REVIEW

Verification of glycemic profiles using continuous glucose monitoring : cases with steroid use, liver cirrhosis, enteral nutrition, or late dumping syndrome

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Abstract : Glycemic control is often difficult to achieve in patients with diabetes, especially in the presence of comorbid diseases or conditions such as steroid-use or liver cirrhosis, or in patients receiving enteral nutrition. Moreover, reactive hypoglycemia due to late dumping syndrome in people having undergone gastrectomy is also a matter of concern. Empirically and theoretically, the typical glycemic profiles associated with these conditions have been determined ; however, what actually happens during a 24-h span is still somewhat obscure. In order to verify and provide information about the 24-h glycemic profiles associated with these conditions, 8 patients with the 4 above-mentioned conditions were monitored using a continuous glucose monitoring system (CGMS). For all 8 patients, CGMS provided detailed information regarding the 24-h glycemic profiles. The CGM results showed typical glycemic patterns for each condition, and we were moreover able to observe the effects of various practical treatments. Based on these cases, we conclude that the CGMS is highly useful for determining the glycemic patterns of patients with the aforementioned conditions in a practical setting ; and this system may be used to monitor the treatment success of such cases. J. Med. Invest. 62 : 1-10, February, 2015

Keywords **:** *Steroid, liver cirrhosis, enteral nutrition, late dumping syndrome, continuous glucose monitoring system (CGMS)*

INTRODUCTION

Diabetes is a multifactorial disease, in which 2 major factors, namely insulin resistance and impaired insulin secretion, or a combination thereof, contribute to the onset or deterioration of the disease. Glycemic control is often difficult to achieve, and when patients with diabetes have comorbid diseases or conditions, the glycemic profiles may become even more complicated and make the treatment more difficult. However, if we can gain an understanding of the pathophysiological causes and typical glycemic profiles of patients with diabetes and certain comorbid diseases and conditions, we may be able to predict the possible glycemic profiles and establish tailor-made treatments for individual cases. Empirically and theoretically, the typical glycemic profiles associated with many of these conditions have been determined ; however, these findings were acquired mainly from finger-prick blood glucose levels at various time intervals, and what actually happens during a 24-h span is still somewhat obscure.

Continuous glucose monitoring system (CGMS) can be used to measure the interstitial glucose concentration, which closely approximates the plasma glucose after a short time lag. CGMS provide detailed information regarding the 24-h glycemic profiles, including nocturnal and postprandial glycemia, which standard finger-prick blood glucose monitoring regimens cannot provide us (1-5). Therefore, the use of CGMS has the potential to provide more informative and precise insights into the glycemic profiles of type 2 diabetes patients with various comorbid diseases or conditions, such as steroid use, liver cirrhosis, or enteral feeding. In order to verify and provide information about the substantial glycemic profiles associated with these conditions, we are presenting examples of results obtained with 2 kinds of CGMS devices (Medtronic MiniMed, CGMS-GOLD and iPro®2, Northridge, CA, USA) (6) in patients with the 3 above-mentioned conditions, together with the actual treatments for the individual cases. Furthermore, we also present a case with late dumping syndrome for which CGMS clearly demonstrated the virtual glucose profile and effectiveness of the treatment.

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STEROID-INDUCED HYPERGLYCEMIA

Glucocorticoids, such as prednisolone, are commonly used to treat a wide variety of both acute and chronic illnesses, and remain a valuable and necessary component of the therapy for many diseases. However, the use of glucocorticoids may be accompanied by multiple side effects, including hyperglycemia, and can result in worsening of preexisting diabetes or in the induction of *de novo* "steroid-induced" diabetes (7, 8). In fact, glucocorticoids are the most common cause of drug-induced diabetes (7), and the incidence rate of diabetes secondary to the use of glucocorticoids has been reported to range between 2-50% (9-15). The odds ratio for new-onset diabetes mellitus in patients treated with glucocorticoids ranges from approximately 1.5-2.5 (15, 16), and the total glucocorticoid dose and duration of therapy have been demonstrated to be strong predictors of diabetes induction, along with age and body mass index (15, 16).

Mechanisms for steroid-induced hyperglycemia development

The mechanisms by which glucocorticoids cause diabetes predominantly involve insulin resistance rather than decreased insulin

production (7, 15, 16), however, a reduction in insulin secretory capacity has been observed at higher doses of corticosteroid use (17). Glucocorticoids decrease the liver's sensitivity to insulin, thereby increasing the hepatic glucose output (15, 18). They moreover inhibit glucose uptake in muscle and fat, thus reducing insulin sensitivity. These observations are thought to be primarily due to a postreceptor effect, or in other words, either due to inhibition of glucose transport or decreased glycogen synthesis (19-25). In addition to these factors, counterregulatory hormones, such as glucagon, have been demonstrated to be augmented by glucocorticoid administration (26).

Management for steroid-induced hyperglycemia

Oral glucocorticoids are often administered in the morning to mimic the diurnal rhythm of cortisol (7), and the peak effect occurs approximately 4 to 6 hours after dosing (7, 27). Therefore, the glucose levels generally start to rise mid-morning or early afternoon and continue to increase until bedtime (7, 27), which is characterized by the development of postprandial hyperglycemia (7, 12). Accordingly, glucose-lowering therapy should be predominantly directed at the time of after lunch and/or dinner.

As for the treatment of steroid-induced hyperglycemia, the currently available agents used in the treatment of type 2 diabetes mellitus, including sulfonylureas, metformin, thiazolidinediones, and insulin have been suggested as potential treatment options for non-critically ill patients (15, 28). While oral agents are available for mild hyperglycemia, marked hyperglycemia, especially in diabetic patients or patients with liver or renal disease, requires insulin. The dose of insulin can be adjusted depending on the glucose levels, and special caution will be necessary when the dose of glucocorticoid is tapered or discontinued because, although the effects of glucocorticoids on hyperglycemia usually remit within 48 hours of discontinuation of oral drug administration (28), the glucose levels may drop dramatically after that, which may consequently lead to an increased risk of hypoglycemia.

Case reports

Case 1 : A 51-year-old female patient with a 7-year history of diabetes. Her glycated hemoglobin (HbA1c) level was 6.2% with medication of metformin (750 mg/day) and the dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor) sitagliptin (100 mg/day). She was diagnosed with autoimmune hepatitis and was consequently admitted to our hospital where oral administration of glucocorticoids 30 mg/day once a day in the morning was initiated. Seven days after drug initiation, the dose was tapered to 25 mg/day. The dosage of metformin and sitagliptin had been maintained throughout the admission period. The results of the CGMS showed postprandial hyperglycemia after lunch and dinner ; however, because the levels of hyperglycemia were relatively mild and the escalation was attenuated when glucocorticoid administration was tapered from 30 mg/day (Fig. 1a) to 25 mg/day (Fig. 1b), insulin therapy was not required in this patient.

Case 2 : A 76-year-old female patient with a 4-year history of diabetes. Her HbA1c level was 7.9% with medication of glimepiride (0.5 mg/day), miglitol (225 mg/day), and alogliptin (12.5 mg/day). She received 20 mg of dexamethasone once a week in the morning as a part of her treatment for multiple myeloma, and she required short-acting human insulin injections (Novolin®R) 3 times a day before every meal on the day of and the day after dexamethasone administration to control steroid-induced hyperglycemia. On the day of dexamethasone administration (Fig. 2b), even with the insulin injections, the CGMS results showed postprandial hyperglycemia mainly in the afternoon, which was not seen the day before drug administration (Fig. 2a). Her postprandial hyperglycemia remained to the next day, even after insulin injections (Fig. 2c) ; however, one day later, it was attenuated without insulin injection (Fig. 2d). This case is a good example of how the effects of glucocorticoids on hyperglycemia may persist to the next day after

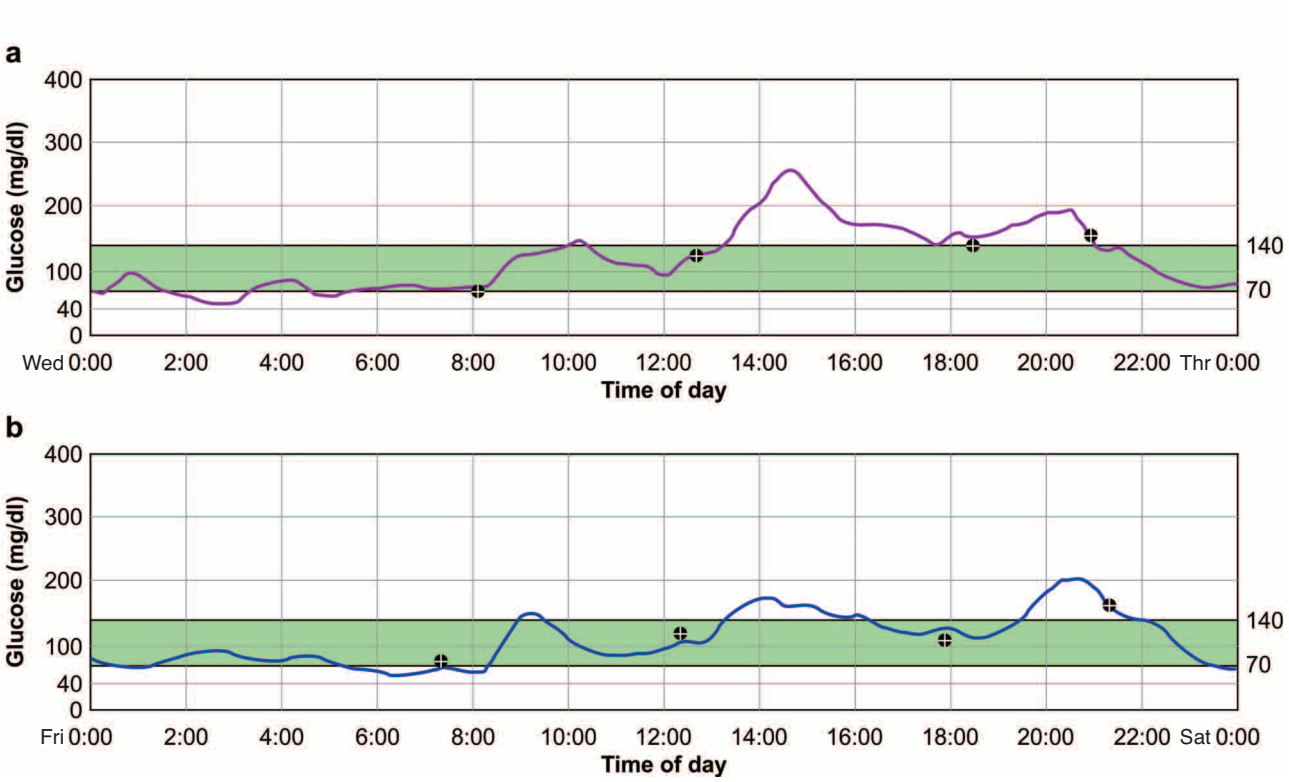

Fig. 1 Results of the continuous glucose monitoring system (CGMS iPro®2) in case 1.
The patient received glucocorticoids (30 mg/day) (a), which were subsequently tapered to 25 mg/day (b).

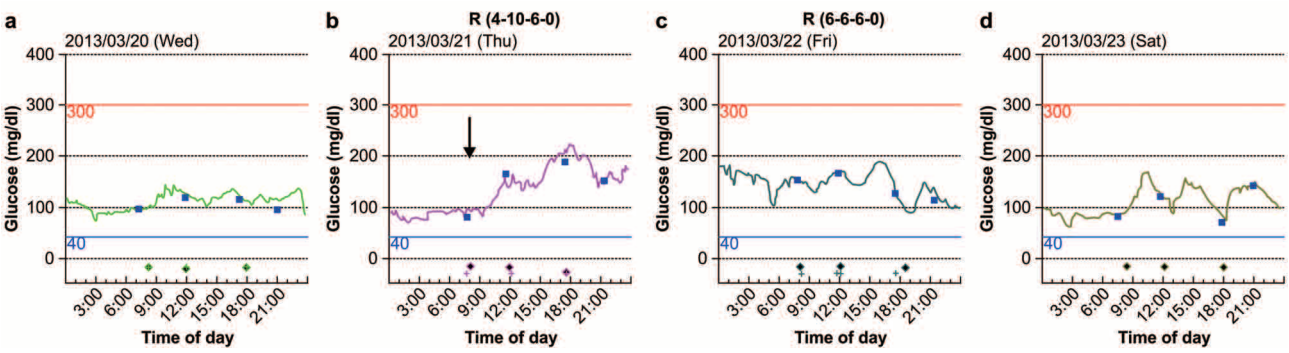

Fig. 2 Results of the continuous glucose monitoring system (CGMS-GOLD) in case 2.
(a) The day before dexamethasone administration. (b) The day of drug administration. (c) Day 2 after drug administration. (d) Day 3 after drug administration. R indicates short-acting human insulin (Novolin®R), and the numbers in parentheses indicate the doses of insulin injections administered before breakfast, lunch, dinner, and sleep, respectively. The arrow in (b) indicates the time of dexamethasone administration.

discontinuation of the drug.

Case 3 : A 71-year-old male patient with a 6-year history of diabetes. His HbA1c level was 7.3%, and he was receiving metformin (1,000 mg/day) and miglitol (1,000 mg/day). One month prior, he was diagnosed with rheumatic polymyalgia, and prednisolone (15 mg/day, administered in the morning) was initiated for treatment. Soon after treatment initiation, the patient was admitted to our hospital, and glycemic control with insulin and a DPP-4 inhibitor, alogliptin (25 mg/day), was initiated. Initially, short-acting human insulin (Novolin®R) was used before breakfast and lunch, and long-acting insulin, glargine (Lantus®), was used before bedtime. During the admission period, because his postprandial hyperglycemia was significant (Fig. 3a ; day 1), short-acting insulin was changed to a rapid-acting insulin, aspart (NovoRapid®), and the doses of insulin were increased. Glargine was also switched to the long-acting degludec (Tresiba®) with changes of dose and timing of injection. These changes attenuated postprandial hyperglycemia after breakfast and lunch, although postprandial hyperglycemia after dinner still remained (Fig. 3b ; day 11). After the doses of insulin administered before lunch and dinner were increased, postprandial hyperglycemia after dinner was also attenuated (Fig. 3c ; day 12).

DIABETES MELLITUS IN LIVER CIRRHOSIS

Patients with liver cirrhosis (LC) often show glucose intolerance. Among LC patients, the incidence of glucose intolerance and defined diabetes has been reported to be 60-80% and 10-60%, respectively (29-34). Diabetes developed secondary to cirrhosis is known as “hepatogeneous diabetes” (HD), and HD is clinically distinct from type 2 diabetes ; it is less frequently associated with positive family history, and the risk of diabetic complication (e.g., macro and microangiopathy) is low (31, 32, 35).

Pathogenesis of diabetes mellitus in cirrhosis

Insulin resistance in muscular, hepatic, and adipose tissues, as well as hyperinsulinemia, seem to be pathophysiologic bases for

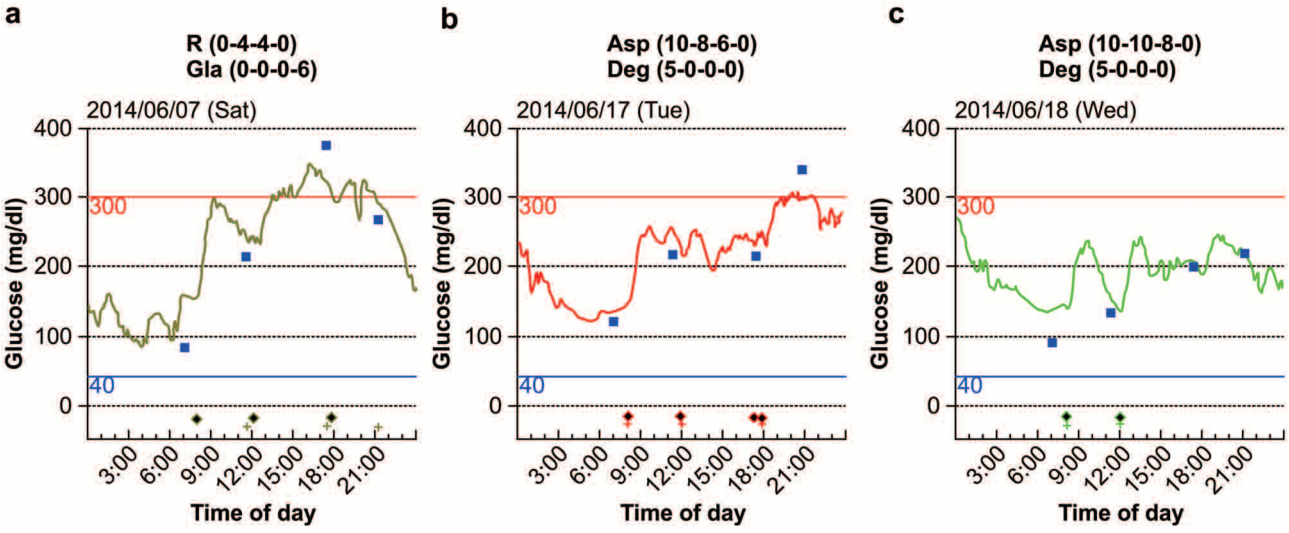

Fig. 3 Results of the continuous glucose monitoring system (CGMS-GOLD) in case 3.
(a) Day 1, (b) day 11, and (c) day 12 of monitoring, R indicates short-acting human insulin (Novolin®R). Gla indicates long acting insulin glargine (Lantus®). Asp indicates rapid-acting insulin aspart (NovoRapid®). Deg indicates long-acting insulin degludec (Tresiba®). The numbers in parentheses indicate the doses of insulin injections administered before breakfast, lunch, dinner, and sleep, respectively.

HD (32, 36-38). Peripheral insulin resistance in HD is reportedly explained by decreased glucose transport and by a defect in insulin-stimulated nonoxidative glucose disposal (glycogen synthesis) (29, 31, 37, 39-41). Peripheral insulin resistance may also occur at the receptor or postreceptor level on target cells (42, 43). Hyperinsulinemia observed in LC patients may be explained as an attempt to overcome insulin resistance (40, 44, 45), diminished hepatic extraction (34, 36, 42), and portocaval/intrahepatic shunting (45-48). In cases of β-cell decompensation, diabetes worsens (33).

Management of diabetes mellitus in cirrhosis

In general, patients with liver disease and standard type 2 diabetes can be treated similarly. However, oral diabetic medications should be used cautiously and may even be contraindicated in patients with decompensated liver failure with ascites or encephalopathy, since these patients are expected to have altered drug metabolism (36, 49). For example, metformin and thiazolenediones have been shown to be effective in improving liver transaminases, in addition to histological improvement in steatosis and inflammation ; however, metformin is not recommended for patients with advanced hepatic disease, given the risk of lactic acidosis (36, 49). Although some LC patients exhibit fasting hypoglycemia, they also have postprandial hyperglycemia (37), and therefore the management of HD may be targeted to control postprandial hyperglycemia and avoid hypoglycemia. Short half-life sulfonylureas (rapid-acting insulin secretagogues) and α-glucosidase inhibitors (α-GIs) can be used for this purpose (31, 49-51).

Insulin treatment is frequently required in patients with diabetes and LC, and insulin requirements may vary between individuals, depending on to reduced gluconeogenesis and decreased hepatic breakdown of insulin (36). On the other hand, some patients may have an increased need for insulin because of insulin resistance. To control postprandial hyperglycemia and to reduce the risk of hypoglycemia, rapid-acting insulin should be considered (36, 49). A late evening snack is beneficial to improve the catabolic state during starvation and to avoid hypoglycemia in early morning fasting (52-55).

Case reports

Case 4 : A 74-year-old female patient with a 13-year history of diabetes and LC caused by idiopathic portal hypertension (IPH). The exact timing of onset of IPH was not clear. Her HbA1c level was 7.5%, with insulin injections of rapid-acting and long-acting insulin, together with the α-GI, miglitol (150 mg/day). After admission, doses of rapid-acting insulin, glulisine (Apidra®), immediately before each meal, and long-acting insulin, glargine, before breakfast, were adjusted. A Rapid-acting insulin secretagogue, repaglinide, was added to miglitol administration, and this was administered immediately before each meal (3 mg/day). During the admission period, even with the aforementioned medications, the patient showed postprandial hyperglycemia (Fig. 4a and 4c), which was not seen when she skipped her breakfast because of an abdominal ultrasound examination (Fig. 4b). In this case, glargine was used, since she showed both insulin resistance and decreased insulin secretion (24 h collected urinary C-peptide : 13.9 μg/day). Glargine was administered before breakfast, rather than before bedtime, to avoid hypoglycemia during the night and early morning.

Case 5 : A 52-year-old male patient suffered from LC, progressed from hepatitis C. His diabetes developed 3 years prior. Repaglinide was initiated, and since it was not able to control his glycemic profiles (HbA1c 7.2%), insulin injections were administered. Since the patient habitually consumed 2 meals a day (brunch and dinner), an altered schedule of glulisine (6 units before brunch and 4 units before dinner) and miglitol (50 mg immediately before each meal) was used to control his postprandial hyperglycemia. On the day when he had brunch and dinner, even with medication, postprandial hyperglycemia was seen after each meal (Fig. 5a). On the day when he had 3 meals, postprandial hyperglycemia was also seen after every meal (Fig. 5b). CGMS results showed hypoglycemia occurred during the night (Fig. 5a and 5b), and therefore a late evening snack may be effective for this patient.

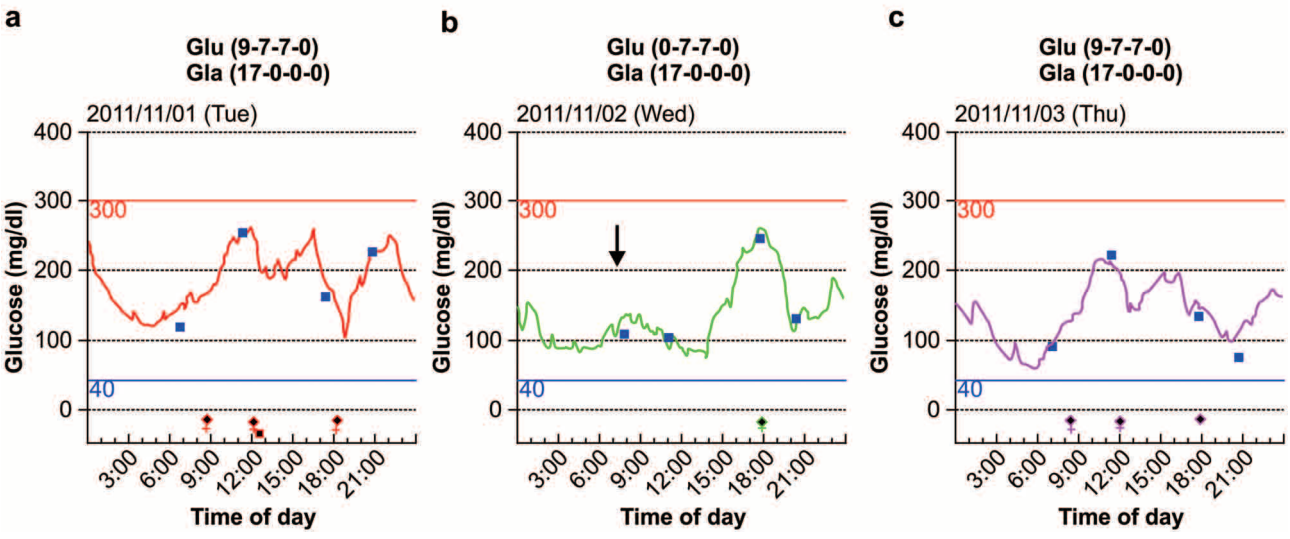

Fig. 4 Results of the continuous glucose monitoring system (CGMS-GOLD) in case 4.
(a) Day 1, (b) day 2, and (c) day 3 of monitoring. Glu indicates rapid-acting insulin glulisine (Apidra®). Gla indicates long acting insulin glargine (Lantus®). The numbers in parentheses indicate the dose of insulin injections administered immediately before breakfast, immediately before lunch, immediately before dinner, and before sleep, respectively. The arrow in (b) indicates the time that the patient skipped her breakfast and insulin injection because of an abdominal ultrasound examination.

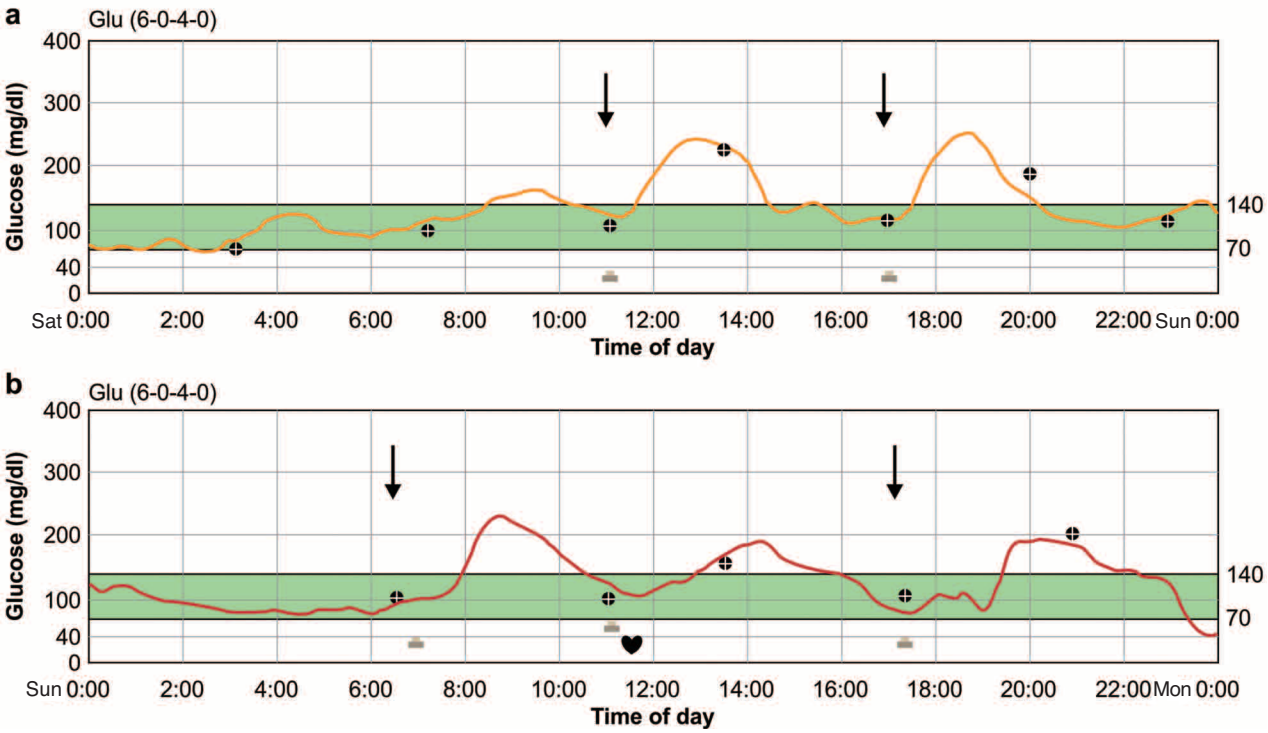

Fig. 5 Results of the continuous glucose monitoring system (CGMS iPro®2) in case 5.
(a) On the day when the patinet had brunch and dinner, (b) On the day when the patient had 3 meals. Glu indicates rapid-acting insulin glulisine (Apidra®). The numbers in parentheses indicate the dose of insulin injections administered immediately before brunch or breakfast and immediately before dinner, respectively. The arrows in (a) indicate the time of his meal (brunch and dinner) and insulin injections. On the day when he consumed 3 meals (b), the arrows indicate the times of his meals with insulin injections only (breakfast and dinner).

HYPERGLYCEMIA IN PATIENTS RECEIVING ENTERAL NUTRITION

Patients receiving continuous enteral feeding are at high risk of developing hyperglycemia (56-58). The prevalence of hyperglycemia as a complication of enteral nutrition therapy has been reported to be as high as 35% of hospitalized adult patients (59) and 50% of elderly patients in long-term care (60). Since extensive evidence indicates that the hyperglycemia during parenteral and enteral nutrition is associated with increased risk of infection and death (57), efforts should be made to maintain appropriate glycemic control during enteral feeding.

Management of hyperglycemia during enteral nutrition

To lower blood glucose levels in case of hyperglycemia, adjustment of the carbohydrate content of the enteral formula, or use of pharmacotherapy, is necessary (56, 57, 61). Compared with standard high carbohydrate formulas, lower carbohydrate enteral formulas, such as diabetes-specific formulas, have been shown to reduce hyperglycemia, improve HbA1c levels, and lower insulin requirements (57, 62-66). In standard formulas, carbohydrates account for 55-60% of the total calories, while in diabetes-specific formulas (low total carbohydrates, high fiber, and high monounsaturated fatty acid), carbohydrates account for only 35-40% of the total calories (61, 64, 65).

Regarding pharmacotherapy, sulfonylureas should be used with caution, in order to avoid hypoglycemia, especially during tube feed interruptions (61). Alpha-GIs, glinides, and DPP-4 inhibitors may provide a measure of glycemic control, but they are less efficacious than rapid-acting insulin (61). In patients with moderate to severe hyperglycemia, insulin injections are necessary, and administration of long-acting insulin in combination with supplemental short-acting insulin is effective in improving glycemic control (58). The combination of long- and short-acting insulin has also been shown to be superior to the sliding scale insulin strategy in patients receiving enteral feedings (57).

Several studies have also recommend alternative insulin regimens, including the administration of regular insulin (every 4-6 h), NPH insulin (every 8-12 h), insulin glargine or detemir (once-or twice daily), and 70/30 biphasic insulin (two or three times daily) (61, 67-70). In all regimens, frequent and cautious reassessment of patients' clinical status is important for maintaining adequate glycemic control and preventing hypoglycemia (57).

Case reports

Case 6 : An 85-year-old male patient was admitted to our hospital because of dysphagia and aspiration pneumonia. The pneumonia resolved but dysphagia persisted ; therefore, percutaneous endoscopic gastrostomy (PEG) was performed and enteral nutrition therapy initiated. The patient received 200 ml of standard formula (Terumeal 2.0α, Terumo Tokyo, Japan), and 200 ml of tepid water in the morning around 8 AM, and again in the evening around 5-6 PM. The patient also received 300 ml of Terumeal 2.0α and 100 ml of tepid water at noon. Terumeal 2.0α contains 7.25 g proteins, 7.5 g lipids, and 26 g of carbohydrates per 100 ml. Each enteral feeding was performed slowly, lasting approximately 2 hours, in order to avoid diarrhea and vomiting. Before admission, the patient had been taking a DPP-4 inhibitor, sitagliptin (100 mg/day) and HbA1c was 7.1% at the time of admission. During admission, sitagliptin (50 mg/day) was administered once in the morning during feeding (around 8 AM), and the patient showed fair glycemic control, without severe hyperglycemia or hypoglycemia (Fig. 6a and 6b).

Case 7 : A 65-year-old male patient with brain hemorrhage was rushed to our hospital after losing consciousness. After craniotomy to remove a hematoma, PEG was performed and enteral nutrition

therapy was initiated. Since the patient exhibited hyperglycemia and elevated HbA1c (7.4%), a diabetes-specific formula (Glucerna®-Ex, Abbot Japan, Tokyo, Japan) was used for enteral feeding. The formula contains 4.2 g proteins, 5.6 g of lipids, 8 g carbohydrates, and 1.4 g of dietary fiber per 100 ml. The patient received 500 ml (500 kcal) of Glucerna®-Ex three times a day, starting at approximately 6 AM, 12 AM, and 5 PM, with each feeding lasting approximately 2 hours. Between feedimgs, 300 ml of tepid water was also administered to avoid dehydration. The patient required insulin injections of Novolin®R at the time of each enteral feeding, and since the patient exhibited hyperglycemia reaching 300 mg/dl, even with 4-10 units of insulin (Fig. 7a and 7b), we were forced to adjust insulin dosage thereafter.

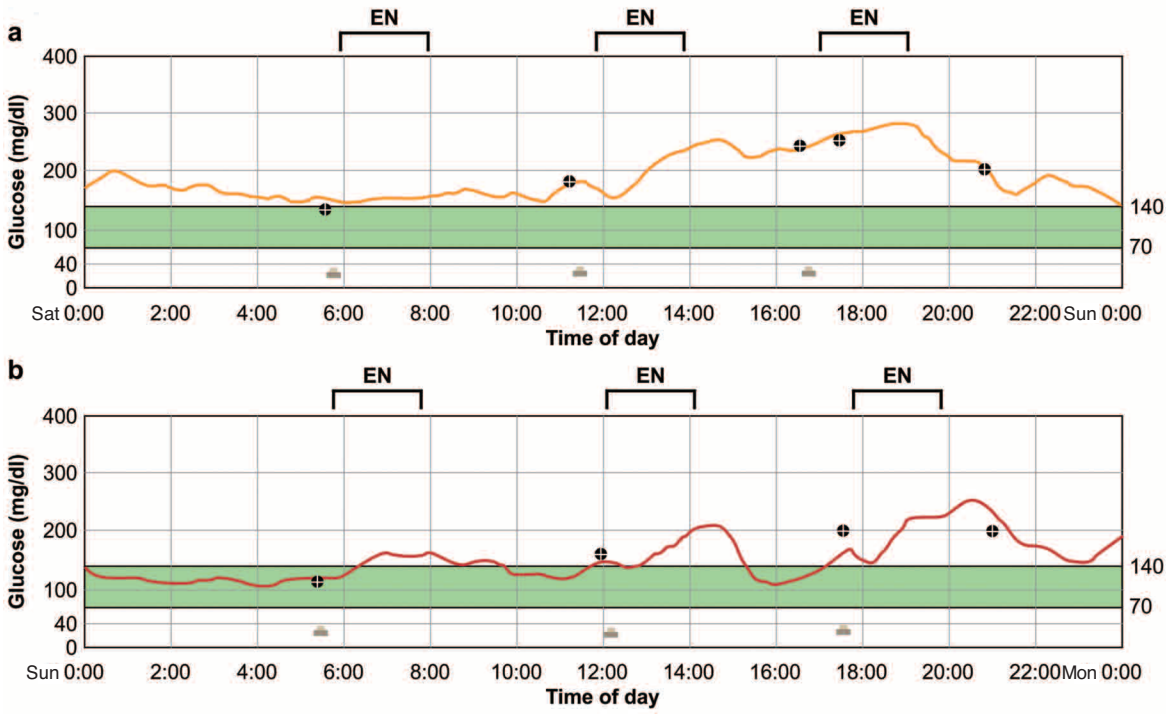

Fig. 6 Results of the continuous glucose monitoring system (CGMS iPro®2) in case 6.
(a) Day 1 and (b) day 2 of monitoring. EN indicates enteral nutrition. The brackets indicate the duration of enteral feeding (approximately 2 hours).

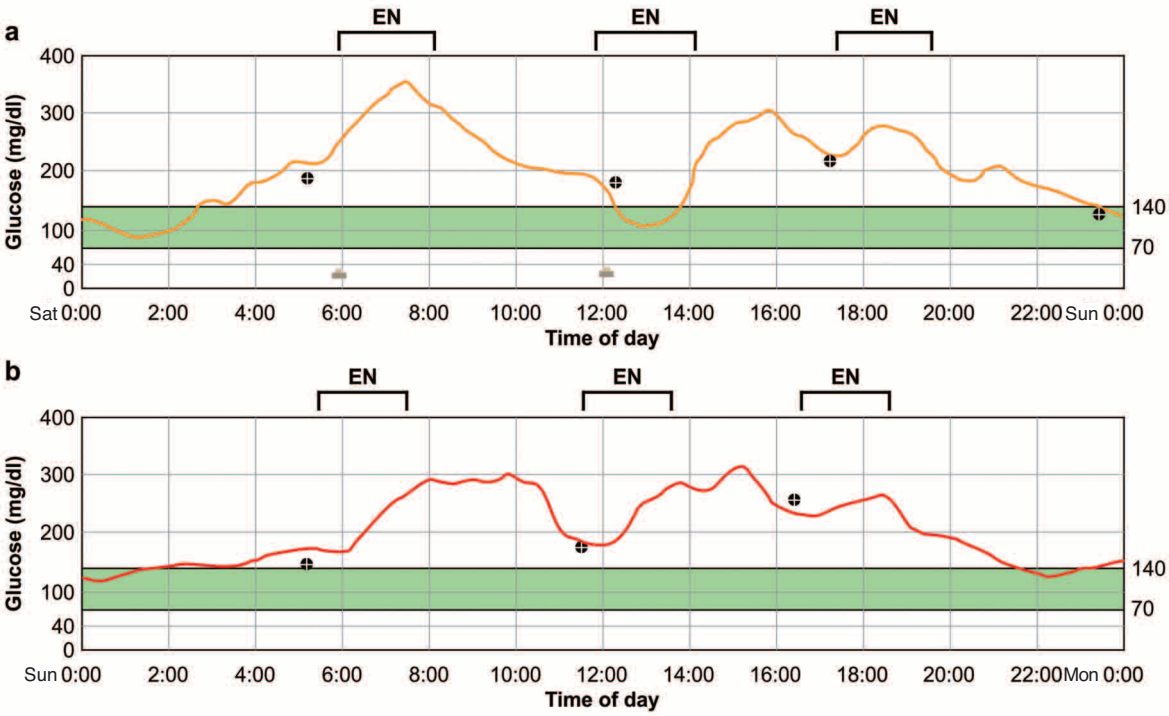

Fig. 7 Results of the continuous glucose monitoring system (CGMS iPro®2) in case 7.
(a) Day 1 and (b) day 2 of monitoring. EN indicates enteral nutrition. The brackets indicate the duration of enteral feeding (approximately 2 hours).

REACTIVE HYPOGLYCEMIA DUE TO LATE DUMPING SYNDROME

Reactive hypoglycemia can be caused by late dumping syndrome in patients who have undergone esophageal or gastric surgery (71-74), with moderate-to-severe dumping reported in approximately 10-40% of cases after gastrectomy (71, 74). The symptoms of dumping syndrome-associated hypoglycemia include sweating, fatigue, disturbed consciousness, tremor, and tachycardia ; these normally occur 1-3 h after a meal (71, 74). The fast delivery of food to the small intestine causes rapid glucose absorption and a rapid rise in the blood glucose levels, which lead to exaggerated secretion of glucagon-like peptide-1 and insulin, and, in turn, causes reactive hypoglycemia (71, 75-77).

Treatment for late dumping syndrome

Most patients with dumping syndrome can be treated by diet and lifestyle modification (71, 74, 78). To prevent rapid delivery of large amounts of glucose from food to the small intestine, reducing the carbohydrate amount of each meal and dividing the food intake into at least five meals per day have been reported to be effective (71). In addition, several other treatments, including surgery and somatostatin administration, have been attempted to relieve late dumping symptoms (74, 79, 80). Furthermore, α-GIs have been demonstrated to inhibit carbohydrate digestion and cause delayed glucose absorption and a diminished rise in blood glucose after meals, thereby resulting in a reduction of postprandial hyperglycemia and insulin release. Therefore, α-GIs are considered efficient in reducing the incidence of reactive hypoglycemia due to late dumping syndrome (71, 81-90).

Case report

Case 8 : A 52-year-old man had undergone total gastrectomy for gastric carcinoma at the age of 45 years. Since then, he had occasionally experienced hypoglycemic symptoms such as sweating, fatigue, and disturbed consciousness after meal intake. CGMS showed a rapid rise in postprandial glucose levels after a meal, which declined shortly afterwards (Fig. 8a). The postprandial hyperglycemia was prominent, especially when he ingested carbohydrate-rich meals, such as curry with rice (Fig. 8a around 1 PM). Acarbose (50 mg) administered just before each meal attenuated his postprandial hyperglycemia, and his hypoglycemic symptoms did not recur even after consuming the same lunch as the previous day (curry with rice of the same portion at the same restaurant) (Fig. 8b, around 1 PM). If he did not take acarbose before a meal, his glucose levels started to rise immediately after dinner (Fig. 8c, around 7 PM), suggesting that the drug was effective for attenuating high postprandial glucose levels and preventing symptoms associated with late dumping syndrome.

SUMMARY

Herein, we described the known pathophysiological backgrounds of hyperglycemia associated with certain conditions ; namely steroid use, liver cirrhosis, enteral nutrition, and reactive hypoglycemia due to late dumping syndrome. We presented the CGMS results of patients with these conditions, which showed typical glycemic patterns for each condition, and observed the effects of various practical treatments. Based on these cases, we conclude that CGMS is a very useful investigative tool to determine the glycemic patterns of the aforementioned conditions in a practical setting, and may be used to monitor the treatment success of such cases.

CONFLICT OF INTEREST

Miyako Kishimoto and Mitsuhiko Noda declare they have no conflict of interest related to this article.

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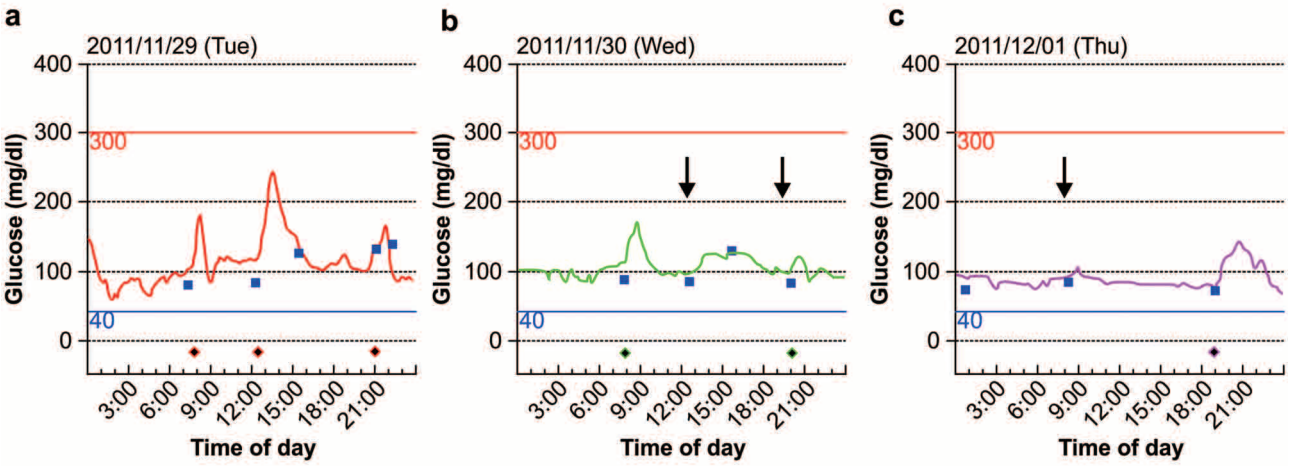

Fig. 8 Results of the continuous glucose monitoring system (CGMS-GOLD) in case 8.
(a) Day 1, (b) day 2, and (c) day 3 of monitoring. The arrows in (b) and (c) indicate the times of acarbose administration.

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