

Nocturnal Blood Glucose Profiles in Patients with Type 1 Diabetes Mellitus on Multiple (≥ 4) Daily Insulin Injection Regimens

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The aim of the study was to examine nocturnal blood glucose profiles in Type 1 diabetic patients on multiple (≥ 4) daily insulin injections. Nocturnal blood glucose profiles were evaluated in 31 patients collecting blood samples half-hourly from 23.00 till 07.30 h, while they were asleep. Nocturnal episodes of hypoglycaemia (blood glucose < 3.0 mmol l⁻¹) occurred in 29 % of these nights; 67 % of episodes were asymptomatic. In the early night (23.00–01.00 h), five episodes occurred with a median duration of 1 h. In the early morning (04.00–07.30 h) seven episodes occurred with a median duration of 3 h. No hypoglycaemia was noted from 01.00 to 04.00 h. Bedtime glucose levels appeared to predict 'early night' hypoglycaemia but not 'early morning' hypoglycaemia. Fasting glucose levels < 5.5 mmol l⁻¹ were indicative of preceding 'early morning' hypoglycaemia. There was a large intra-individual variation in nocturnal blood glucose profiles. It is concluded that daily monitoring of bedtime and fasting blood glucose levels may be both more reliable and convenient for the prevention of nocturnal hypoglycaemia than periodic testing of blood glucose at 03.00h as is often advised. Setting a target of > 5.5 mmol l⁻¹ for fasting blood glucose may decrease the frequency of nocturnal hypoglycaemia.

KEY WORDS Nocturnal hypoglycaemia IDDM Intensive insulin therapy Self-monitoring of blood glucose

Introduction

Patients with Type 1 (insulin-dependent) diabetes mellitus are at constant risk of treatment-induced hypoglycaemia.¹ Intensifying insulin therapy has been associated, although not consistently, with an increased incidence of this complication, particularly during the night.^{2–7} Nocturnal hypoglycaemia is traumatic for both diabetic patients and their relatives. Warning symptoms may not occur, so that initially mild hypoglycaemia may progress into more severe hypoglycaemia, requiring intervention of others.^{1,8} It has been suggested that nocturnal hypoglycaemia may induce hypoglycaemia unawareness, which in turn increases the risk of severe hypoglycaemia at any time during the day.^{8–12} Meticulous prevention of hypoglycaemia (including nocturnal) is capable of reversing hypoglycaemia unawareness, even in long-standing diabetes.^{13,14} Furthermore, a variety of non-specific symptoms like fatigue, irritability and headache have been associated with nocturnal hypoglycaemia. Strict avoidance of nocturnal hypoglycaemia should be one of the cornerstones of intensive insulin therapy.

Most of the advice given to patients in order to prevent

nocturnal hypoglycaemia is based on extrapolation of scarce data obtained from studies with infrequent nocturnal blood glucose measurements in conventionally treated diabetic patients.^{15–20} To our knowledge, only one report concerning nocturnal hypoglycaemia in intensively treated Type 1 diabetes has been published.²¹ In order to extend these few observations we performed a study in which we measured detailed nocturnal blood glucose profiles in Type 1 diabetic patients on multiple (≥ 4) daily insulin injections.

Patients and Methods

Thirty-one Type 1 diabetic patients, all treated with short-acting insulin at least three times a day and intermediate-acting insulin at night were randomly selected from the population of the diabetes outpatient clinic of the Maria Hospital Tilburg. All patients had been stable for more than 1 year on multiple daily injection therapy. They had all received intensive education including the use of simple algorithms to correct their blood glucose levels according to Schiffrin,²² with goals of therapy similar to those of the DCCT.^{6,7} NPH-insulin dosage was based upon fasting blood glucose and 03.00 h blood glucose concentrations. Informed consent was obtained from all patients and the study was approved by the medical ethical committee of the Maria Hospital

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Tilburg, The Netherlands. The clinical data of the patients are shown in Table 1.

All patients were admitted to the hospital at 20.00 h, after their evening meal, on a normal working day. An antecubital intravenous cannula was inserted to take blood samples without awakening the patients at night; the cannula was kept patent by infusion of 0.9 % saline. In the evening, patients were free to snack as if they were at home. They made their own decisions about insulin dose and measuring their blood glucose. NPH insulin was given subcutaneously in the thigh at 23.00 h. Patients were instructed to report symptoms of hypoglycaemia any time during the study. Only symptomatic hypoglycaemia was treated by the observers. Between 23.00 and 07.30 h venous blood samples were drawn into Na-fluoride/K-oxalate bottles half-hourly, while the patients were asleep. The samples were analysed within 2 h by a glucose oxidation method.²¹ Blood glucose concentrations were not known to patients or observers during the study period.

Blood glucose levels were measured during 45 patient-nights in 31 Type 1 diabetic patients. Six patients were observed more than one night in order to get some information about the intra-individual variability of nocturnal blood glucose profiles. Analysis of the blood glucose profiles is based on the data of the first night of these 6 patients and the other 25 patient-nights ($n = 31$). HbA_{1c} was assayed by an HPLC method (reference values 4.0–6.1 %).

Statistical Analysis

Comparison for means between subjects was performed using unpaired *t*-test for normally distributed data and Mann-Whitney U-test for non-normally distributed data. Linear regression (Pearson) was used for calculation of the correlation coefficient. Results are expressed as mean \pm SD or median (range) when non-Gaussian distribution was observed. Area under the curves (AUC) were determined using the trapezoidal rule for glucose profiles from the 8.5 h of the nocturnal blood glucose curve.

Table 1. Clinical data of Type 1 diabetic patients

Number	31
Sex (F/M)	11/20
Age (yr)	40.4 [19–67]
Diabetes duration (yr)	17.6 [2–57]
Total insulin dose (IU kg ⁻¹)	0.68 \pm 0.15
NPH insulin dose (IU kg ⁻¹)	0.27 \pm 0.07
NPH insulin dose (% of total dose)	40.5% \pm 9.8
HbA _{1c} (%)	8.6 [6.1–11.6]

Results are expressed as mean \pm SD or [range].

Values of $p < 0.05$ were considered to be statistically significant.

Results

In the first overnight blood glucose profiles from each of 31 patient, hypoglycaemia (defined as a blood glucose level < 3.0 mmol l⁻¹) occurred in 29 %; 67 % of these hypoglycaemic episodes were asymptomatic; 2 patients woke up during the night (1 at 01.00 h and 1 at 05.00 h) with sweating and heart pounding and 1 patient experienced neuroglycopenic symptoms of confusion, inability to concentrate and irritability before bedtime. The nadir of blood glucose ranged from 2.5 to 2.7 mmol l⁻¹ in these symptomatic cases, whereas it ranged from 0.9 to 2.5 mmol l⁻¹ in the asymptomatic group. There were no patients with hypoglycaemic symptoms and blood glucose values > 3.0 mmol l⁻¹.

The distribution of nocturnal hypoglycaemia is shown in Figure 1. Two separate intervals of hypoglycaemia were observed during the night. One occurred in the early night from 23.00 to 01.00 h and the other in the early morning from 04.00 to 07.30 h. No hypoglycaemic episodes were noted from 01.00 to 04.00 h. There were 5 subjects with hypoglycaemic episodes in the early night and 6 subjects with episodes in the early morning; 2 patients experienced an 'early night' as well as an 'early morning' hypoglycaemia.

The median duration of all hypoglycaemic episodes was 1.0 (range 0.5–3.5) h. The median duration of the 'early night' hypoglycaemic episodes was 1.0 (range 0.5–1.5) h and of the 'early morning' hypoglycaemic episodes 2.5 (range 0.5–3.5) h, $p = \text{NS}$.

Figure 2 shows the association between the nadir of blood glucose in the 'early morning' and fasting blood glucose levels. Linear regression showed a correlation coefficient of 0.98, $p < 0.0001$. A fasting glucose of ≥ 5.5 mmol l⁻¹ was never preceded by 'early morning' hypoglycaemia. A fasting blood glucose level at 07.30 h of < 5.5 mmol l⁻¹ was associated with 'early morning' hypoglycaemia in 6 of 12 patient-nights; in 4 cases a fasting glucose < 3.0 mmol l⁻¹ at 07.30 h was measured.

'Early night' hypoglycaemia was already apparent at 23.00 h in 4 of 5 cases. These glucose values were all taken before a bedtime snack, as were all but 6 of the 23.00 h readings. There was a significant correlation between bedtime glucose and the nadir of blood glucose in the 'early night' (correlation coefficient 0.87, $p < 0.0001$) as shown in Figure 3. Bedtime glucose values > 7.5 mmol l⁻¹ were never followed by 'early night' hypoglycaemia whether these glucose values were post- or pre-snack. In 16 subjects glucose was ≤ 7.5 mmol l⁻¹ at bedtime. Nine out of 11 patients who did not experience an 'early night' hypoglycaemia snacked before sleeping. The 2 patients who did not snack before sleeping had a nadir of blood glucose of, respectively, 3.0 and 5.8 mmol l⁻¹.

No predictive value was found for bedtime blood

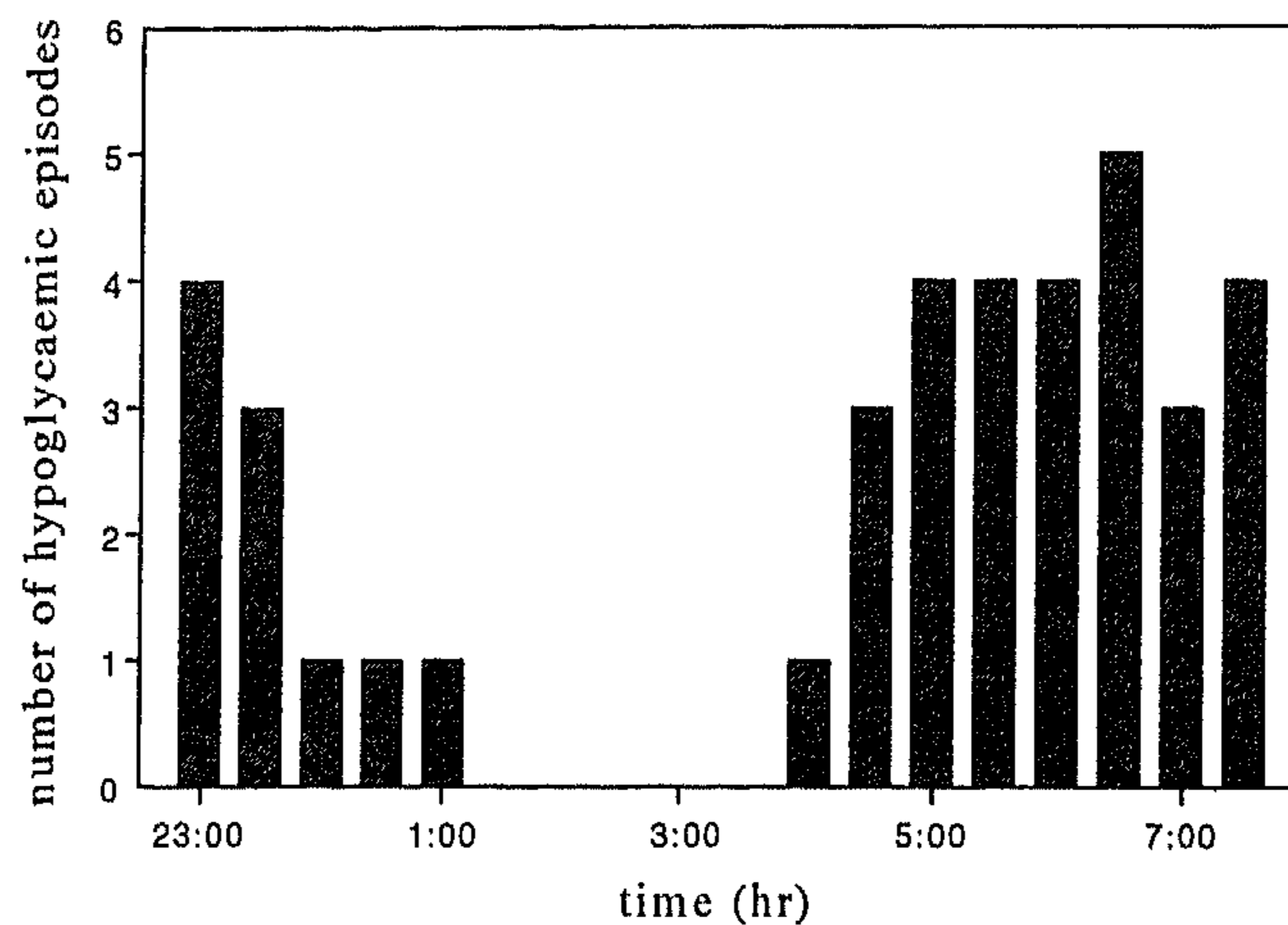


Figure 1. Time related frequency of nocturnal hypoglycaemia

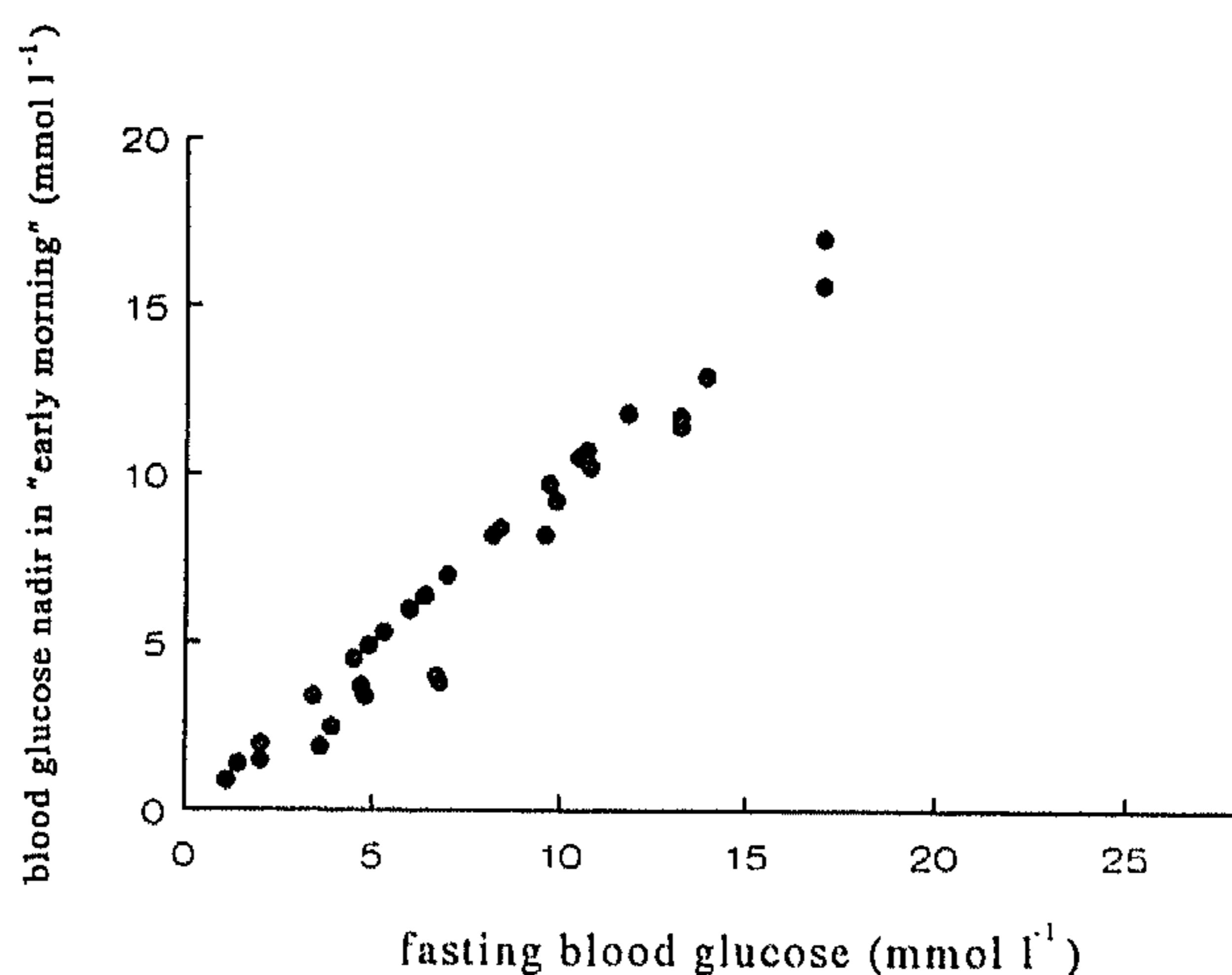


Figure 2. Correlation between fasting blood glucose and blood glucose nadir in the 'early morning'; (Pearson) correlation coefficient 0.98; $p < 0.0001$

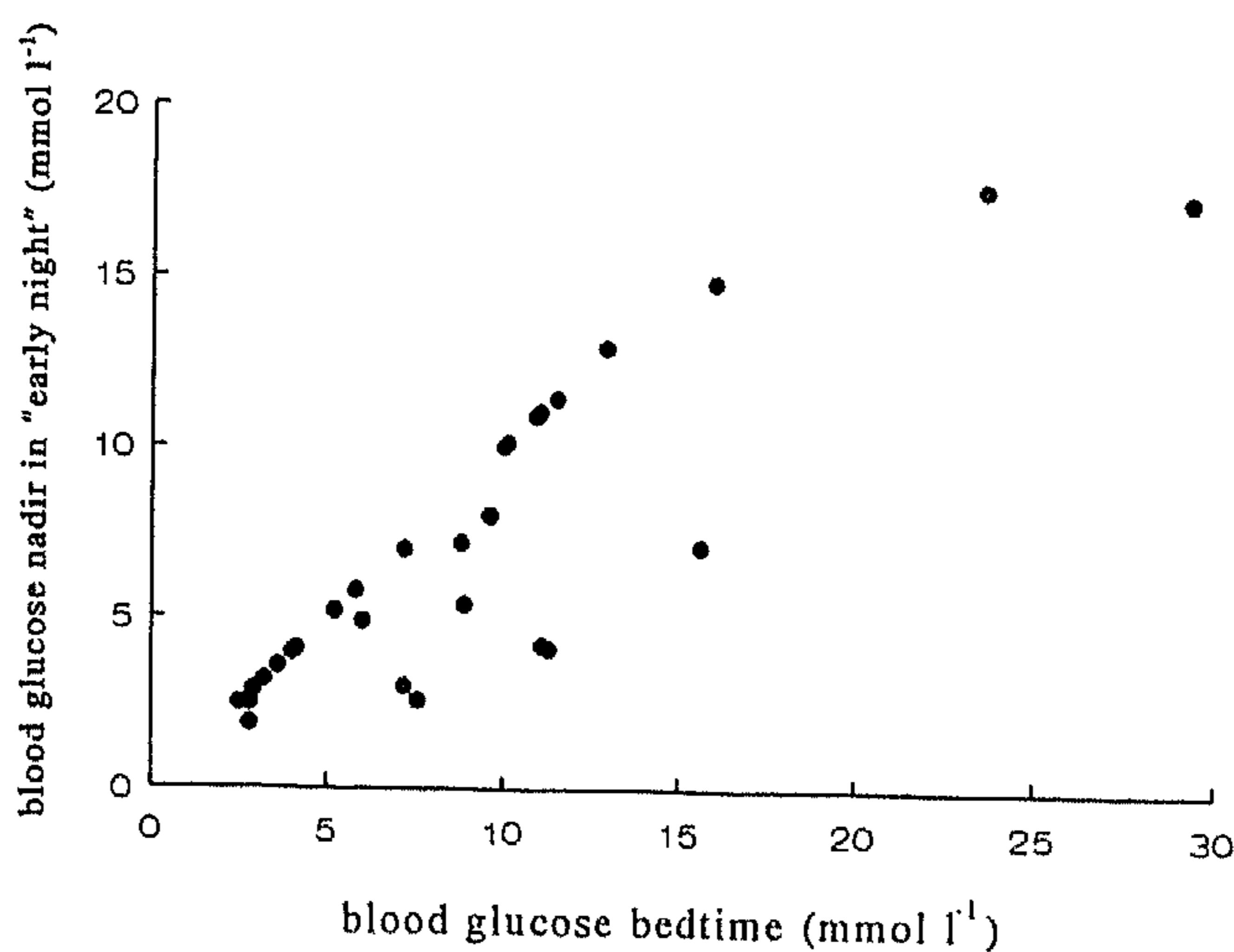


Figure 3. Correlation between bedtime blood glucose and blood glucose nadir in the 'early night'; (Pearson) correlation coefficient 0.87; $p < 0.0001$

Table 2. Intra-individual variation of nocturnal blood glucose profiles in 6 diabetic patients who were observed for 20 nights

Patient number	Nights of observation	AUC (CV)	Number of hypoglycaemic episodes
A	5	72.7 (39%)	2
B	5	88.0 (28%)	1
C	2	86.3 (54%)	1
D	3	93.8 (14%)	0
E	3	71.6 (49%)	2
F	2	64.7 (62%)	0

Area under curve for glucose profiles from the 8.5 h of the nocturnal blood glucose curve (AUC) and coefficient of variation (CV)

glucose levels at 23.00 h with respect to 'early morning' hypoglycaemia. Whether there was evening-snacking or not, it did not influence the frequency or timing of 'early morning' hypoglycaemia. The mean bedtime blood glucose level before the nights with 'early morning' hypoglycaemia was 10.3 ± 4.0 mmol l⁻¹ and 9.8 ± 6.5 mmol l⁻¹ before the nights without 'early morning' hypoglycaemia.

Mean total daily insulin dose was 0.68 ± 0.15 IU kg⁻¹. Total NPH insulin dose was 0.27 ± 0.07 IU kg⁻¹ as shown in Table 1. There was a significant difference between NPH insulin dose in patients with 'early morning' hypoglycaemia, 0.32 ± 0.06 IU kg⁻¹ and in patients without 'early morning' hypoglycaemia, 0.26 ± 0.06 IU kg⁻¹ ($p < 0.05$). No such difference was found with respect to 'early night' hypoglycaemia. HbA_{1c} was 8.4 ± 1.4 % in the group without nocturnal hypoglycaemia compared to 9.3 ± 1.5 % in the group with nocturnal hypoglycaemia ($p = \text{NS}$).

Six subjects were observed during 20 patient-nights. There was a marked intra-individual variation in nocturnal blood glucose values as shown in Table 2. The area under the curve (AUC_{0-8.5 h}) of nocturnal blood glucose curves showed a coefficient of variation ranging from 14 to 62 %. The coefficient of variation of nocturnal blood glucose values at certain time points varied from 14 to 111 % (Table 3).

Table 3. Intra-individual variation of nocturnal blood glucose values

Number	Bedtime glucose	Nadir night	03.00h	Nadir morning	Fasting glucose
A	9.5 (36%)	6.9 (59%)	9.7 (41%)	6.3 (59%)	7.5 (47%)
B	7.2 (37%)	5.9 (62%)	11.9 (30%)	10.3 (33%)	12.3 (35%)
C	12.4 (41%)	9.3 (84%)	9.3 (84%)	6.1 (104%)	7.9 (48%)
D	11.1 (55%)	10.3 (49%)	12.5 (14%)	7.5 (23%)	7.5 (23%)
E	11.2 (49%)	8.3 (50%)	8.5 (53%)	4.2 (111%)	4.5 (105%)
F	4.8 (29%)	4.8 (29%)	8.3 (60%)	6.8 (60%)	8.4 (71%)

Nocturnal blood glucose values at certain time-points during the night are expressed as means; coefficient of variation between brackets

Discussion

The present study shows a high frequency (29 %) of nocturnal hypoglycaemia, defined as a blood glucose level <3.0 mmol l⁻¹, in Type 1 diabetic patients on multiple insulin injection regimens. This finding is in agreement with the one comparable study in the literature²¹ and with the DCCT, which showed an increase of 'severe' hypoglycaemia in the intensively versus conventionally treated subjects.^{6,7} In the DCCT, 43 % of episodes of severe hypoglycaemia occurred between midnight and 8 am. In our study 67 % of episodes were asymptomatic, in agreement with previous studies of nocturnal hypoglycaemia independent of insulin regimen used.¹⁵⁻²⁰

Our study showed two clearly separated episodes of hypoglycaemia during the night, 'early night' hypoglycaemia occurring between 23.00 and 01.00 h and 'early morning' hypoglycaemia occurring between 04.00 and 07.30 h. None of the patients exhibited a hypoglycaemic episode between 01.00 and 04.00 h. 'Early night' hypoglycaemia most probably has to be attributed to the extended action of the evening dose of soluble insulin, whereas 'early morning' hypoglycaemia, occurring between 04.00 and 07.30 h, is probably due to the bedtime NPH insulin. Although Bendtson *et al.* found no such definitive separate intervals they stated that a blood sample at 03.00 h would have detected only 13 % of the episodes of biochemical hypoglycaemia in their patients on multiple insulin injections. They found a peak incidence of nocturnal hypoglycaemia at 04.00 h in their patients.²¹ The DCCT found that even 26 % of all severe hypoglycaemic events occurred between 04.00 and 08.00 h.⁷

We found that 'early night' hypoglycaemia was already apparent at 23.00 h in all but one case. Bedtime glucose >7.5 mmol l⁻¹ was not followed by an 'early night' hypoglycaemia. Similarly, Bendtson *et al.* showed that a bedtime blood glucose at 23.00 h <6.0 mmol l⁻¹ in patients on multiple insulin injections increased the risk of getting nocturnal hypoglycaemia to 100%.²¹ No predictive value was found in our study for bedtime glucose levels with respect to 'early morning' hypoglycaemia but fasting blood glucose levels were strongly

indicative of preceding 'early morning' hypoglycaemia. This contrasts with Bendtson's data where there was no significant difference between fasting blood glucose in patients with and without nocturnal hypoglycaemia but the failure to distinguish 'early night' and 'early morning' hypoglycaemia in the earlier study may explain the discrepancy. Also the more frequent sampling of blood in our study could be relevant, since 30% of the 'early morning' hypoglycaemic events lasted only 30 min. The overall duration of nocturnal hypoglycaemia however was not different in the two studies.

We found no indication of the 'Somogyi' effect in our study. Higher fasting blood glucose levels generally reflected higher blood glucose levels during the night and nocturnal hypoglycaemia was associated with low fasting blood glucose. Posthypoglycaemic insulin resistance may result in rebound hyperglycaemia especially after breakfast.⁸ We did not measure blood glucose after 07.30 am but HbA_{1c} levels did not differ between the hypoglycaemic and non-hypoglycaemic groups.

A marked intra-individual variation of nocturnal blood glucose profiles was seen in patients on different nights. The variable absorption of NPH insulin most likely is the main reason for this variation²⁴ although fluctuations of glucose due to mental stress or physical activities in the days before the measurement may also contribute.

In extrapolating the results of this study to clinical practice, one has to keep in mind the inevitably artificial circumstances in which we made our observations. Nevertheless, our findings have important clinical implications. Firstly, as 'early night' hypoglycaemia appeared to be present already at bedtime in most instances, daily monitoring of bedtime glucose and taking appropriate action such as the intake of extra carbohydrates could abolish or at least attenuate 'early night' hypoglycaemia. Secondly, as 'early morning' hypoglycaemia was exclusively associated with fasting blood glucose below 5.5 mmol l⁻¹, we would suggest the target value for fasting blood glucose levels should be slightly above this level. This is in contrast to the guidelines used in the DCCT which aimed at fasting glucose levels between 3.9 and 6.7 mmol l⁻¹. We would suggest these targets may have contributed to the high prevalence of severe nocturnal hypoglycaemia in the DCCT.^{6,7} Thirdly, the results of our study do not lend support to the advice in the IDDM consensus guidelines of weekly monitoring 03.00 am blood glucose.²⁵ The chance of detecting hypoglycaemia in this way must be very low, even if the patient complies with this advice. Our data suggest that daily monitoring of fasting blood glucose, aiming at levels >5.5 mmol l⁻¹ and taking immediate and appropriate action with regard to evening NPH insulin dosing could abolish almost all 'early morning' hypoglycaemic episodes. The large variation from day to day in NPH insulin absorption must however be remembered so that dose adjustments are made only after observing high fasting blood glucose levels on consecutive mornings over one week or more. Nevertheless we submit that in view of the strong

variability of the absorption of NPH insulin and the corresponding variation of fasting blood glucose levels, relatively high fasting blood glucose levels may have to be accepted from time to time to avoid nocturnal hypoglycaemia. Prompt correction of these values with extra short-acting insulin before breakfast should be carried out by the patient on a daily basis to reach overall glycaemic control as satisfactorily as possible.

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