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The Somogyi phenomenon revisited using continuous glucose monitoring in daily life

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To the Editor:

In 1959, Michael Somogyi reported that hypoglycaemia during the night was often followed by heavy glycosuria next morning [1]. Moreover, a high morning fasting blood glucose value was later attributed to nocturnal hypoglycaemia and the need to reduce the evening or bedtime dose of insulin. The Somogyi phenomenon—hypoglycaemia begetting hyperglycaemia—is believed to be due to the release of counterregulatory hormones in response to (nocturnal) insulin-induced hypoglycaemia. Despite the fact that experimental studies have rejected the existence of the Somogyi phenomenon [2–4], it is, in our experience, still widely believed to exist by health care professionals. Previous experimental research has been based on hospitalised patients using nocturnal blood glucose profiles or real life data with a single nocturnal blood glucose measurement. The sensitivity of the latter method for the detection of nocturnal hypoglycaemia is low [3, 5], which may explain some of the reluctance to accept that the phenomenon does not exist. The recent development of continuous glucose monitoring systems has made it possible to monitor patients with type 1 diabetes in daily life. Using this technology, we tested the existence of the Somogyi phenomenon in daily life in a large cohort of type 1 diabetic subjects.

All 262 patients with type 1 diabetes from a cohort included in a study of hypoglycaemia in 1999 [6] were invited to participate in a prospective observational study in 2002. The protocol was approved by the regional ethics committee. Of the patients invited, 126 (48%) gave written informed consent to participate, while four (2%) were dead, 23 (9%) had moved or did not participate for other specific reasons, 37 (14%) did not respond to the invitation, and 72 (27%) declined to participate. The participants (35%

women) had a mean (SD) age of 46 (12) years and a diabetes duration of 21 (12) years. Most (86%) of the patients were on basal bolus treatment with NPH and human insulin. The remaining patients were receiving one- or two-dose therapy, and the mean HbA_{1c} was 8.5±1.0%. Patients underwent 6 days of continuous subcutaneous glucose monitoring using a continuous glucose monitoring system (CGMS) (Medtronic MiniMed; Medtronic Diabetes, Northridge, CA, USA). At day 1, the sensor was inserted into the abdominal wall. Following careful instruction about the device and protocol, initial calibration was performed and patients went home with instructions to live as normally as possible. At day 4, the sensors were replaced, and at day 7 the sensors were dismantled and data were analysed. Calibration measurements were performed four times daily with a glucose analyser (HemoCue B; HemoCue, Vedbaek, Denmark) in order to obtain optimal accuracy of the calibration curve. The glucose analysers used in the present study were calibrated identically by the manufacturer. Participants kept a diary during the entire study period, documenting insulin doses, meals and snacks, episodes of symptomatic hypoglycaemia, and the blood glucose level during these episodes, if measured.

Data files were generated by means of the most recent Medtronic MiniMed CGMS software, version 1.7A. Graphs were initially evaluated to identify periods with valid data, which were defined as the interval between first entered calibration value and last accepted calibration value [7]. We discarded periods containing less than four calibrations in 24 h and periods with no electrical signal. Night was defined as the time between bedtime calibration value and morning calibration value (data obtained by diary). Nocturnal glycaemia was classified according to nadir CGMS readings. Hypoglycaemic nights were defined by CGMS glucose readings of 2.2 mmol/l (lower detection limit of the CGMS) lasting for at least 10 min. Such episodes represent true hypoglycaemia with an 84% probability, when compared with conventional blood glucose measurements [7]. Possibly hypoglycaemic nights were defined by nadir CGMS glucose readings of 2.3–3.5 mmol/l, and non-hypoglycaemic nights by nadir glucose readings

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above 3.5 mmol/l. Primary endpoint was the self-monitored blood glucose concentration in the morning as measured by the glucose analyser after valid nights. We used standard parametric and non-parametric statistics when appropriate. A p value of <0.05 (two-sided) was considered statistically significant.

Valid data were obtained on 594 (79%) of 756 nights. The distribution of nights according to presence of nocturnal hypoglycaemia appears in Table 1. The vast majority of nocturnal hypoglycaemic episodes (218, 93%) were asymptomatic (silent), and no episodes of severe hypoglycaemia occurred. No patients reported nocturnal hypoglycaemic symptoms while having normal or high CGMS readings. Fasting morning blood glucose was significantly lower after hypoglycaemic and possibly hypoglycaemic nights when compared to non-hypoglycaemic nights (Table 1). Blood glucose values below 7 mmol/l in the morning were associated with increased risk of nocturnal hypoglycaemia (Fig. 1). No difference was observed in the morning blood glucose value after symptomatic hypoglycaemic nights (treated with carbohydrate), compared with nights with silent hypoglycaemia (8.5 vs 8.5 mmol/l, $p=0.94$).

Thus the existence of the Somogyi phenomenon is rejected by our data, which show that mean morning blood glucose concentrations after hypoglycaemic nights are more than 5 mmol/l lower than after nights without hypoglycaemia, and that the risk of nocturnal hypoglycaemia increases progressively as morning blood glucose values decrease. This finding was obtained by continuous glucose monitoring, which enables comprehensive assessment of nocturnal glycaemia without interfering with daily activities including sleep. As such, our finding extends results from inpatient studies to the daily life situation. These earlier studies, using conventional glucose measurements ranging from once each night to once every hour during the night, reported that nocturnal hypoglycaemia was not followed by hyperglycaemia the following morning [2–4] and, furthermore, that a high glucose value after a nocturnal hypoglycaemic episode was due to lack of insulin rather than to hormonal counterregulation [2, 4]. Thus, in patients treated with basal-bolus insulin regimens, nocturnal hypoglycaemia should be suspected when fasting blood glucose

Table 1 Breakdown of 594 nights according to mean fasting morning blood glucose and presence of nocturnal hypoglycaemia

	Number of nights (%)	Morning blood glucose (mmol/l) ^a	
Hypoglycaemia	139 (23)	6.1±0.3	$p<0.0001^b$
Possible hypoglycaemia	96 (16)	7.8±0.4	$p<0.0001^b$
No hypoglycaemia	359 (61)	11.5±0.2	

^aMeans±SEM

^bCompared to non-hypoglycaemic nights

Fig. 1 Risk of nocturnal hypoglycaemia according to fasting morning blood glucose (95% CI) in 594 nights. Black bars, hypoglycaemic nights; shaded bars, possibly hypoglycaemic nights

concentrations are low and should be verified by nocturnal blood glucose measurement or by continuous glucose monitoring. There is no evidence to suggest that high fasting morning blood glucose values indicate that silent nocturnal hypoglycaemia has occurred.

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Duality of Interest

There are no dualities of interest.

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