conducted across Japan, insulinoma has the highest incidence among functional pancreatic NETs (Ito *et al.* 2015). Insulinomas are diagnosed on the basis of Whipple's triad composed of (1) symptoms of hypoglycemia, (2) hypoglycemia, that is, blood glucose level (BG) < 50 mg/dL, and (3) symptom relief following ingestion of glucose (Whipple 1942). However, patients often experience treatment-refractory hypoglycemia, and some are unaware that they are experiencing hypoglycemia because of similar frequent episodes (Maggio *et al.* 2020). These may result to poor clinical outcomes. In this context, continuous glucose monitoring (CGM) has proven useful in the detection of hypoglycemia in patients with insulinoma (Sugawa *et al.* 2018). However, because the standard reference values for the accuracy and algorithm of sensor glucose (SG) values in CGM have been determined in patients with diabetes, these same values may not be applicable in healthy subjects or individuals with other non-diabetic hypoglycemic pathologies (Sekido *et al.* 2017). In addition, one

form of CGM, intermittently scanned CGM (isCGM), has insufficient accuracy in the hypoglycemic range (Bailey *et al.* 2015; Adolfsson *et al.* 2018).

The Parkes error grid analysis (PEGA), mean absolute relative difference (MARD), and mean absolute difference (MAD) have widespread acceptance for their accuracy in CGM (Bailey *et al.* 2015a; Adolfsson *et al.* 2018; Bailey *et al.* 2015b). Each of the zones of PEGA analysis represents the degree of risk of an adverse outcome due to the error in the measured BG. The MARD was calculated using the following formula: MARD (%) = 100 × [(CGM-SG-reference BG]/BG.

Dexcom G4 Platinum (DG4P) is one of the modern CGM tools with better accuracy, especially in the hypoglycemic range, and it has recently become available for clinical use in Japan (Adolfsson *et al.* 2018; Bailey *et al.* 2015b). The Dexcom G6 sensor algorithm is used in Japan for the DG4P, as it has better accuracy than that of the DG4P (MARD= 9%) (Adolfsson *et al.* 2018; Bailey *et al.* 2015b). However, there are currently only a few reports on insulinoma managed by DG4P to prevent severe hypoglycemia. In this report, we present a case of a patient with insulinoma who was managed by DG4P. Additionally, we investigated the accuracy of SG in DG4P values (DG4P-SG) in the hypoglycemic range.

CASE REPORT

A 41-year-old woman had a sudden pre-lunch seizure and was taken to a hospital by her family members. Her point-of-care BG was 30 mg/dL, and the seizure rapidly improved after glucose administration. The patient was then referred to our hospital for further evaluation and management of severe hypoglycemia. There were no remarkable findings on physical examination. The patient's height and body weight were 158.9 cm and 65.8 kg, respectively. She had a history of weight gain over several years. The patient had no history of antidiabetic medication use, and none of her laboratory data suggested other endocrine diseases (Table 1). In a fasting sample, the plasma BG decreased to 40 mg/dL with an associated serum insulin level of 7.4 μU/mL (Table 1). Abdominal dynamic computed tomography (CT) scan revealed an early enhanced tumor with a diameter of 23 mm at the head of the pancreas and other small tumors throughout the pancreas (Fig. 1A). Endoscopic ultrasonography (EUS) showed four tumors (Fig. 1B), and EUS-guided fine needle aspiration cytology of the tumor yielded positive results for insulin staining. The selective artery calcium injection (SACI) test revealed autonomous insulin secretion in the tumors. Based on these findings, we diagnosed the patient with insulinoma, and she underwent elective total pancreatectomy (Fig. 2A). Immunohistochemistry showed multiple tumor cells that positively stained for insulin and chromogranin A (Fig. 2B–D), and these were diagnosed as neuroendocrine tumors (NET), specifically insulinoma (NET, G2: Grade 2 gastrointestinal). Postoperatively, the patient had no hypoglycemia, but she developed hyperglycemia due to the total pancreatectomy. She was then started on basal bolus insulin therapy for hyperglycemia.

As the patient often had severe treatment-resistant hypoglycemia before her diagnosis, and considering her lack of awareness of her hypoglycemic episodes, we decided to introduce DG4P to prevent life-threatening hypoglycemia as it can detect incipient severe hypoglycemia (Fig. 3A). To evaluate the accuracy of DG4P, we conducted PEGA of the DG4P-SG and self-monitoring of BG (SMBG; OneTouch Verio IQ®; Lifescan Inc, CA, USA) and found that all data were within zones A and B (Fig. 3B, 3C). More importantly, the MARD and MAD between the DG4P-SG and SMBG values were 11.7%±9.0% and 9.1±7.4 mg/dL, respectively, whereas the MARD and MAD in the hypoglycemic range were 10.8%±8.3% and 6.8±5.7 mg/dL, respectively (Fig. 3D).

DISCUSSION

Approximately 90% of insulinomas are benign, but uncontrollable insulin overproduction often causes treatment-refractory hypoglycemia (Maggio *et al.* 2020). Insulinoma-induced hypoglycemia is typically severe and causes hypoglycemia unawareness secondary to desensitization and downregulation of insulin counterregulatory hormones due to chronic hypoglycemia (Maggio *et al.* 2020; Cryer 1999). The difficult and delayed diagnosis of insulinoma also contributes to the challenges in managing hypoglycemia. Because the unawareness of severe hypoglycemia is life-threatening, the detection of hypoglycemia is very important not only for the diagnosis of insulinoma but also for the initiation of life-saving treatment.

Studies have shown that CGM not only improves the overall glycemic control but also reduces the duration of hypoglycemic episodes (Advani 2020). Modern CGM for personal use falls into two categories: (1) intermittently scanned CGM (isCGM) and (2) real-time CGM (rtCGM) (Advani 2020; Rodbard 2017). For isCGM, patients are required to scan the sensor inserted into their body to check their SG. On the other hand, patients equipped with rtCGM can check SG with the monitor wirelessly connected to the sensor, without any need for scanning (Adolfsson 2018; Advani 2020). In addition, rtCGM can generate alerts on hypoglycemia. Patients with BG < 54 mg/dL have decreased symptom awareness, placing them at increased risk of severe hypoglycemia and mortality. Therefore, BG should be checked regularly even in asymptomatic patients (Advani 2020; Agiostratidou *et al.* 2017; International Hypoglycaemia Study Group 2017). In this regard, rtCGM has greater efficacy for the detection of hypoglycemia compared to isCGM (Cryer 1999; Reddy *et al.* 2018).

The algorithm of the SG values of CGM is based on patients with diabetes; therefore, CGM is considered to have insufficient accuracy in the hypoglycemic

Tab. 1. Laboratory values in post-glucose administration and fasting blood glucose test samples in a patient with insulinoma

Parameters at admission, post glucose administration	Values (standard reference)	Parameters on the fasting sample	Values (standard reference)
Blood glucose (mg/dL)	108 (80–110)	Blood glucose (mg/dL)	40 (80–110)
Immunoreactive insulin (μg/mL)	4.3 (1.0–21.74)	Immunoreactive insulin (μg/mL)	7.4 (1.0–21.74)
Serum C-peptide (ng/mL)	0.39 (1.1–3.3)	Serum C-peptide (ng/mL)	0.56 (1.1–3.3)
Free T3 (pg/mL)	2.77 (1.88–3.18)	Adrenaline (pg/mL)	41 (<100)
Free T4 (ng/dL)	0.95 (0.70–1.48)	Noradrenaline (pg/mL)	261 (100-450)
IGF-1 (ng/mL)	76 (95-240)	Dopamine (pg/mL)	6 (<20)
Adrenocorticotropic hormone (pg/mL)	12.8 (7.2–63.3)	Adrenocorticotropic hormone (pg/mL)	11.5 (7.2–63.3)
Cortisol (μg/dL)	7.2 (3.0–19.6)	Cortisol (μg/dL)	10.6 (3.0–19.6)
Human growth hormone (ng/mL)	<0.07 (<2.10)	Human growth hormone (ng/mL)	<0.07 (<2.10)
Glucagon (pg/mL)	183 (70-174)	Glucagon (pg/mL)	183 (71–174)
Gastrin (pg/mL)	92 (<200)		
WBC (cells/μL)	4400 (4000–9600)		
Hb (g/dL)	11.7 (13.2–17.3)		
Platelets $\times 10^4$ (cells/μL)	23.2 (16–35)		
Total protein (g/dL)	7.0 (6.3–7.9)		
Albumin (g/dL)	4.3 (3.9–5.0)		
Total bilirubin (mg/dL)	0.8 (0.3–1.2)		
AST (U/L)	80 (13–33)		
ALT (U/L)	79 (8–42)		
LDH (U/L)	374 (119–229)		
ALP (U/L)	162 (115–359)		
γGTP (U/L)	27 (10–47)		
AMY (U/L)	129 (49–136)		
Blood urea nitrogen (mg/dL)	19 (8–20)		
Creatinine (mg/dL)	0.88 (0.65–1.07)		
Na (mEq/L)	140 (137–145)		
K (mEq/L)	4.4 (3.5–4.8)		
Cl (mEq/L)	104 (100–107)		
T-Cho (mg/dL)	173 (128–219)		
TG (mg/dL)	33 (30–149)		
HbA1c (%)	4.5 (4.6–6.2)		
Insulin antibody	Negative		
CEA (ng/mL)	2.6 (0–5.0)		
NSE (ng/mL)	11.6 (0–12)		
ProGRP (pg/mL)	53.8 (<80)		

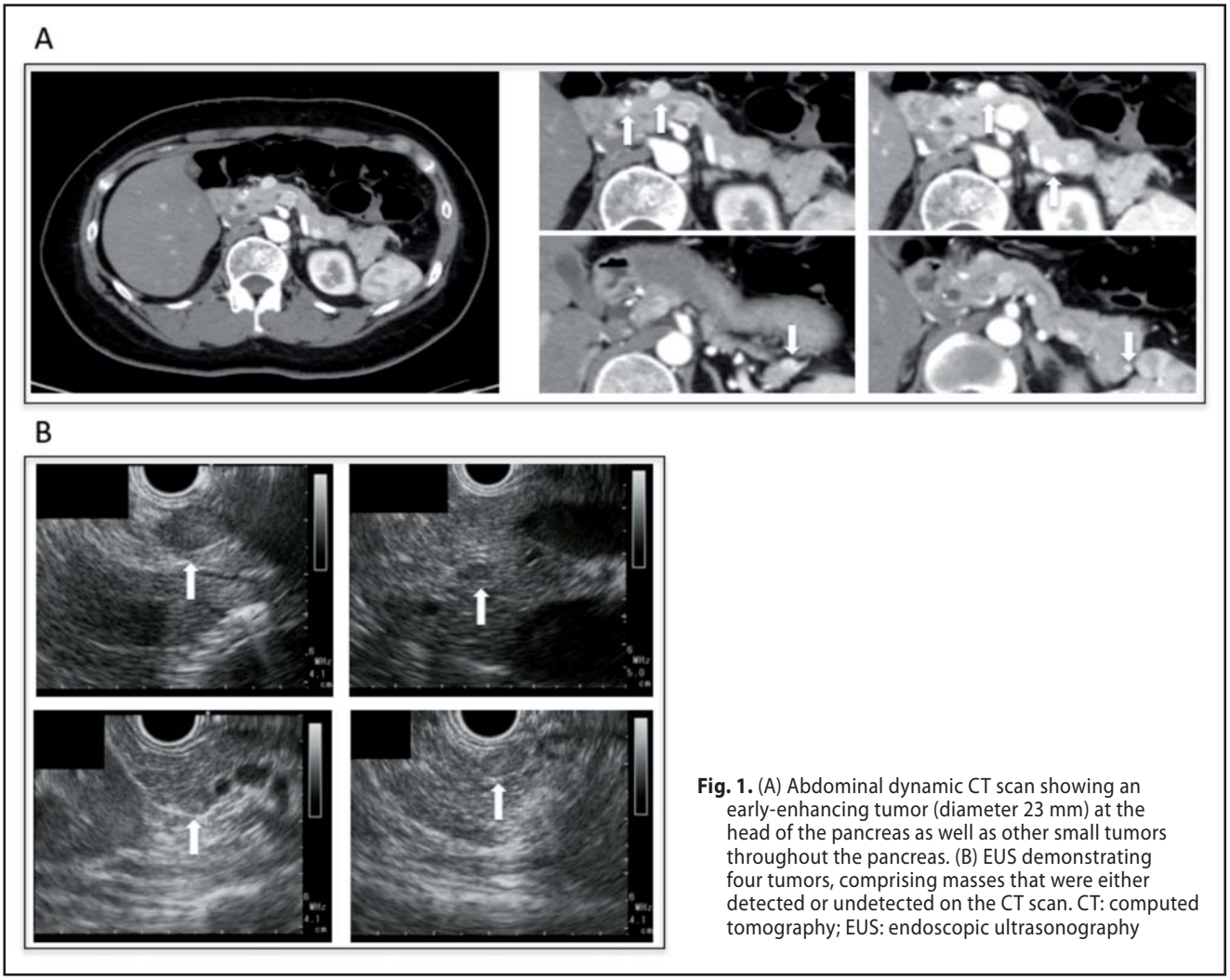

Fig. 1. (A) Abdominal dynamic CT scan showing an early-enhancing tumor (diameter 23 mm) at the head of the pancreas as well as other small tumors throughout the pancreas. (B) EUS demonstrating four tumors, comprising masses that were either detected or undetected on the CT scan. CT: computed tomography; EUS: endoscopic ultrasonography

range, and it is neither advisable nor covered by medical insurance for patients with insulinoma in Japan (Bailey *et al.* 2015a; Adolfsson *et al.* 2018). Previous reports indicate that the accuracy of isCGM is questionable in the hypoglycemic range, and the MAD between SG and SMBG is 13.4 mg/dL for BG < 100 mg/dL (Sekido *et al.* 2017). Although isCGM is a potentially useful diagnostic tool for insulinoma (Sugawa *et al.* 2018), the accuracy of isCGM may be insufficient for a definitive diagnosis. Therefore, we introduced DG4P in a patient with insulinoma. In the hypoglycemic range, DG4P-SG has high accuracy, because the MAD between DG4P-SG and SMBG is 6.4 mg/dL for BG < 70 mg/dL (Bailey *et al.* 2015a; Adolfsson *et al.* 2018). In our patient, the MARD was 10.8%±8.3% and the MAD was 6.8±4.9 mg/dL at BG < 70 mg/dL, which supports previous reports of the accuracy of DG4P in the hypoglycemic range (Bailey *et al.* 2015a; Adolfsson *et al.* 2018). To our knowledge, this is the first report of the utility of DG4P in hypoglycemia monitoring not only for patients with diabetes but also for patients with insulinomas.

In summary, because of its high accuracy in the hypoglycemic range, DG4P could be potentially useful for the detection of hypoglycemia in patients with hypoglycemia unawareness as well as in the prevention of severe hypoglycemia in patients with insulinoma. However, larger-sample studies are necessary to validate the above-mentioned results.

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DISCLOSURE

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Data Availability

Some or all datasets generated during the current study are not publicly available but are available from the corresponding author on reasonable request.

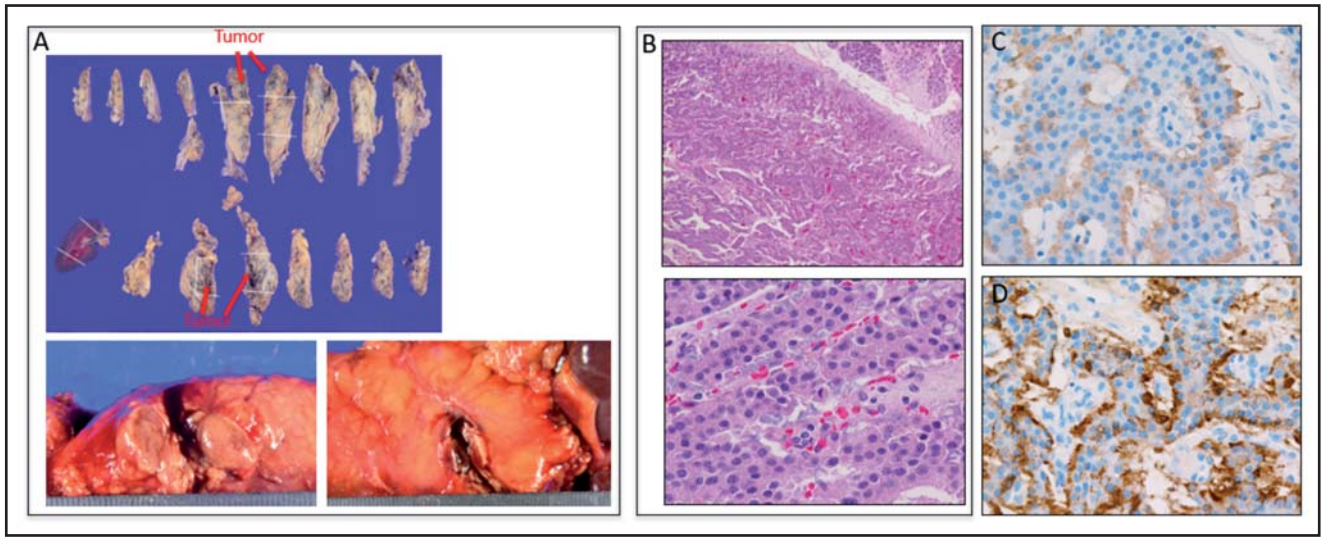
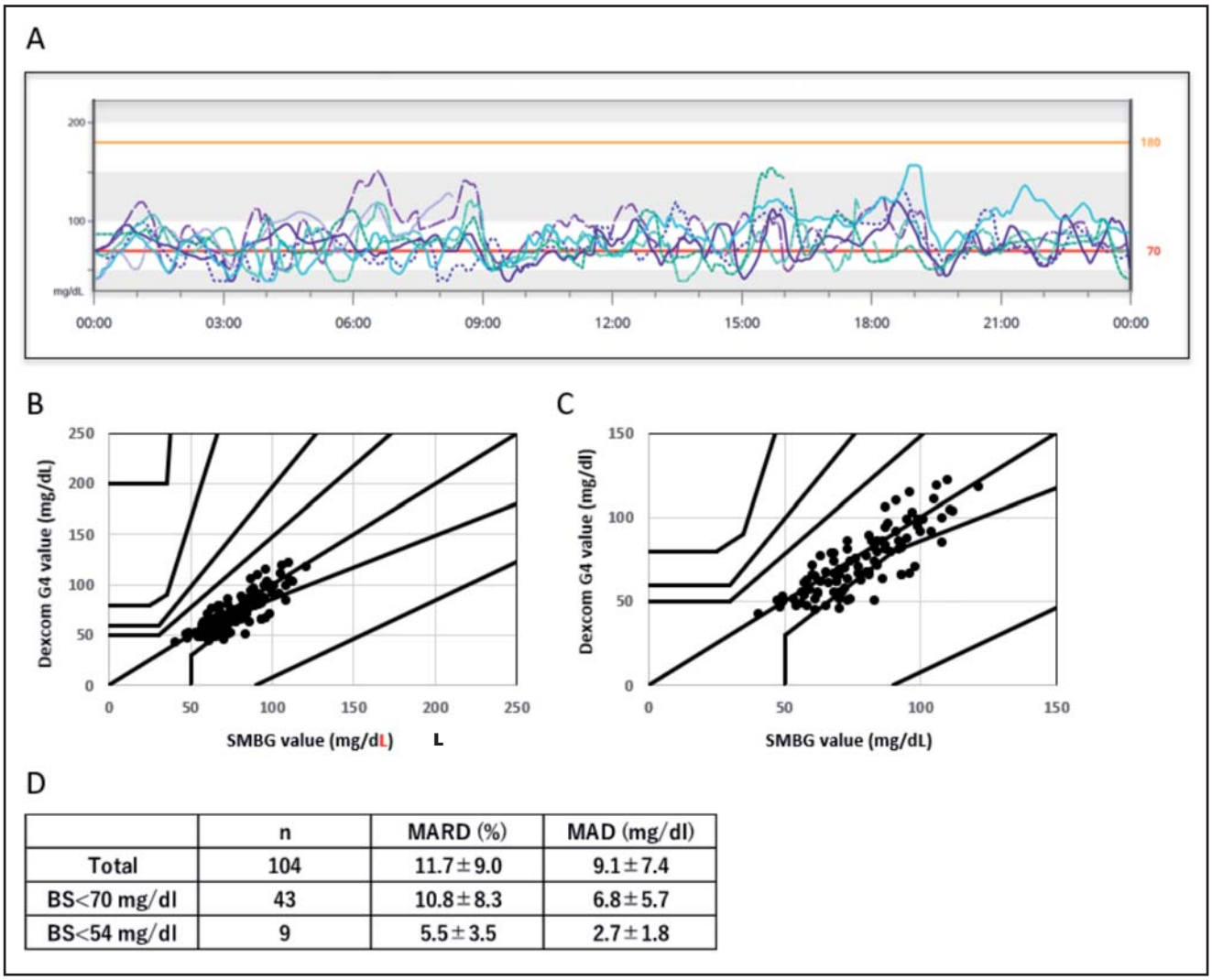


Fig. 2. (A) Histopathological examination of resected pancreas (total). (B) HE, Hematoxylin and Eosin staining of a surgical specimen in a low-power field (upper panel) and high-power field (lower panel). (C) Insulin staining of the surgical specimen in the high-power field. (D) Chromogranin A staining in the high-power field.



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	n	MARD (%)	MAD (mg/dl)
Total	104	11.7±9.0	9.1±7.4
BS<70 mg/dl	43	10.8±8.3	6.8±5.7
BS<54 mg/dl	9	5.5±3.5	2.7±1.8

Fig. 3. (A) Summary of daily glucose profiling of patients with DG4P. (B, C) Parkes error grid analyses of the sensor glucose values of DG4P and values from SMBG at 0–250 mg/dL (B) and 0–150 mg/dL (C). (D) MARD and MAD between the sensor glucose values of DG4P and SMBG. DG4P: Dexcom G4 Platinum; MAD: mean absolute difference; MARD: mean absolute relative difference; SMBG: self-monitoring of blood sugar

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