

Assessment of hypoglycaemia awareness using continuous glucose monitoring

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Abstract

Aims To investigate the possibility of assessing hypoglycaemia awareness in patients with Type 1 diabetes using continuous glucose monitoring.

Methods Twenty patients with Type 1 diabetes were investigated. Ten patients with Type 1 diabetes and strongly impaired hypoglycaemia awareness were compared with 10 patients with intact hypoglycaemia awareness regarding quality of hypoglycaemia perception (number of undetected hypoglycaemic episodes per 24 h, glucose level < 3.3 mmol/l). Hypoglycaemia detection was assessed using the event function of the Continuous Glucose Monitoring System (CGMS™; Medtronic MiniMed®, Northridge, CA, USA). Patients were instructed to enter an event upon suspecting being hypoglycaemic.

Results Satisfactory CGMS performance could be achieved [mean $r = 0.893$ between calibration measurements and CGMS data, mean absolute difference (MAD) = 20.6%], although artefacts were observable and had to be controlled. Hypoglycaemia unaware patients showed a significantly higher total number of hypoglycaemic episodes ($P < 0.05$), number of undetected hypoglycaemic episodes ($P < 0.01$), and mean glucose levels ($P < 0.05$). Even in aware patients, undetected hypoglycaemia was observable. No significant differences regarding occurrence of nocturnal hypoglycaemia were observable.

Conclusions The possibility of direct assessment of hypoglycaemia awareness using continuous glucose monitoring was demonstrated. Its application in clinical practice could be of use for assessing hypoglycaemia perception and evaluating the impact of treatment changes on hypoglycaemia awareness.

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Keywords Type 1 diabetes, hypoglycaemia, hypoglycaemia awareness, continuous glucose monitoring

Introduction

Intensified insulin therapy and tight glycaemic control are associated with a marked increase in risk of severe hypoglycaemia in Type 1 diabetes mellitus [1]. One major additional risk factor for occurrence of severe hypoglycaemia is impaired hypoglycaemia awareness [2,3], being common in insulin-treated diabetes with estimated prevalence rates of 20–30% [4,5].

No consensus exists concerning measures of hypoglycaemia awareness. Common measures range from self-ratings [2] to structured questionnaires [3]. Heterogeneity of measures limits comparability of studies and evaluation of treatment results with regard to their impact on hypoglycaemia perception. Furthermore, in clinical care, no standardized assessment methods are available, the practitioner having to rely largely on clinical judgement.

Glucose monitoring has potential advantages concerning detection of hypoglycaemia over conventional blood glucose testing [6–8]. In this pilot study, the possibility of assessing patients' hypoglycaemia awareness using continuous glucose measurement was addressed. The focus of the study was the initial validation of a parameter for hypoglycaemia awareness obtained via glucose monitoring.

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Table 1 Patient characteristics and glucose monitoring results

	'Aware' N = 10	'Unaware' N = 10	
<i>Patient characteristics</i>			
Age (years)	34.3 (11.3)	37.7 (1.8)	NS
Gender [<i>n</i> (%) male]	4 (40)	6 (60)	NS
HbA _{1c} (%)†	7.6 (1.5)	6.4 (1.2)	<i>P</i> = 0.052
Duration of disease (years)	16.8 (10.2)	18.9 (9.7)	NS
<i>Insulin regimen</i>			
Multiple daily injections [<i>n</i> (%)]	1 (10)	2 (20)	NS
Insulin pump [<i>n</i> (%)]	9 (90)	8 (80)	NS
<i>Glucose monitoring results</i>			
Mean sensor glucose (mmol/l)	7.5 (1.1)	6.0 (1.3)	*
SD sensor glucose	2.9 (0.8)	2.7 (0.8)	NS
Time system worn (h)	55.8 (15.6)	56.9 (15.9)	NS
Valid monitoring time (h)	54.0 (11.9)	52.6 (12.4)	NS
No. of hypoglycaemic episodes/24 h‡	2.1 (1.5)	4.6 (2.6)	*
No. of nocturnal hypoglycaemic episodes/24 h‡§	0.7 (1.2)	1.6 (1.2)	NS
No. of undetected hypoglycaemic episodes/24 h‡	1.3 (1.4)	4.1 (2.2)	**

Data displayed as mean (SD), or *n* (%) where applicable; *t*-tests/ χ^2 tests used for significance testing
NS, Not significant; **P* < 0.05; ***P* < 0.01.

†Range in non-diabetic persons: 5.0 ± 0.8% (mean ± SD).

‡Glucose levels < 3.3 mmol/l.

§22.00 to 06.00 h.

Patients and methods

To study the validity of continuous glucose monitoring for assessment of hypoglycaemia awareness, a total of 20 Type 1 diabetic inpatients treated at the Diabetes Centre Mergentheim, Germany, were assigned to two groups (Table 1): (i) hypoglycaemia aware group (*n* = 10) with intact hypoglycaemia awareness (no subjectively reported impairment, no history of severe hypoglycaemia in the past 12 months); (ii) hypoglycaemia unaware group (*n* = 10) with strongly impaired awareness (strong impairment reported, history of severe hypoglycaemia as based on clinical interview and patient records). All patients studied were using intensified insulin therapy. During the study, the patients stayed at the centre for treatment, but were free to move around the centre, to go outside and to exercise, as well as to choose their amount of daily carbohydrate intake.

Glucose monitoring

To assess hypoglycaemia awareness the Medtronic MiniMed® Continuous Glucose Monitoring System™ (CGMS; Medtronic MiniMed, Northridge, CA, USA) was used, with subjects wearing the device for 72 h. Participants were instructed to use the CGMS's event function, i.e. to enter an event whenever they thought of being hypoglycaemic while wearing the sensor system. No event was to be entered if recent conventional blood glucose measurements had alerted the patient to hypoglycaemia. The CGMS does not display actual glucose levels, leaving the patient 'blind' to prevailing glucose. MiniMed Solutions Sensor™ 2.0B software package was used to download data. Only days with at least four performed calibrations were considered. First, the manufacturer's accuracy criteria were applied [correlation *r* ≥ 0.79; mean absolute difference (MAD) ≤ 28% [9]]. Then, days not satisfying these criteria were subjected to

further inspection, and data between two inaccurate calibrations were excluded. Furthermore, recorded events were compared with conventional patients' blood glucose logs and calibration data to control for plausibility and artefacts. Raw data provided by the CGMS were used in order to compute the number of mild hypoglycaemic episodes.

A hypoglycaemic episode was defined as a period with CGMS glucose below 3.3 mmol/l of at least 10 min duration with an antecedent non-hypoglycaemic episode of at least 30 min. The threshold of 3.3 mmol/l was chosen, as this refers to the blood glucose level patients in Germany are commonly told to treat low blood glucose. Duration was defined to prevent near-hypoglycaemic glucose fluctuations from being counted as several hypoglycaemic episodes. It also prevented overestimation of low blood glucose exposure [10] due to the restoration period of hypoglycaemic glucose levels measured interstitially being prolonged.

Assessment of hypoglycaemia awareness

A single recorded hypoglycaemic episode was defined as 'detected' if an event entered by the patient was associated with the hypoglycaemic time window (±10 min), and considered 'undetected' if no event was entered. As a measure of hypoglycaemia awareness, the number of undetected hypoglycaemic episodes per 24 h was evaluated, as detection rates (% detected) are biased by frequency of hypoglycaemia.

Statistical analysis

To identify group differences, *t*-tests were computed. Data analysis was performed using Systat® 9.01 for Windows® statistical software package (SPSS Science, Chicago, IL, USA).

Results

Sensor performance

Participants performed 8.8 ± 4.9 calibrations per day with laboratory standard readings (glucohexokinase assay, EBIOplus; Eppendorf, Hamburg, Germany). The overall correlation between CGMS and calibration data of mean $r = 0.893$ (based on Fisher's Z transformed individual correlations) and a MAD of 20.6% was satisfactory. Agreement between sensor and calibration measurements for hypoglycaemic (glucose < 3.3 mmol/l), euglycaemic ($3.3 \text{ mmol/l} \leq \text{glucose} < 10.0$ mmol/l) and hyperglycaemic readings (glucose ≥ 10.0 mmol/l) amounted to 77% (Cohen's $\kappa = 0.573$, $P < 0.05$; agreement hypoglycaemic vs. euglycaemic vs. hyperglycaemic target range: 62.3% vs. 86.5% vs. 69.4%). This is consistent with other studies showing lower agreement in the hypoglycaemic range than during euglycaemia [10,11]. A total valid monitoring time of 53.3 h over both patient groups was achieved, with no between groups differences observable. Mean loss of monitoring time due to artefacts amounted to 3.05 h (Table 1).

Assessment of hypoglycaemia awareness

Mean CGMS-based glucose levels were significantly lower in unaware patients ($P < 0.05$), whereas no difference regarding standard deviations in glucose levels as a measure of individual glucose fluctuations was observable (Table 1). Groups did not differ with regard to nocturnal hypoglycaemic episodes (22.00 to 06.00 h). Unaware patients experienced significantly more hypoglycaemic episodes in 24 h (2.1 ± 1.5 vs. 4.6 ± 2.6 episodes/24 h; $P < 0.05$). A highly significant difference regarding number of undetected hypoglycaemic episodes per 24 h was observed. The number of undetected episodes amounted to 1.1 ± 1.7 episodes/24 h in aware patients compared with 4.1 ± 2.1 in unaware participants ($P < 0.01$). Large interindividual differences regarding hypoglycaemia detection were observed. Individual hypoglycaemia detection rates (Fig. 1) revealed five aware participants experiencing at least one episode of undetected hypoglycaemia, whereas no patient classified as unaware showed intact awareness with any episode. Three patients experienced more than one episode. The subgroup of patients experiencing undetected hypoglycaemia though classified as aware had a lower mean sensor glucose and more hypoglycaemic episodes compared with the rest of the group (7.1 ± 0.1 vs. 7.9 ± 0.8 mmol/l sensor glucose; 2.8 ± 1.2 vs. 1.5 ± 1.6 episodes/24 h), but did not differ in other characteristics.

Discussion

Despite the clinical relevance of impaired hypoglycaemia awareness, no consensus regarding assessment has been achieved. This is mainly due to methodological difficulties: hypoglycaemia perception can hardly be assessed directly, but

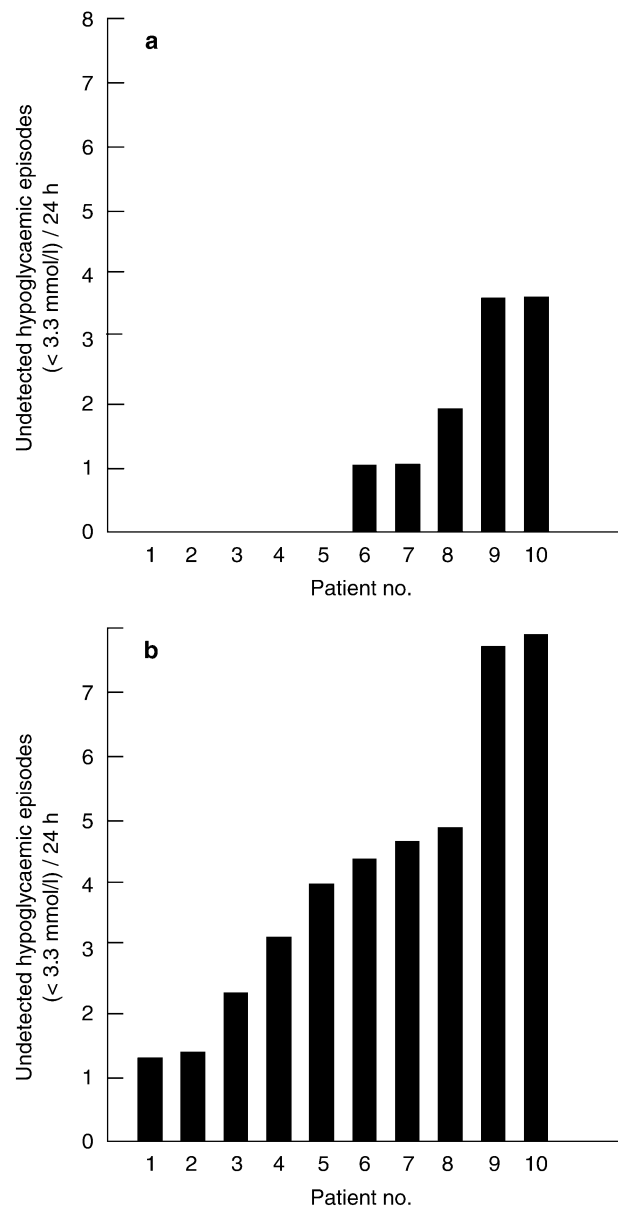


Figure 1 Bar charts depicting individual numbers of Continuous Glucose Monitoring System (CGMS)-based undetected hypoglycaemic episodes/24 h in aware (a) and unaware (b) patients (patients sorted by ascending order of number of hypoglycaemia episodes for the sake of readability).

relies on retrospective overall ratings. Furthermore, when trying to assess awareness directly via symptom reports during experimental glucose manipulation settings [12] or by using hand-held computers [3,13], the data are subject to reactivity and may lack external validity [14].

This pilot study demonstrates the possibility of 'non-reactive' direct assessment of hypoglycaemia awareness via using continuous glucose monitoring; hypoglycaemia aware and unaware diabetics differ significantly with regard to hypoglycaemia detection. Surprisingly, undetected episodes in five out of 10 subjects were also observed, though they claimed to

have 'intact awareness'. This finding confirms that hypoglycaemia awareness is not 'all-or-nothing' [15]. Furthermore, this suggests that relying on self-report and history of severe hypoglycaemia may not be sufficient to rule out impaired awareness.

The methodical limitations associated with glucose monitoring should be noted. One drawback of the method is a limited maximal monitoring time of approximately 72 h, which poses difficulties regarding the representativeness of the measurement; the mean monitoring time reached in this study was 53.3 h over both groups with satisfactory accuracy. Furthermore, the method used is prone to signal artefacts, and sensor performance may not be as accurate in the hypoglycaemic range, requiring rigorous artefact control. Whereas identification of hypoglycaemic episodes can be realized using the algorithm described, artefact control to date still relies on visual control and comparison of individual glucose courses and monitoring data, possibly limiting objectivity when put to clinical application. Data quality strongly depends on the patients' cooperation (performing calibrations, entering events). This is a pilot study with a small sample size, and larger samples are needed. This might lead to the definition of a 'normal range' or clinically relevant cut-off scores.

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