DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2004; **20**(Suppl 2): S50–S55.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/dmrr.518

RESEARCH ARTICLE

Continuous glucose monitoring in conditions other than diabetes

Alberto Maran[1]*
Cristina Crepaldi[1]
Angelo Avogaro[1]
Susanna Catuogno[2]
Alberto Burlina[2]
Alessandro Poscia[3]
Antonio Tiengo[1]

[1]*Cattedra di Malattie del Metabolismo, Università di Padova, Italy*

[2]*Clinica Pediatrica, Università di Padova, Italy*

[3]*A. Menarini Diagnostics, Firenze, Italy*

*Correspondence to: Alberto Maran, Cattedra di Malattie del Metabolismo, Via Giustiniani 2, 35 123 Padova, Italy.
E-mail: alberto.maran@unipd.it

Received: 15 March 2004
Revised: 9 July 2004
Accepted: 19 July 2004

Abstract

Background The development of new systems for continuous glucose monitoring has recently increased the interest for their potential applications among physicians involved in diabetes care. One of the most common applications of such devices is the identification of hypoglycaemic events in insulin-treated diabetic patients (particularly during the night) and the evaluation of the full daily glucose excursions.

Methods Among commercially available glucose sensors, the Glucoday® system has been utilized for practical clinical application in the last two years. One of the most important features of this device is the accuracy in monitoring interstitial glucose values, specifically in the hypoglycaemic range. This feature is clinically relevant when applied in the clinical setting of patients with type 1 diabetes mellitus. The ability to monitor glucose continuously could be indeed a useful tool for the study of hypoglycaemic conditions other than diabetes.

Results In patients with hyperinsulinaemic hypoglycaemia, recurrent episodes of asymptomatic hypoglycaemia are common, and in patients with glycogen storage diseases, avoidance of recurrent and prolonged hypoglycaemic episodes usually require frequent determinations by mean of home blood glucose monitoring.

Conclusions Experimental preliminary evidences suggest that this new technology could be applied in the clinical setting to help the physician to identify mainly nocturnal hypoglycaemic events, otherwise not revealed by traditional self blood-glucose monitoring, even in those patients who are not treated by conventional insulin therapy.

Keywords continuous glucose monitoring; hypoglycaemia; glycogen storage disease; insulinoma

Introduction

Hypoglycaemia is the most common acute complication in insulin-treated diabetic patients and still represents the limiting factor for the optimization of glucose control [1]. The Diabetes Control and Complication (DCCT) study has clearly demonstrated that intensified insulin therapy delays the onset and reduces the progression of microvascular complications in type 1 diabetic patients [2]. Self-monitoring of blood glucose (SMBG) (particularly before meals and bedtime) is an essential key in achieving and maintaining glycaemic control in insulin-treated diabetic patients. However, patients often complain

of the discomfort of finger-pricking, thus limiting the number of measurements per day. Furthermore, from a clinical point of view, SMBG reflects only single points in time, and glucose trends and 24-h fluctuations (particularly during the night) can be missed [3].

The new systems that are now commercially available for continuous glucose monitoring are the continuous glucose monitoring system (CGMS®) by Medtronic Minimed [4], Northridge, CA; the Glucowatch Auto Biographer ® by Cygnus, Redwood City, CA [5]; and the Glucoday® by A. Menarini Diagnostics, Florence, Italy [6].

The advantage is that these techniques will help to identify more accurately individual glucose patterns and assess the frequency and timing of asymptomatic hypoglycaemia. We have applied one of these new glucose sensors, the Glucoday®, to investigate uncommon causes of hypoglycaemia in patients who are not involved in insulin therapy.

The Glucoday® system

The Glucoday® system is the only commercially available glucose sensor that is based on the microdialysis technique. The major advantage of the microdialysis technique, as compared with different glucose sensor, such as electrodes, is the avoidance of a foreign body reaction that can interfere significantly with the performance of the glucose sensor. The device is intended for professional rather than for direct patient use. The Glucoday® allows continuous glucose monitoring over a period of 48 to 72 h. Detailed characteristics of the system have been previously described [7].

Once the catheter is inserted into the subcutaneous tissue of the abdomen, a buffer solution is pumped continuously at a rate of 10 μL/min and because of diffusion across the membrane the dialysate is enriched with glucose and transported to an external unit, where the glucose-oxidase reaction takes place with immediate effect.

Calibration is performed by single venous glucose measurement at least 2 h after the catheter insertion for a 24-h continuous monitoring and a second calibration value is needed after 24 h, for the 48 to 72-h observation period.

The Glucoday® has demonstrated to be accurate and reliable in monitoring subcutaneous glucose excursions in diabetic patients. In one multicentre analysis [7] of patients with type 1 and type 2 diabetes, subcutaneous glucose measured with this system was found to be well correlated with venous glucose measurements ($r = 0.9$) for 24 h of continuous monitoring using a single calibration point. It is relevant to note that the system demonstrated to be particularly accurate in the hypoglycaemic range (<68 mg/dL) as compared to venous glucoses, with a mean absolute difference of less than 2%.

Moreover, in a second study performed in T1DM, patients with unawareness of hypoglycaemia, the system was able to detect unrecognized prolonged hypoglycaemic events over 48 h of continuous glucose monitoring [8].

Indeed, one of the most important features of the system is the possibility to monitor subcutaneous glucose in real time. In Figure 1, the recovery from a hypoglycaemic episode by means of oral glucose administration was recorded in real time in a patient with hypoglycaemia unawareness admitted to our hospital for hypoglycaemic coma.

Glycogen storage disease

In glycogen storage disease (GSD), the lack of enzyme glucose 6-phosphatase or translocase results in repeated asymptomatic hypoglycaemia episodes, increased production of lactic acid, triglyceride and uric acid as a consequence of the impaired production of glucose from glycogenolysis and gluconeogenesis [9]. New techniques in molecular genetics have led to the identification of the multiple genetic abnormalities responsible for the specific impairments of enzyme function of the various GSDs [10].

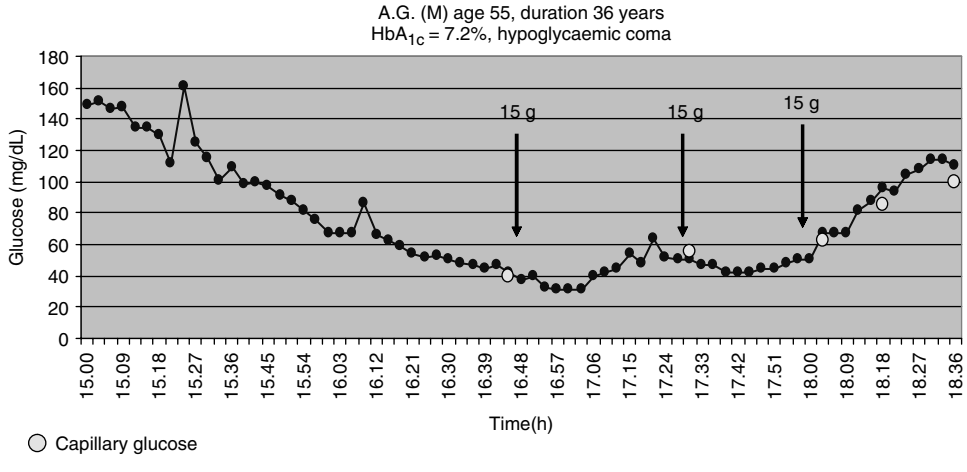

Figure 1. Real-time continuous glucose monitoring and glucose recovery during hypoglycaemia

Table 1. Clinical data

Patient	Age	Clinical manifestation	Medication	Diet (uncooked cornstarch)	Hypoglycaemia (<60 mg/dL) (min per day) Day 1	Day 2
B.L. (GSD 1a)	25	Hyperuricaemia, hypertension	Allopurinol, ramipril	50 g at midnight	160	220
S.G. (GSD 1a, hepatocytes transplantation)	47	Hyperuricaemia, dyslipidaemia	tacrolimus 0.5 mg b.d., allopurinol	50 g at midnight	100	80
S.A. (GSD 1a)	14	hyperuricaemia	Allopurinol	40 + 40 + 40 + 40 g	80	70
S.G. (GSD 1a)	25	none	None	50 + 50 + 50 g	0	30
A.A. (GSD 1b)	22	Neutropenia, gastritis,	Granulokine, omeprazole	100 + 100 + 50 g	90	0
T.D. (GSD 3)	10	LVH	None	40 g 3 a.m.	0	0

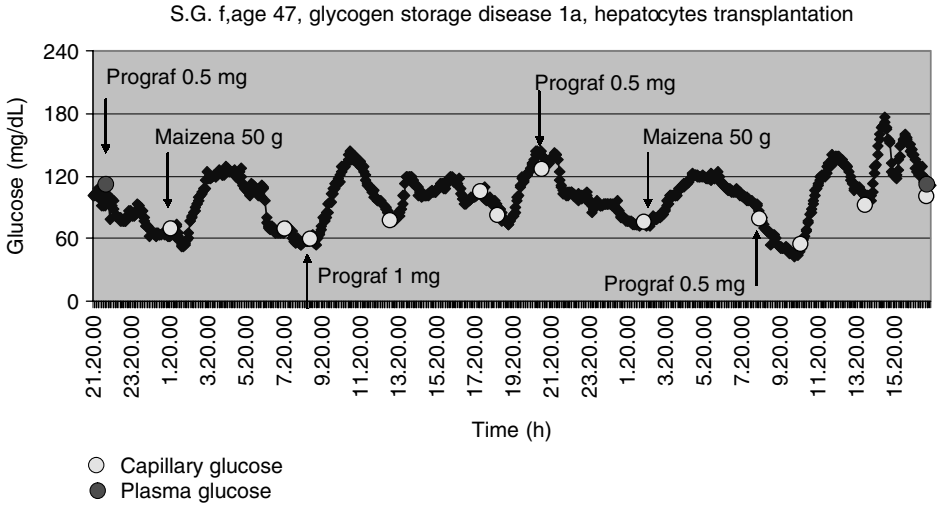

Figure 2. Patient profile

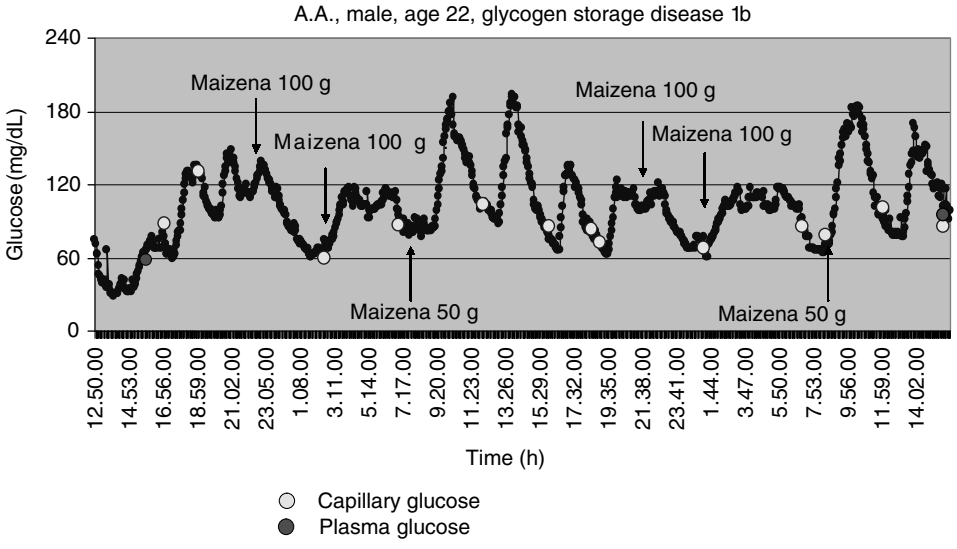

Figure 3. Patient profile

Hypoglycaemic episodes occur after meals and during the night and are prevented by provision of continuous dietary source of glucose such as uncooked cornstarch (e.g. Maizena) to prevent blood glucose fall [11].

We have investigated four patients with GSD Ia, one patient with GSD Ib and one patient with GSD III, aged 11 to 47 years, with continuous glucose monitoring using the Glucoday® device. Patients characteristics are listed

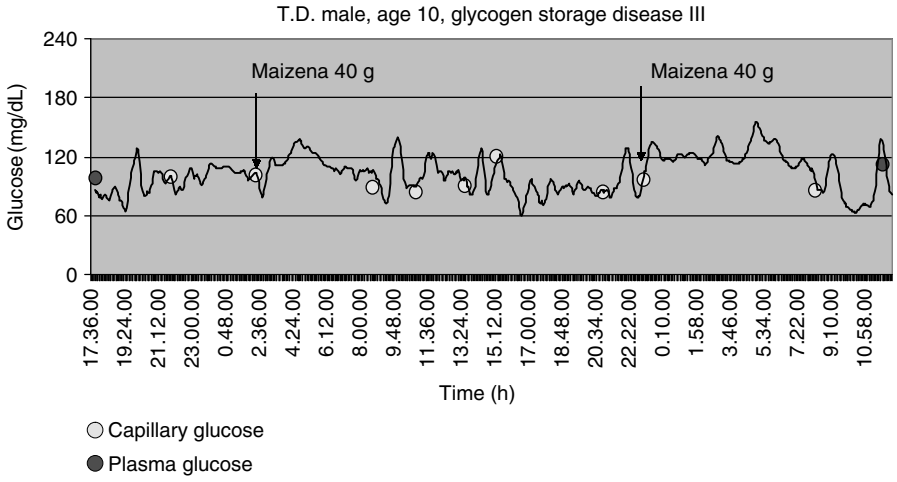

Figure 4. Patient profile

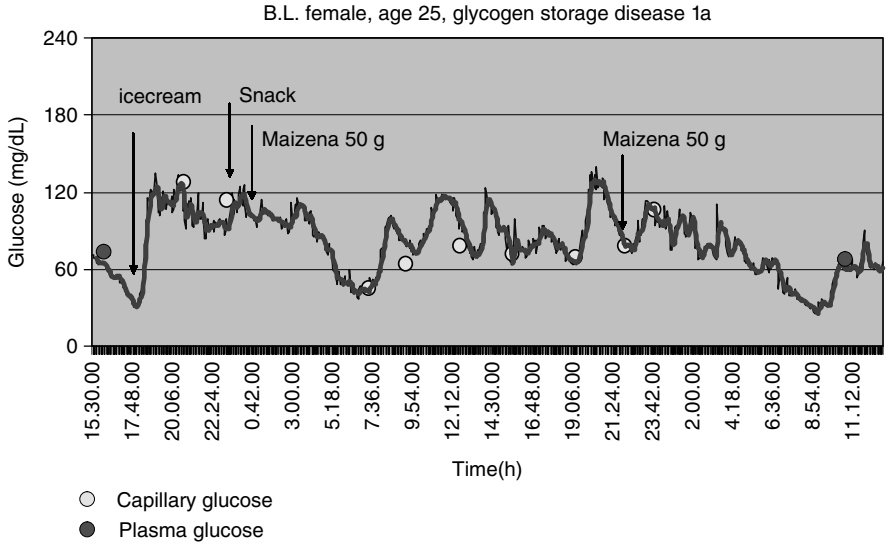

Figure 5. Patient profile

in Table 1. Self–blood-glucose monitoring was performed by each patient during monitoring as scheduled (before meals and at bedtime).

In four out of six patients, 48 h of continuous monitoring revealed unrecognized episodes of hypoglycaemia (<60 mg/dL), ranging from 80 min to 160 min during the first day, and 30 min to 220 min during the second day, most of them occurring during the night or after meals, despite provision of additional snacks (Figures 2–5). In one female patient (B.L.), a prolonged hypoglycaemic episode was recorded during two consecutive nights (160 and 220 min) whilst the patient was asleep (Figure 5).

Hyperinsulinaemic hypoglycaemia

Although rare, the most common cause of endogenous hyperinsulinaemic hypoglycaemia is insulinoma, which is characterized by inappropriately elevated insulin, proinsulin and C-peptide plasma concentrations [12]. Prolonged fasting (48 to 72 h) with monitoring of serial glucose and insulin levels remains the standard test for diagnosis, showing most patients with a positive test within 48 h [13]. However, because of the prolonged duration of this test, this method is uncomfortable for the patient and requires close supervision during hospitalization due to the risk of neuroglycopenia. The availability of continuous glucose monitoring may be surely helpful for the physician to characterize hypoglycaemic episodes in patients with suspected organic hypoglycaemia. We have applied a similar technique to non-diabetic individuals with suspected insulinoma. Figure 6 represents a 48-h glucose profile in a patient (female, age 26 years) with suspected organic hypoglycaemia during a 48-h prolonged fast. The test did not reveal any hypoglycaemic event in simultaneous plasma glucose samples and continuous glucose monitoring. So, accordingly, the diagnosis of insulinoma was excluded. On the other hand, in another patient (female, 24 years) a prolonged fast was performed

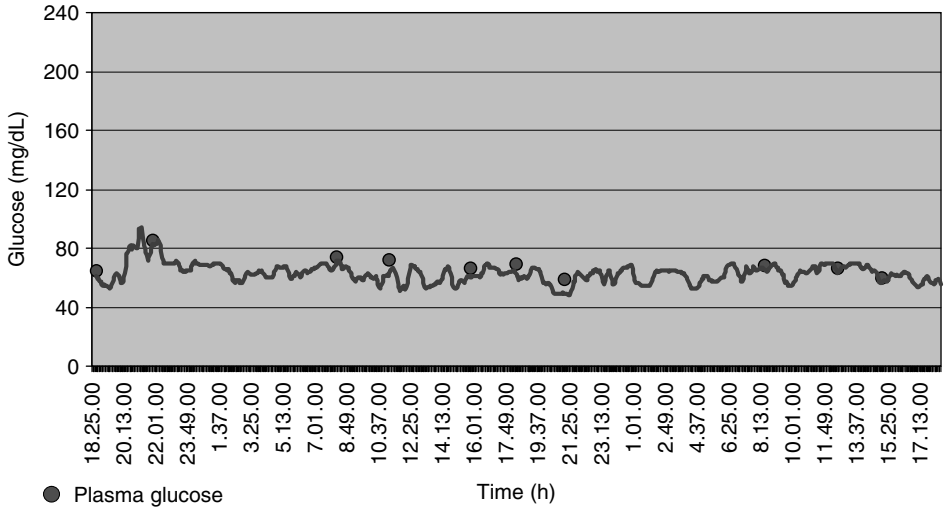

Figure 6. Prolonged fast test in a young lady (26 years) with suspected insulinoma. Forty-eight hours continuous glucose monitoring and plasma glucose measurements did not demonstrate any hypoglycaemic episode

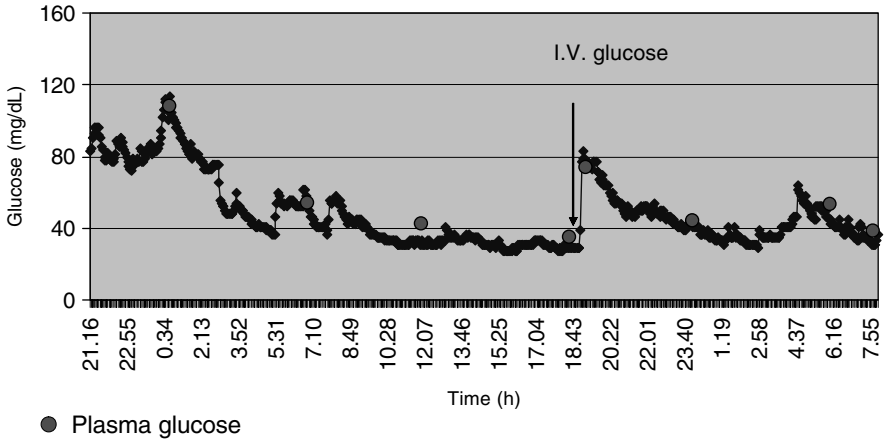

Figure 7. Patient profile: continuous glucose monitoring in a 24-year-old female insulinoma patient. Profound hypoglycaemia (nadir 34 mg/dL) was recorded and test interrupted after 11 h

and continuous glucose monitoring started in parallel (Figure 7). The monitoring revealed a profound and prolonged hypoglycaemic episode (with a glucose nadir of 34 mg/dL) during fasting, well correlated with serial plasma glucose measurements, and the test had to be interrupted with intravenous glucose infusion due to neuroglycopenia. This was interpreted as possible insulinoma, which was subsequently diagnosed by CT scan and successfully removed.

Conclusions

Continuous glucose monitoring allows the investigation of hypoglycaemia in clinical conditions other than diabetes, such as GSDs and hyperinsulinaemic hypoglycaemia.

In patients with GSDs, a detailed 48-h glucose profile, obtained with continuous glucose monitoring, could provide rationale changes in their strict dietary regime in order to avoid recurrent asymptomatic hypoglycaemia.

Moreover, continuous glucose monitoring could be a promising tool to assist the physician in the diagnosis of clinically relevant hypoglycaemia in non-diabetic patients, where organic hyperinsulinaemia must be excluded.

References

1. Cryer PE. Hypoglycemia is the limiting factor in the management of diabetes. *Diabetes Metab Res Rev* 1999; **15**: 42–46.
2. The Diabetes Control and Complication Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus. *New Engl J Med* 1993; **329**: 997–1036.
3. Bolinder J, Hagstrom-Toft E, Ungerstedt U, Arner P. Self-monitoring of blood glucose in type I diabetic patients: comparison with continuous microdialysis measurements of glucose in subcutaneous adipose tissue during ordinary life conditions. *Diabetes Care* 1997; **20**: 64–70.
4. Bode BW, Gross TM, Thornton KR, Mastrototaro JJ. Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. *Diabetes Res Clin Pract* 1999; **46**: 183–190.

5. Robert JJ. Continuous monitoring of blood glucose. *Horm Res* 2002; **1**: (Suppl. 57) 81–84.
6. Varalli M, Marelli G, Maran A, *et al*. A microdialysis technique for continuous subcutaneous glucose monitoring in diabetic patients (part 2). *Biosens Bioelectron* 2003; **18**: 899–905.
7. Maran A, Crepaldi C, Tiengo A, *et al*. Continuous subcutaneous glucose monitoring in diabetic patients: a multicenter analysis. *Diabetes Care* 2002; **25**: 347–352.
8. Maran A, Crepaldi C, Ninkovic S, *et al*. Accuracy of continuous subcutaneous glucose monitoring in detecting hypoglycemia in diabetic patients. *Diabetes* 2002; Suppl. 1. A499.
9. Wolfsdorf JI, Weinstein DA. Glycogen storage diseases. *Rev Endocr Metab Disord* 2003; **4**: 95–102.
10. Chou JY. The molecular basis of type 1 glycogen storage diseases. *Curr Mol Med* 2001; **1**: 25–44.
11. Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GP. Guidelines for management of glycogen storage disease type I – European Study on Glycogen Storage Disease Type I (ESGSD I). *Eur J Pediatr* 2002; **1**(Suppl. 161): S112–S119.
12. Service FJ. Classification of hypoglycemic disorders. *Endocrinol Metab Clin North Am* 1999; **28**: 501–517, vi.
13. Hirshberg B, Livi A, Bartlett DL, *et al*. Forty-eight-hour fast: the diagnostic test for insulinoma. *J Clin Endocrinol Metab* 2000; **85**: 3222–3226.