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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 $\leq 4$ 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.

*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'hypoglycémie nocturne ont diminué de 60 à 14 % ($P < 0{,}001$).

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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,