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Nocturnal hypoglycaemias in type 1 diabetic patients: what can we learn with continuous glucose monitoring?

THÈSE

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Rapport de synthèse

Hypoglycémies nocturnes chez les patients diabétiques de type 1 : que pouvons-nous apprendre de la mesure de la glycémie en continu ?

But : les hypoglycémies nocturnes sont une complication majeure du traitement des patients diabétiques de type 1; des autocontrôles de la glycémie capillaire sont donc recommandés pour les détecter. Cependant, la majorité des hypoglycémies nocturnes ne sont pas décelées par un autocontrôle glycémique durant la nuit. La mesure de la glycémie en continu (CGMS) est une alternative intéressante. Les buts de cette étude rétrospective étaient d'évaluer la véritable incidence des hypoglycémies nocturnes chez des patients diabétiques de type 1, la meilleure période pour effectuer un autocontrôle permettant de prédire une hypoglycémie nocturne, la relation entre les hyperglycémies matinales et les hypoglycémies nocturnes (phénomène de Somogyi) ainsi que l'utilité du CGMS pour réduire les hypoglycémies nocturnes.

Méthode : quatre-vingt-huit patients diabétiques de type 1 qui avaient bénéficié d'un CGMS ont été inclus. Les indications au CGMS, les hypoglycémies nocturnes et diurnes ainsi que la corrélation entre les hypoglycémies nocturnes et les hyperglycémies matinales durant le CGMS ont été enregistrées. L'efficacité du CGMS pour réduire les hypoglycémies nocturnes a été évaluée six à neuf mois après.

Résultats : la prévalence des hypoglycémies nocturnes était de 67% (32% non suspectées). La sensibilité d'une hypoglycémie à prédire une hypoglycémie nocturne était de 37% (OR = 2,37, P = 0,001) lorsqu'elle survient au coucher (22-24 h) et de 43% lorsqu'elle survient à 3 h (OR = 4,60, P < 0,001). Les hypoglycémies nocturnes n'étaient pas associées à des hyperglycémies matinales, mais à des hypoglycémies matinales (OR = 3.95, P < 0.001). Six à neuf mois après le CGMS, les suspicions cliniques d'hypoglycémies nocturnes ont diminué de 60% à 14% (P < 0.001).

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Original article

Nocturnal hypoglycaemias in type 1 diabetic patients: what can we learn with continuous glucose monitoring?

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Abstract

Aim. – In type 1 diabetic patients (T1DM), nocturnal hypoglycaemias (NH) are a serious complication of T1DM treatment; self-monitoring of blood glucose (SMBG) is recommended to detect them. However, the majority of NH remains undetected on an occasional SMBG done during the night. An alternative strategy is the Continuous glucose monitoring (CGMS), which retrospectively shows the glycaemic profile. The aims of this retrospective study were to evaluate the true incidence of NH in T1DM, the best SMBG time to predict NH, the relationship between morning hyperglycaemia and NH (Somogyi phenomenon) and the utility of CGMS to reduce NH.

Methods. – Eighty-eight T1DM who underwent a CGMS exam were included. Indications for CGMS evaluation, hypoglycaemias and correlation with morning hyperglycaemias were recorded. The efficiency of CGMS to reduce the suspected NH was evaluated after 6–9 months.

Results. – The prevalence of NH was 67% (32% of them unsuspected). A measured hypoglycaemia at bedtime (22–24 h) had a sensitivity of 37% to detect NH (OR = 2.37, $P = 0.001$), while a single measure ≤ 4 mmol/l at 3-hour had a sensitivity of 43% (OR = 4.60, $P < 0.001$). NH were not associated with morning hyperglycaemias but with morning hypoglycaemias (OR = 3.95, $P < 0.001$). After 6–9 months, suspicions of NH decreased from 60 to 14% ($P < 0.001$).

Conclusion. – NH were highly prevalent and often undetected. SMBG at bedtime, which detected hypoglycaemia had sensitivity almost equal to that of 3-hour and should be preferred because it is easier to perform. Somogyi phenomenon was not observed. CGMS is useful to reduce the risk of NH in 75% of patients.

Résumé

Hypoglycémies nocturnes chez les patients diabétiques de type 1 : que pouvons-nous apprendre de la mesure de la glycémie en continu ?

But. – Les hypoglycémies nocturnes sont une complication majeure du traitement des patients diabétiques de type 1; des autocontrôles de la glycémie capillaire sont donc recommandés pour les détecter. Cependant, la majorité des hypoglycémies nocturnes ne sont pas décelées par un autocontrôle glycémique durant la nuit. La mesure de la glycémie en continu (CGMS) est une alternative intéressante. Les buts de cette étude rétrospective étaient d'évaluer la véritable incidence des hypoglycémies nocturnes chez des patients diabétiques de type 1, la meilleure période pour effectuer un autocontrôle qui permet de prédire une hypoglycémie nocturne, la relation entre les hyperglycémies matinales et les hypoglycémies nocturnes (phénomène de Somogyi) ainsi que l'utilité du CGMS pour réduire les hypoglycémies nocturnes.

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Conclusions. – Les hypoglycémies nocturnes ont une prévalence élevée et ne sont souvent pas détectées par les autocontrôles. La détection d'une hypoglycémie au coucher a une sensibilité équivalente à celle de 3 h pour prédire une hypoglycémie nocturne. Par conséquent, un autocontrôle au coucher, moins contraignant qu'à 3H, peut donc être une stratégie conseillée. Le phénomène de Somogyi n'a pas été observé. Le CGMS est utile pour réduire les hypoglycémies nocturnes suspectées chez 75 % des patients.

Keywords: Continuous glucose monitoring system; Nocturnal hypoglycaemia; Self-monitoring of blood glucose; Type 1 diabetes mellitus

Mots clés : Diabète de type 1 ; Hypoglycémie nocturne ; Contrôle de la glycémie en continu ; Autocontrôle de la glycémie capillaire

1. Introduction

The DCCT study has shown that intensive insulin therapy has a major effect on the prevention of micro-vascular complications in type 1 diabetic patients (T1DM) [1]. This study has also shown that intensive glycaemic control induces three times more severe hypoglycaemic episodes. Other studies suggested a high prevalence of nocturnal hypoglycaemia in T1DM [2–4,28]. These hypoglycaemic episodes often go unnoticed and may have serious consequences on cognitive functions [5,6]. Moreover, these patients are at high risk for major hypoglycaemia [6]. It is therefore important to evaluate the glucose profile during the night. Classically, nocturnal hypoglycaemia evaluation is performed by self-monitoring of blood glucose (SMBG) at a precise moment, arbitrarily set at 03 h. Thus, patients have to wake up to perform this test. Furthermore, when a physician is dealing with marked hyperglycaemia in the morning, he has to investigate if it is a rebound phenomenon as described by Somogyi [7], a dawn phenomenon caused by an increase of counterregulatory hormones, an omission of insulin or a hearty meal the previous evening [8]. Somogyi reported in 1959 that undetected nocturnal hypoglycaemia could cause rebound morning hyperglycaemia secondary to an increase in glucose production due to activation of glucose regulatory systems [7]. This phenomenon has been widely accepted by clinicians to explain morning hyperglycaemias; however, it is controversial and some studies rejected this hypothesis [8–10].

Since the development of SMBG, it seems obvious that daily glucose measurements, at strategically chosen moments, help to individually adapt the insulin regimen. The objective is to reach the best possible glycaemic control with the lowest rate of hypoglycaemic events. If SMBG are done regularly, they allow to significantly reducing glycosylated hemoglobin (HbA_{1c}) [11,12]. Glucosensor®, a continuous glucose monitoring system (CGMS), which measures interstitial glucose level by an abdominal subcutaneous sensor, shows its usefulness by giving complete glycaemic profiles of patients. It allows evaluation or glycaemic variations between SMBG measures and is therefore particularly useful to evaluate postprandial excursions [2,4,13], nocturnal and diurnal hypoglycaemias [14–16]. It brings educative information to the patient, who is confronted with his continuous glycaemic profile [17,18] and can see effects of food intake, physical activity, inappropriate insulin corrections and importance of SMBG [17]. The CGMS is not routinely used because of high cost, discomfort for the patient and problems of availability in some centers. A great limitation to CGMS is its accuracy, especially during hypoglycaemic episodes. Clarke's study suggests that the CGMS misses the nadir of hypoglycaemia and underevaluates the duration of hypoglycaemia [19]. Guerci et al. observed that the data of the CGMS were less accurate compared to capillary measurement by SMBG to evaluate the real glycaemia [20]. Then we considered the CGMS principally as an educational tool for our patients and physicians and not as a gold standard.

In this study, the aim was to identify information from the CGMS applicable to patients who cannot routinely benefit from this technique. We have collected the indications for CGMS use, and have evaluated the real prevalence of nocturnal hypoglycaemia (NH) in T1DM, correlated to the frequency of clinical suspicion of NH. We tested the potential efficiency of SMBG at bedtime (22–24 h) and at 03 h in predicting the risk of NH. We compared the population of patients who had NH during the CGMS with patients who had not, to determine predicting factors of NH. We have also studied the relationship between NH and fasting glycaemia to understand if morning hyperglycaemia was related to NH as described by Somogyi [7], or with the persistence of hyperglycaemia during the night [8]. Finally, we assessed the potential glycaemic and metabolic improvement and the reduction of NH 6 to 9 months after CGMS.

2. Methods

2.1. Subjects

In this retrospective study, CGMS data from T1DM of the clinical outpatient consultation of the University Hospital in Lausanne, Switzerland, were collected from August 2001 to December 2003 and then analyzed. Only T1DM who underwent a CGMS exam were included. Medical records of these patients were reviewed: age, sex, diabetes duration, antidiabetic treatment, diabetes complications, smoking, sedentarity, body mass index (kg/m^2), SMBG values of the days before CGMS, HbA_{1c} before CGMS, clinical suspicion of nocturnal hypoglycaemia, CGMS indications and CGMS values of the entire record were evaluated. Then SMBG values, HbA_{1c} (normal values 4.9–6.5%) and suspicion of nocturnal hypoglycaemias 6–9 months after CGMS were recorded.

2.2. Continuous glucose monitoring of blood glucose (CGMS)

Patients came to the diabetology outpatient clinic for the installation of CGMS (Medtronic Minimed, Sylmar, California,

USA). Installation and operation of CGMS are described elsewhere [21]. Patients were asked to behave as usual and to report in a diary food intake and doses of insulin, physical activity and symptoms of hypoglycaemia. Those are classically described as: abnormal sweat, tremor, hunger, pallor, headache, irritability and cognitive alteration; nocturnal hypoglycaemia is recognized by abnormal sweat, disturbed sleep and nightmares [6]. Patients were instructed to perform four times daily SMBG (with their own device for glucose control) to calibrate the CGMS. Each sensor was installed for 72 hours. After removal of the sensor, data were analyzed (Medtronic Minimed CGMS Software, version 1.7 A). A graphical report of glycaemic profile was printed and discussed with the patients. Comments were reported in a medical file. Then, precise objectives were fixed in order to improve the metabolic profile of the patient. These objectives were based on the indications for Glucosensor and on other problems revealed by this test.

3. Data analysis

We used only the CGMS records that were not interrupted. We defined early morning as the period between 06 h and 10 h, bedtime as the period between 22 h and 24 h and the night as the period between 24 h and 06 h. We studied for each period the duration (minutes) of euglycaemia, hypoglycaemia and hyperglycaemia. Hypoglycaemia was defined as a glucose level ≤ 4 mmol/l and hyperglycaemia ≥ 8 mmol/l. A hypoglycaemic event was defined as a glucose level ≤ 4 mmol/l during ≥ 15 minutes, a hyperglycaemic event as a glucose level ≥ 8 mmol/l during ≥ 30 minutes. Early morning, bedtime and nocturnal hypoglycaemia were defined by ≥ 1 hypoglycaemic event between 06–10 h, 22–24 h and 24–06 h, respectively. To evaluate the potential usefulness of the SMBG at 03 h, we chose a single CGMS measure at 03 h and correlated it with the presence of NH. We also studied the correlation between bedtime hypoglycaemia and NH and early morning hyperglycaemia and between NH and early morning hypoglycaemia.

Associations between the level of blood glucose at 03 h and the presence of NH, between the presence of hypoglycaemia at bedtime and NH and finally between the glycaemia on the morning and the presence of NH, were studied for each night separately (1st, 2nd and 3rd). The results were given for the two nights with the highest correlation (higher odd ratio).

3.1. Statistical analysis

Continuous variables, normally distributed, were expressed in means with standard deviation and the Student's *t*-test was used for comparisons. Non-normally distributed continuous variables were expressed as median, with 10th–90th percentiles and the Mann–Whitney *U* test was used for comparisons. Categorical variables were expressed in frequency and differences were based on the chi-square test. All statistical analyses were performed using JMP 5.0 (SAS Institute, Cary, USA) and a P value ≤ 0.05 was considered statistically significant.

4. Results

4.1. Indications for CGMS

The two most frequent indications for CGMS were diabetes imbalance (56%) and suspicion of nocturnal hypoglycaemia (NH) (27%). After study of all preliminary data, NH were suspected in 60% of the patients. Other indications were hyperglycaemia, daytime hypoglycaemia, patient's educative interest, glycaemia's evaluation before the initiation of pump therapy and suspicion of Somogyi phenomenon.

4.2. Population description

The clinical characteristics of the study population are shown in Table 1. Eighty-eight T1DM were included, aged 39 ± 12 years. Fifty-six percent were males ($N = 49$) and median diabetes duration was 13 years (5–35). Median HbA_{1c} was 8.4% (6.8–9.9).

4.3. CGMS

The global evaluation of the CGMS is shown in Fig. 1. Concerning NH, 67% of the patients ($N = 59$) had at least one episode during the recording. In the group of patients who had NH during CGMS, 32% were not clinically suspected and were detected by CGMS only (OR = 1.39, $P = 0.039$). The prevalence of hypoglycaemia during the day was already high: 82% of patients had at least one episode of diurnal hypoglycaemia during the recording. The median coefficient correlation R of the CGMS recordings was 0.91 (0.67–0.99).

4.4. Capacity of hypothetical SMBG to detect NH

In the 2nd and 3rd nights, there was a strong correlation between NH and bedtime hypoglycaemia (OR = 2.37, $P = 0.001$) and between a single CGMS measure ≤ 4 mmol/l at 03 h and NH (OR = 4.60, $P < 0.001$). The sensitivity of an

Table 1
Population characteristics

N		88
Male gender		56%
Age (years)[a]		39 ± 12
Diabetes duration (years)‡		13 (5–35)
Current smoking		27%
BMI (kg/m^2)‡		22.9 (19.7–28.8)
HbA_{1c} (%)‡		8.4 (6.8–9.9)
Retinopathy		19%
Sensitive neuropathy		34%
Nephropathy		16%
Coronary artery disease		5%
Lower limb arteriopathy		4%
Insulin treatment		
Basal bolus	NPH + Fast-acting analog	34%
	Glargine + Fast-acting analog	22%
	NPH + Normal	7%
Insulin pump		30%
Mixed insulin		7%

‡Median (p10–p90).
[a] Mean ± S.D.

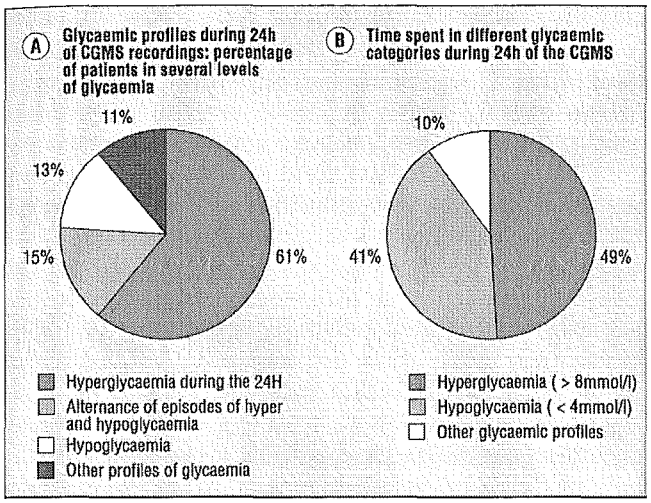

Fig. 1. Global evaluation of the CGMS.

episode of hypoglycaemia at bedtime to detect NH was 37% (negative predictive value NPV 74%), while a single CGMS measure ≤ 4 at 03 h had a sensitivity to detect NH of 43% (NPV 78%), Sensitivity and NPV not significantly different (Table 2).

4.5. Univaried predictors of NH

Table 3 compares data of patients with and without NH during CGMS measures. In patients with NH, HbA_{1c} was significantly lower than in patients without NH (8.1 vs. 9.3%, $P = 0.007$), current smoking habit was already less frequent (OR = 0.36, $P = 0.010$). Non-smokers also had a lower HbA_{1c} than smokers: 8.4% (6.3–10.3) versus 9.1% (8.1–9.7), $P = 0.124$. Lantus® was not a significant preventive factor of NH (OR = 0.78, $P = 0.192$). However, it produced less NH than treatment with NPH, mixed insulin and normal insulin (OR = 0.71, $P = 0.076$).

Table 2
Detection of nocturnal hypoglycaemias (24–06 h)

	Hypoglycaemia 22–24 h	Hypoglycaemia 3 h
Sensitivity	37%	43%
Specificity	89%	100%
VPP	62%	100%
VPN	74%	78%
OR	2.37	4.6
P	< 0.01	< 0.01

4.6. Effect of NH on fasting glycaemia

In the 2nd and 3rd nights, NH was associated with early morning hypoglycaemia (OR = 9.63, $P<0.001$) and inversely associated with early morning hyperglycaemia (OR = 0.70, $P < 0.001$). In patients who presented early morning hyperglycaemia, 23% had NH, while 77% were euglycaemic or hyperglycaemic during the night.

5. Evolution 6 to 9 months after CGMS

Median HbA_{1c} was 8.4% (6.8–9.9) before CGMS and lowered to 8.0% (7.2–10.4) 6–9 months after CGMS ($P < 0.001$). In the group of patients with NH ($N = 59$), median HbA_{1c} was 8.1% (6.7–9.3) before CGMS and 7.4% (7.0–9.3) after ($P < 0.001$). In the group without NH ($N = 29$), HbA_{1c} lowered from 9.3% (7.1–10.3) to 8.9% (8.1–11.3) ($P < 0.001$). After CGMS, more patients did SMBG (from 20 to 43%) particularly at bedtime. Suspicion of clinical NH decreased from 60 to 14% during this time ($P < 0.001$).

6. Discussion

In this study, there was a high prevalence of nocturnal hypoglycaemias (67%) that were often clinically unsuspected

Table 3
Univaried predictors of nocturnal hypoglycaemias (NH)

	NH	No NH	OR	*P*
$N = 88$	59 (67%)	29 (33%)		
Male gender	56%	55%	1.00	0.946
Age (years)[a]	37 ± 12	39 ± 13		0.974
Diabetes duration (years)‡	14 (5–35)	11 (4–30)		0.432
Current smoking	17%	46%	0.36	0.010
BMI (kg/m^2)‡	23.1 (19.5–28.1)	22.9 (19.4–30.2)		0.879
HbA_{1c} (%)‡	8.1 (6.7–9.3)	9.3 (7.1–10.3)		0.007
Microangiopathy	46%	45%	1.02	0.919
Macroangiopathy	8%	8%	1.01	0.962
Insulin treatment				
Fast-acting analog insulin	58%	55%	1.03	0.827
Normal	8%	3%	1.27	0.379
NPH	46%	28%	1.28	0.102
Mix	8%	3%	1.27	0.379
Glargine	19%	31%	0.78	0.192
Pump	32%	41%	0.87	0.397
Glargine vs. NPH + Mix + Normal	28%	53%	0.71	0.076
Glargine + pump vs. NPH	52%	72%	0.75	0.067

‡Median (p10–p90).
[a] Mean ± S.D.

(32%). Physicians often underestimate the prevalence of NH that CGMS was useful to detect.

An episode of hypoglycaemia at bedtime (22–24 h) had a sensitivity of 37% to detect NH, while a single measure ≤ 4 mmol/l at 03 h had a sensitivity of 43%, $P = 0.57$. Therefore, a SMBG at bedtime is not less efficient than at 03 h to detect NH and is more convenient for the patient. In this line, Kaufmann et al. demonstrated, in a cohort of pediatric T1DM, that the level of glycaemia at bedtime (21 h) was correlated with the glycaemia measured by CGMS during the entire night [14]. Zavalkoff et al. studied correlations between four standard SMBG tests (breakfast, lunch, dinner and bedtime) and CGMS values [22]. They concluded that SMBG at bedtime was correlated with the glycaemic level during the night.

A treatment with Lantus® or with insulin pump was correlated with fewer NH. New treatments with Lantus® are clinically useful to reduce the risk of NH. A recently published study compared the frequency of hypoglycaemia in T1DM treated with Lantus® compared to patients treated with Ultralente® [23]. They concluded that the number of total and diurnal, but not nocturnal hypoglycaemic events were lower on Lantus® than Ultralente®. In our study, patients who have presented NH had a lower HbA_{1c}, as expected, and were less often smokers. A Swedish study showed that T1DM who smoke had a poorer HbA_{1c} values than non-smokers. They explained this observation by the fact that smokers had weaker degree of belief in health care professionals and are therefore less prone to follow instructions from the diabetes care team [24].

Other authors demonstrated that smoking decreases peripheral insulin sensitivity [25]. In our study, smokers had a higher HbA_{1c} compared to non-smokers and had respectively less NH. But level of HbA_{1c} and current smoking were independent predictors of NH, then, we cannot purpose a correlation between absence of current smoking, low level of HbA_{1c} and presence of NH altogether.

Concerning Somogyi phenomenon, we observed that only 23% of early morning hyperglycaemias are related to NH. In 77% of the patients with early morning hyperglycaemia, patients were euglycaemic or hyperglycaemic during the night ($P < 0.001$). Therefore, in our study, we did not observe the Somogyi phenomenon, but quite the opposite. In a recently published study, Hoi-Hansen et al. evaluated the probability of hypoglycaemic events in the night in T1DM, with the use of CGMS: this one was higher in case of low morning blood glucose [26]. Therefore, they also rejected the Somogyi phenomenon. To our knowledge, there is no study that confirmed the existence of the Somogyi phenomenon with the use of CGMS [27]. This observation is important for the physicians because 77% of fasting hyperglycaemias are related to hyper or normoglycaemia during the night. The hypothetical risk of NH is low (23%). We observed that the clinical benefits of CGMS 6–9 months later were a decrease of HbA_{1c} (from 8.4 to 8.0%) as described by Salardi et al. [4] and a significant reduction of clinical suspicion of NH (from 60 to 14%). This decrease of NH suspicion was important and may be partially explained by an increase of patients who performed SMBG at bedtime (from 20 to 43%). Indeed, CGMS was useful as an educational tool for the patients who could see by this way their glycaemic profile and the effects of food intake and daily activities [17,18]. However CGMS cannot be used as a gold standard for the evaluation of the level of blood glucose. This device is very useful to access to the glycaemic profile of the patients and the trends to hypo or hyperglycaemia. This great option is now developed and used in combination with an insulin pump as in Gardian sensor system and Real Time sensor pump. The sensor informs the patient on the trends to high or low glucose levels. This instrument offers new perspectives for better anticipating glucose level variations.

7. Limitations of the study

This was a retrospective study and prospective studies of type 1 adult patients are needed to confirm our results. Some prospective studies have been done with a small cohort of preschool children and adolescents [14–16], but not yet with adults. In our study, we evaluated only the evolution a short time after CGMS; therefore we have no evidence that metabolic improvement of the diabetes still remains after more than 9 months. We included only T1DM and it would be interesting to evaluate the CGMS in type 2 diabetic patients or gestational diabetes. Furthermore, only patients who had an indication for CGMS were included, so these patients were not representative of the entire type 1 diabetic population.

A limitation of our study is the accuracy and ability of CGMS to evaluate hypoglycaemias. Clarke and all observed that the CGMS missed the nadir of hypoglycaemias and underestimated the duration of hypoglycaemias [19]. The CGMS was introduced in our center in 1999 and the first analyses were relatively of low quality. However, our study was performed from 2001 to 2003, for this period we had acquired the expertise with relatively good quality for CGMS registration.

8. Conclusion

In our study, we showed that the prevalence of NH was high (67%) and that NH was often clinically unsuspected (32%). SMBG at bedtime were as efficient as at 03 h to predict NH, and more convenient for the patient.

Somogyi phenomenon is rarely observed. Three quarters of fasting hyperglycaemias are related to hyper or normoglycaemia during the night rather then NH. If this observation is confirmed, we should modify our educational message for patients and health professionals.

The CGMS is not an accurate device for the detection of NH, however the use of the trend curves can partially compensate this defect. It is helpful to motivate patients to perform more SMBG and, for the medical team, to adjust treatment. This assertion was confirmed by a significant decrease of the HbA_{1c} values and of the rate of NH, 6–9 months after CGMS exam.

New perspectives for the CGMS include use of this device with an insulin pump to inform the patient about pathological glycaemic patterns. This is a great step towards the closed loop, the artificial pancreas.

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References

[1] The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the diabetes control and complications trial. Diabetes 1997; 46:271–86.

[2] Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV. Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care 2001;24: 1858–62.

[3] Banarer S, Cryer PE. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes: reduced awakening from sleep during hypoglycemia. Diabetes 2003;52:1195–203.

[4] Salardi S, Zucchini S, Santoni R, et al. The glucose area under the profiles obtained with continuous glucose monitoring system relationships with HbA(lc) in pediatric type 1 diabetic patients. Diabetes Care 2002; 25:1840–4.

[5] Fanelli CG, Paramore DS, Hershey T, et al. Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes. Diabetes 1998;47:1920–7.

[6] Frier F, Thow H. Nocturnal hypoglycaemia. In: Hypoglycaemia and Diabetes. 1993. p. 199–211.

[7] Somogyi M. Exacerbation of diabetes by excess of insulin action. Am J Med 1959;26:169–91.

[8] Lerman IG, Wolfsdorf JI. Relationship of nocturnal hypoglycemia to daytime glycemia in IDDM. Diabetes Care 1988;11:636–42.

[9] Gale EA, Kurtz AB, Tattersall RB. In search of the Somogyi effect. Lancet 1980;2:279–82.

[10] Hirsch IB, Smith LJ, Havlin CE, Shah SD, Clutter WE, Cryer PE. Failure of nocturnal hypoglycemia to cause daytime hyperglycemia in patients with IDDM. Diabetes Care 1990;13:133–42.

[11] Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care 2003;26:1153–7.

[12] Guerci B, Drouin P, Grange V, et al. Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance Intervention Active (ASIA) study. Diabetes Metab 2003;29:587–94.

[13] Schaepelynck-Belicar P, Vague P, Simonin G, Lassmann-Vague V. Improved metabolic control in diabetic adolescents using the continuous glucose monitoring system (CGMS). Diabetes Metab 2003;29:608–12.

[14] Kaufman FR, Austin J, Neinstein A, et al. Nocturnal hypoglycemia detected with the continuous glucose monitoring system in pediatric patients with type 1 diabetes. J Pediatr 2002;141:625–30.

[15] McGowan K, Thomas W, Moran A. Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes. Diabetes Care 2002;25:1499–503.

[16] Jeha GS, Karaviti LP, Anderson B, et al. Continuous glucose monitoring and the reality of metabolic control in preschool children with type 1 diabetes. Diabetes Care 2004;27:2881–6.

[17] Ludvigsson J, Isacson E. Clinical use of glucose sensors in the treatment of diabetes in children and adolescents. Pract Diabetes Int 2003;20:7–12.

[18] Weintrob N, Schechter A, Benzaquen H, et al. Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs continuous subcutaneous insulin infusion. Arch Pediatr Adolesc Med 2004;158:677–84.

[19] Clarke WL, Anderson S, Farhy L, et al. Evaluating the clinical accuracy of two continuous glucose sensor using continuous glucose-error grid analysis. Diabetes Care 2005;28:2412–7.

[20] Guerci B, Floriot M, Böhme P, et al. Clinical performance of CGMS in type 1 diabetic patients reated by continuous subcutaneous insulin infusion using insulin analogs. Diabetes Care 2003;26:582–9.

[21] 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;46:183–90.

[22] Zavalkoff SR, Polychronakos C. Evaluation of conventional blood glucose monitoring as an indicator of integrated glucose values using a continuous subcutaneous sensor. Diabetes Care 2002;25:1603–6.

[23] Kudva YC, Basu A, Jenkins GD, et al. Randomized controlled clinical trial of glargine versus ultralente insulin in the treatment of type 1 diabetes. Diabetes Care 2005;28:10–4.

[24] Stenstrom U, Andersson P. Smoking, blood glucose control, and locus of control beliefs in people with type 1 diabetes mellitus. Diabetes Res Clin Pract 2000;50:103–7.

[25] Borissova AM, Tankova T, Kirilov G, Dakovska L, Krivoshiev S. The effect of smoking on peripheral insulin sensitivity and plasma endothelin level. Diabetes Metab 2004;30:147–52.

[26] Hoi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B. The Somogyi phenomenon revisited using continuous glucose monitoring in daily life. Diabetologia 2005;48:2437–8.

[27] Havlin CE, Cryer PE. Nocturnal hypoglycemia does not commonly result in major morning hyperglycemia in patients with diabetes mellitus. Diabetes Care 1987;10:141–7.

[28] Pramming S, Thorsteinsson B, Bendtson I, Ronn B, Binder C. Nocturnal hypoglycaemia in patients receiving conventional treatment with insulin. BMJ 1985;291:376–9 (Clin Res Ed).