Abstract  Nocturnal hypoglycemia is reported in 13%–56% of adolescents with type 1 diabetes mellitus. It may be asymptomatic in more than 50% of patients. No noninvasive method for detecting asymptomatic nocturnal hypoglycemia (ANH) has so far proven successful. The aim of the present study was to evaluate quantitative changes of motor activity by actigraphy during episodes of ANH in adolescents with type 1 diabetes mellitus. A total of 18 patients aged 10–16 years with a history of ANH were investigated. Blood was sampled at half-hourly intervals between 22.30 and 06.00 hours with a micropump, and an actigraph was fastened to the right wrist. Blood glucose concentrations were measured and compared to motor activity. Nocturnal hypoglycemia was recorded in 10 patients (55%), with blood glucose during periods of hypoglycemia of 3.00±0.17 mmol/l (range, 1.2–3.4 mmol/l), and duration of hypoglycemia of 1.95±1.34 hours (range, 0.5–5.0 hours). All periods of hypoglycemia were clinically asymptomatic. Regression analysis revealed a statistically significant linear correlation ($p=0.03$) between blood glucose concentration and the respective 30-min activity counts. Activity counts in patients with nocturnal hypoglycemia were significantly (ANOVA, $p<0.02$) higher than in patients with normoglycemia. We conclude that low blood glucose was significantly correlated with an increase in motor activity as detected by actigraphy. This implies the possibility of noninvasive screening of asymptomatic nocturnal hypoglycemia.

Key words  Type 1 diabetes • Nocturnal hypoglycemia • Hypoglycemia unawareness • Detection

Introduction

Hypoglycemia is the major obstacle to successful intensive insulin therapy of type 1 diabetes mellitus. The reported prevalence of at least one serious episode of hypoglycemia per year is 10% in patients on classic insulin therapy and 26% in patients on intensive insulin therapy [1]. Nocturnal hypoglycemia represents a special problem; the reported prevalence is 13%–56% [2, 3], but it may be asymptomatic in more than 50% of patients [4, 5]. Adolescents with type 1 diabetes mellitus treated with intensive insulin therapy are particularly prone to asymptomatic nocturnal hypoglycemia (ANH) [3]. Frequent ANH severely worsen the overall metabolic control [4], and it often results in patients and their families living in fear of a serious hypoglycemic event with possible deleterious consequences.
Noninvasive methods for detecting ANH have so far proven unsuccessful. The morning urinary cortisol/creatinine concentration ratio does not differ between nights with normoglycemia and nights with ANH [6]. Furthermore, polysomnographic sleep analysis shows no significant difference between nights with normoglycemia and nights with ANH [7]. Although diabetic patients have more sleep disturbances and wake more frequently during the night, episodes of nocturnal hypoglycemia with blood glucose below 3.3 mmol/l do not influence the quality and structure of sleep [8, 9]. Thus, frequent measurements of blood glucose (BG) or, recently, continuous subcutaneous monitoring of glucose concentration [10], both invasive methods, remain the only way to detect ANH at home.

Actigraphy is used to record body movements. The actigraph underestimates electromyographic activity, but correlates significantly with it [11]. Motor activity, detected by actigraphy, shows no significant differences between different sleep phases in healthy adults [12]. Motor activity during nocturnal hypoglycemia has so far not been investigated quantitatively.

The aim of the present study was to evaluate quantitative changes of motor activity during episodes of ANH using an actigraph in adolescent patients with type 1 diabetes mellitus.

**Patients and methods**

We studied 18 adolescents (8 boys and 10 girls) with type 1 diabetes mellitus for 5 years (median), aged 13 years, with a history of frequent episodes of ANH (home BG monitoring during night in patients at risk of severe hypoglycemia, episodes of morning hyperglycemia). None had signs of late diabetic complications or other concomitant diseases. Five patients were on classic therapy (2 injections of combined regular and intermediate-acting insulin daily), while the others received intensive therapy (at least 3 injections of regular insulin or insulin lispro and one injection of long-acting insulin daily). Their average daily insulin dose was 0.89 IU/kg body weight (SD±0.30 IU/kg), and their mean glycosylated hemoglobin AIC (DCCT standardized) was 9.4% (SD±1.9%).

Patients were admitted to the hospital in the afternoon. After a regular dinner and the usual insulin dose, an intravenous catheter (ConFlo, coated with Carmeda Bioactive Surface; Carmeda, Stockholm, Sweden) was introduced into the left antecubital vein. A micropump (Swemed labpump 3003; Carmeda, Stockholm, Sweden) sampled 1.3 ml blood every 30 minutes continuously from 22.30 to 06.00 hours. Fifteen samples from each patient were collected into 2.5 ml plastic vials coated with dried K₃EDTA+NaF anticoagulant. Blood glucose from all samples was measured in the morning by a standard calorimetric glucose oxidase method (Monarch plus; Instrumentation Laboratory, Lexington, USA). An actigraph (Z80–32k V1; Gaehwiler Electronic, Hombuchtilon, Switzerland) was fastened to the wrist of the dominant hand before the patient went to sleep. The actigraph weighed 65 grams and recorded acceleration in one axis with the sensitivity threshold of 0.1 g (gravity acceleration). The frequency range filter of the piezoelectric sensor was set at 0.25–3 Hz. The over-threshold movements were sampled with a frequency of 8 Hz in repetitive measurement intervals of 15 seconds, thus making an observation of activity every 125 milliseconds. The numbers of over-threshold movements in those intervals were stored as the actimetric index (AI) [13]. The data from the actigraph were transferred to a personal computer (Activity Monitor Program, version 1.3; Gaehwiler Electronic, Hombuchtilon, Switzerland) for analysis and presentation.

An investigator, blinded to the blood glucose concentrations, observed all patients throughout the night. A written protocol of clinical observations was kept for each individual patient. Parallel, patients were routinely periodically observed by an experienced registered nurse on duty. All patients were discharged from the hospital by 10:00 A.M. the next morning. The study protocol was approved by the State Ethics Committee. Written informed consent was obtained from all patients and their parents.

**Statistical analysis**

Statistical analysis was performed using the program package Analyse-It (version 1.50 for Microsoft Excel 2000; Microsoft, WA, USA). To correlate the AI with the blood glucose sampling (sampled in 30-min intervals), the AI from 120 intervals of 15 seconds were analyzed and summed to obtain activity count (AC) for 30 minutes. These 30-min ACs were correlated with blood glucose concentrations for the same time periods, using regression analysis. All intervals of wakefulness were excluded from the analysis. AC from periods of hypoglycemia (blood sugar <3.5 mmol/l, group A), normoglycemia (group B), and hyperglycemia (blood sugar >6.1 mmol/l, group C) were grouped. These data sets were analyzed with ANOVA and subsequently with Tukey’s test to determine differences between groups. Sensitivity and specificity of the actigraphy for detecting ANH were determined using receiver operator characteristics (ROC) curves [14]. Descriptive parameters were analyzed with the t test. A value p<0.05 was considered statistically significant.

**Results**

Nocturnal hypoglycemia (blood glucose <3.5 mmol/l) was recorded in 10 (55%) of 18 adolescents with type 1 diabetes mellitus (Table 1). In 7 of these, blood glucose fell below 3.0 mmol/l. Mean blood glucose during periods of hypoglycemia was 3.00 mmol/l (SD±0.17 mmol/l; 1.2–3.4 mmol/l). The mean duration of hypoglycemia was 1.95 hours (SD±1.34 h; range, 0.5–5.0 hours). The mean sleeping time was 7.5 (SD±1.5 h). Overall, 70% of hypoglycemic periods occurred between 02.00 and 04.00 hours. All periods of hypoglycemia were clinically asymptomatic and could not be appreciated by the observing investigator or the registered nurse on duty.