

Hypoglycemia Prevalence in Prepubertal Children With Type 1 Diabetes on Standard Insulin Regimen: Use of Continuous Glucose Monitoring System

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OBJECTIVE — To determine hypoglycemia prevalence in prepubertal children on thrice (TID) and twice (BID) daily insulin regimens, using the Medtronic Minimed Continuous Glucose Monitoring System.

RESEARCH DESIGN AND METHODS — Twenty-eight children aged <12 years (median 9.8, range 6.9–11.8) wore the sensor for three consecutive days and nights. Hypoglycemia was defined as glucose <60 mg/dl for >15 min. Data are expressed as the percentage of time period spent hypoglycemic.

RESULTS — Hypoglycemia prevalence was 10.1% (mean 2.6 h · subject⁻¹ · day⁻¹). Hypoglycemia was more common at night compared with daytime (18.81 vs. 4.4%, $P < 0.001$); 78 and 43% of subjects showed hypoglycemia on at least one night and two or more nights, respectively. Nocturnal episodes were prolonged (median 3.3 h) and asymptomatic (91% of episodes). Prevalence was greater between 0400 and 0730 h than between 2200 and 0400 h (25.5 vs. 15.4%, $P < 0.001$). On a TID compared with a BID regimen, nocturnal hypoglycemia prevalence was reduced, particularly between 0400–0730 h (22.9 vs. 27.4%, $P = 0.005$), whereas hypoglycemia the following morning (0730–1200 h) was greater (7.8 vs. 2.8%, $P < 0.001$). Nocturnal hypoglycemia risk was associated with decreasing age (by a factor of 0.6 for a year less in age), increased insulin dose (by 1.6 for an increase of 0.1 units · kg⁻¹ · day⁻¹), insulin regimen (by 0.2 on a BID compared with a TID regimen), and increased weight standard deviation score (SDS) (by 2.7 for a one SDS rise).

CONCLUSIONS — Use of standard insulin regimens results in high prevalence and large intraindividual variation in hypoglycemia, particularly at night. Independent risk factors for nocturnal hypoglycemia were younger age, greater daily insulin dose, insulin regimen, and increasing weight.

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The development of microvascular complications in type 1 diabetic subjects is recognized to be related to poor glycemic control (1). It is now acknowledged that prepubertal glycemic

control may contribute to this risk (2), and as a result, there has been a call for more strict metabolic control in this age group. However improved glycemic control comes at an increased risk of hypo-

glycemia, which is already present in up to 50% of children on standard insulin regimens, with episodes being largely nocturnal, prolonged, and profound (3).

In our experience, most children in the U.K. are on standard thrice (TID) or twice (BID) daily insulin regimens. Due to timing of injections, free insulin levels differ between these regimens (4) and contribute to hypoglycemic risk. This risk may be influenced further by other factors that alter intraindividual rate of insulin absorption (5) and counter-regulatory responses (3). Although data are conflicting (6–18), in children risk factors for hypoglycemia include lower HbA_{1c} (6,9,10,16), younger age (9,14), duration of diabetes (9,12,16,17), insulin dose (7,18), previous hypoglycemia (7,16,18), and multiple injection therapy (10,15). However, current data suggest no difference in hypoglycemia prevalence on thrice versus twice a day insulin regimens. The variations in findings are in part related to differences in populations, collection of data, definitions of outcome, and data analysis, thus making comparisons between studies difficult. In addition, little data exist as to the intraindividual variations in hypoglycemia prevalence.

The Medtronic Minimed Continuous Glucose Monitoring System (CGMS) records 5-min subcutaneous glucose readings for up to 3 consecutive days. The CGMS allows reliable assessment of true glycemic fluctuation through the day and night (19), and it provides an opportunity to study, relatively noninvasively, intra- and interindividual variation in hypoglycemia prevalence. We used the CGMS to determine characteristics and risk factors for hypoglycemia in prepubertal type 1 diabetic children on standard insulin regimens.

Study design

Thirty-four prepubertal subjects with type 1 diabetes were recruited from the pediatric diabetes clinics at the John Rad-

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Abbreviations: BID, twice a day; CGMS, Continuous Glucose Monitoring System; GH, growth hormone; HPLC, high-performance liquid chromatography; IQR, interquartile range; SDS, standard deviation score; TID, three times a day.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

cliffe Hospital (Oxford) and Addenbrooke's Hospital (Cambridge). All subjects were at least 1 year from diagnosis of diabetes and were receiving treatment with either a TID or BID insulin regimen. After receiving local ethical approval and assent from the subject, written informed consent was obtained from parents for their child to participate.

All subjects had weight and HbA_{1c} measured. Weight standard deviation scores (SDS) were calculated using reference data based on the British 1990 Growth Reference and Cole's LMS method supplied by the Childhood Growth Foundation (20). Prescribed insulin dose remained unaltered throughout the study period. The Medtronic Minimed CGMS was attached to each subject by the same investigator in each center. Subjects were instructed on the use of the CGMS and were asked to enter a minimum of four finger-prick blood glucose measurements, taken each day, into the sensor for calibration purposes and to record into the sensor times of insulin injections and symptomatic hypoglycemic episodes. Each subject was asked to wear the sensor for 3 consecutive days and nights. After 3 days, the subject returned and data were downloaded using the MiniMed Solutions Software version 2.0b (Northridge, CA).

RESEARCH DESIGN AND METHODS

The CGMS

The CGMS has a glucose oxidase-based platinum electrode sensor, which is inserted using a spring-loaded device into the subcutaneous tissue of an appropriate site (e.g., the abdominal wall). Glucose oxidase catalyzes glucose oxidation in the interstitial fluid and generates an electrical current every 10 s, which is recorded by a pager-size monitor via a cable. The monitor records average values every 5 min, giving a total of 288 readings per day. Sensor readings are calibrated by the monitor against capillary blood glucose measurements obtained with conventional glucose meters. The majority of subjects used the One Touch Ultra (Lifescan, Milpitas, CA), Accu-Chek Active (Roche, Mannheim, Germany), or Esprit 2 (Bayer, Munich, Germany) conventional glucose meters. Data show mild performance differences between commonly used meters and when compared

Table 1—Baseline characteristics of those on a TID and BID regimen and hypoglycemia prevalence

	TID regimen	BID regimen
<i>n</i>	16	12
Duration of diabetes (years)	3.3 (2.8–4.6)	2.6 (1.3–4.0)
Age at assessment (years)	10.2 (8.9–11.8)	8.4 (6.9–10.1)
HbA _{1c} (%)	8.8 (1.1)	8.6 (1.1)
Daily insulin dose (units/kg)	1.0 (0.2)	0.9 (0.2)
Weight SDS	0.8 (0.9)	0.7 (0.9)
Hypoglycemia prevalence		
Over 24 h	10.5	9.8
0730–1200 h	7.8*	2.8*
2200–0730 h	16.9†	19.3†
0400–0730 h	22.9‡	27.4‡

Data are expressed as median (interquartile range), except HbA_{1c} and insulin dose, which are expressed as mean (SD). Hypoglycemia prevalence is expressed as % of observed time period <60 mg/dl (<3.5 mmol/l). * $\chi^2 = 40.3$, $P < 0.001$; † $\chi^2 = 7.8$, $P = 0.005$; ‡ $\chi^2 = 8.0$, $P = 0.005$.

against central laboratory measurements, albeit improved in the newer generation meters (21). To date, however, these meters remain the only practical option to carry out prevalence studies in the community. Glucose values outside the range of 40–430 mg/dl (2.2–24 mmol/l) were reported as <40 or >430 mg/dl (<2.2 or >24 mmol/l), respectively.

HbA_{1c}

Glycated hemoglobin was measured by high-performance liquid chromatography (HPLC) (Diamat; Bio-Rad, Hemel Hempstead, U.K.). The within-batch CV was 2.2 and 1.3% at an HbA_{1c} level of 5.4 and 9.8%, respectively. The between-batch CV was 3.5 and 2.2% at an HbA_{1c} level of 5.6 and 10.1%, respectively. The normal population range was 4.0–6.5%.

Statistical analysis

Hypoglycemia was defined as a sensor glucose value of 60 mg/dl (<3.5 mmol/l) for >15 min. Hypoglycemia prevalence was summarized for each subject as the percentage of a specified time period spent hypoglycemic. This percentage was compared between the groups using the χ^2 test. All other data were compared using a Student's *t* test and are expressed as mean (SD) or median (interquartile range [IQR]) unless otherwise stated. A logistic regression model was used to determine independent associations of covariates with hypoglycemia risk. To measure the agreement between data from the CGMS and conventional glucose meters, glucose readings from meters were paired with corresponding calibrated glucose values

obtained at the same time point from the CGMS. The agreement between these methods was compared using the Bland Altman method (22). Correlation between the two methods was determined by linear regression. A *P* value <0.05 was considered significant. Analyses were performed with SPSS version 10.

RESULTS

Cohort characteristics

A total of 34 patients (20 males) were recruited (22 from Oxford, 12 from Cambridge). In six subjects, the sensor was either dislodged or disconnected within 24 h of starting the study; these subjects were thus excluded from analysis. The system was well tolerated by subjects, and there was no evidence of inflammation at the sensor insertion site.

For the remaining 28 subjects, median age at diagnosis of diabetes was 6.1 years (3.1–8.3), median duration of diabetes was 3.1 years (1.3–4.6), and median age at assessment was 9.7 years (6.9–11.8). Mean HbA_{1c} was 8.7% (± 1.1). Sixteen subjects were on a TID insulin regimen (involving a mixed insulin injection before breakfast, short-acting insulin injection before the evening meal, and a medium-acting insulin injection before bedtime), and 12 subjects were on a BID regimen (involving a mixed insulin injection before breakfast and evening meal). Medium-acting insulin was administered as isophane NPH insulin, and short-acting soluble insulin was administered as human actrapid, except in eight subjects who were prescribed a rapid-

Table 2—Characteristics of hypoglycemia, nighttime versus daytime

	Nighttime (2200–0730 h)	Daytime (0730–2200 h)
Number of hypoglycemic episodes	36	45
Hypoglycemia prevalence (%)	18.0*	4.4*
Days/nights with hypoglycemia (%)	51	70
Duration of episodes (h)	3.2 (1.2–5.0)*	0.6 (0.4–1.2)*
Episodes <1 h duration (%)	16	51
Symptomatic episodes (%)	9*	56*

Data are expressed as % of observations during a specified time period (night: 2200–0730 h, day: 0730–2200 h), except duration of episodes, which is expressed as median hours (interquartile range). Hypoglycemia was defined as <60 mg/dl (<3.5 mmol/l) for >15 min. * $P < 0.001$.

acting analog (insulin lispro). No significant difference in age of diagnosis of diabetes, duration of diabetes, and HbA_{1c} was found between subjects recruited from the Oxford or Cambridge clinics or subjects on a TID compared with a BID regimen (Table 1).

Comparison of data from CGMS and conventional meters

Paired glucose readings ($n = 312$) from the CGMS and conventional meters correlated significantly ($P < 0.001$, $r^2 = 0.85$). For all data, the mean glucose difference was 3.6 mg/dl (95% CI –1.8 to 9), with no relationship seen with magnitude, i.e., the CGMS reads a mean of 3.6 mg/dl lower than conventional glucose meters (range –1.8 to 9). For CGMS values ≤ 60 mg/dl, the mean glucose difference rose to 12.6 mg/dl (95% CI 3.6–21.6). For example, for a glucose reading of 60 mg/dl, the CGMS will read between 55.5 and 64.5 mg/dl 60% of the time, with a sensitivity of 92% and a specificity of 73%.

Characteristics of hypoglycemia

The total period of monitoring was 1,886 h (median 67 h per subject, range 59.7–69.6); 59.1% of observations were from those on a TID regimen, while 40.9% were for those on a BID regimen. Of all observations, 10.1% were in the hypoglycemic range, which was equivalent to a median of 2.6 h per subject per day (IQR 0.1–6.5). A total of 81 episodes of hypoglycemia were identified, of which 45 were in the daytime and 36 were at nighttime (Table 2). Episodes were more prolonged at night compared with day (night versus day: 3.2 h [IQR 1.2–5.0] vs. 0.6 h [IQR 0.4–1.2], $P < 0.001$) (Table 2). Only 5 of 36 (16%) nocturnal episodes were under 1 h compared with 22 of 45

(51%) daytime episodes. Three (9%) nocturnal episodes were symptomatic compared with 25 (56%) daytime episodes, while no symptoms were identified for glucose levels >60 mg/dl. Of 28 subjects, 6 (21%) showed no evidence of nocturnal hypoglycemia, while 22 (78%) and 12 (43%) showed hypoglycemia on at least one night and on two or more nights, respectively.

Hypoglycemia was more prevalent at night (2200–0730 h) compared with daytime (0730–2200 h) (night versus day: 18.0 vs. 4.4%, $\chi^2 = 105.5$, $P < 0.001$) (Table 2 and Fig. 1). During the night, hypoglycemia was most prevalent between 0400 and 0730 h compared with 2200–0400 h (25.5 vs. 15.4%, $\chi^2 = 154.6$, $P < 0.001$).

If glucose measurements <45 mg/dl (<2.5 mmol/l) were used as the definition of hypoglycemia, then overall prevalence was 6.0% (median of 1.4 h \cdot subject⁻¹ \cdot day⁻¹). Hypoglycemia was mainly nocturnal (night versus day: 12.4 vs. 2.1%), when duration of episodes were longer (day versus night: 0.3 h [0.2–3.7] vs. 3.3 h [1.2–4.9], $P < 0.001$).

Characteristics of hypoglycemia prevalence in relation to insulin regimen

Mean glucose levels were no different on a TID compared with a BID regimen at 2200 h (TID versus BID: 173 mg/dl [86] vs. 202 mg/dl [88], $P = 0.41$) or at 0730 h (TID versus BID: 175 mg/dl [94] vs. 142 mg/dl [81], $P = 0.2$). Overall, there was no difference in hypoglycemia prevalence on a TID compared with a BID regimen (Table 1). However, daytime prevalence was greater on a TID regimen, particularly between 0730 and 1200 h, while at night, prevalence was greater on a BID regimen, particularly between 0400 and 0730 h (Table 1 and Fig. 2). We found no difference in prevalence for those on a regimen incorporating a rapid-acting insulin analog ($n = 8$) compared with those on regular soluble insulin ($n = 20$).

Determinants of hypoglycemia

A logistic regression model was used to determine factors related to hypoglycemia risk, with presence or absence of hypoglycemia as the dependent variable, and HbA_{1c}, duration of diabetes, age, insulin dose (IU/kg), insulin regimen, and weight SDS as independent covariates. Over a 24-h period, an increase in hypoglycemia risk was independently associated with decreasing age (by a factor of 0.5 for a reduction of 1 year in age), increased daily insulin dose (by a factor of 1.5 for a 0.1 unit \cdot kg⁻¹ \cdot day⁻¹ increase in dose), and increased weight SDS (by a factor of 1.9 for a 1.0 increase in weight SDS) (Table 3). Increase in nocturnal hypoglycemia risk was independently associated with decreasing age (by a factor of 0.6 for a year less in age), increased daily insulin dose (by a factor of 1.6 for a 0.1 unit \cdot

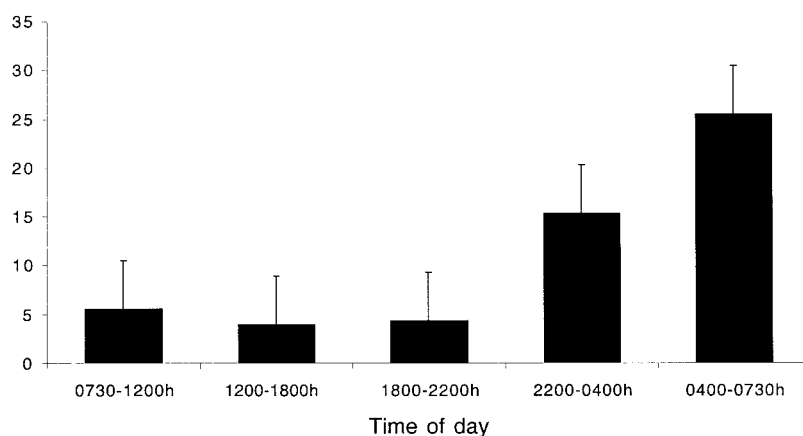


Figure 1—Hypoglycemia prevalence (%) in relation to time of day.

kg⁻¹ · day⁻¹ increase in dose), insulin regimen (by a factor of 0.2 on a BID compared with a TID regimen), and increased weight SDS (by a factor of 2.7 for a 1.0 increase in weight SDS) (Table 3). There was no relationship with HbA_{1c} or duration of diabetes.

CONCLUSIONS— Use of the Medtronic Minimed CGMS detects glucose variability that is not identified by conventional finger-prick measurements (23) and has been used to previously confirm the high prevalence of childhood hypoglycemia (24). Extensive studies have validated the agreement and accuracy of sensor readings compared with conventional glucose monitors (19). However, other evidence suggests the gradient between blood and interstitial fluid glucose may be increased when plasma glucose is lowered, which may result in artificially lower sensor estimates of blood glucose concentrations (25). Our data show that the CGMS has a tendency to read lower glucose values than conventional meters, with decreasing agreement between the two methods for glucose values in the hypoglycemic range. However, our data on accuracy of the CGMS together with consistency of our findings using different definitions of hypoglycemia (<60 and <45 mg/dl) show that these discrepancies are modest and our results are reliable. This is the first study using the CGMS to describe and compare the characteristics and risk factors for hypoglycemia in children on standard insulin regimens.

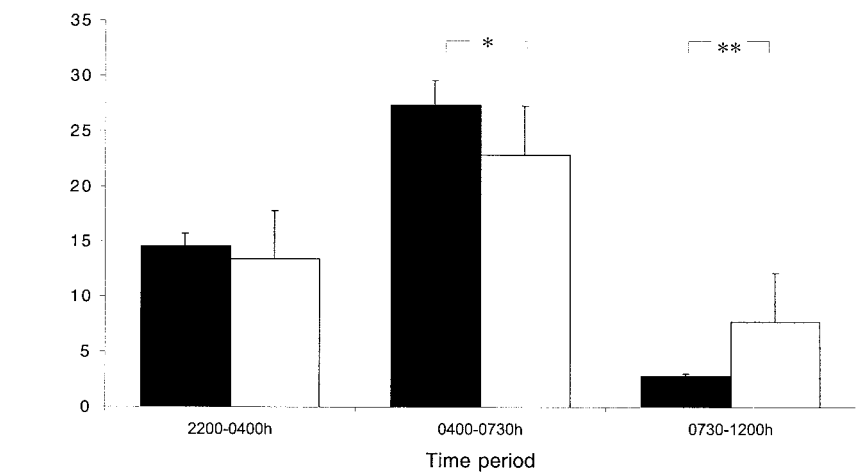


Figure 2—Hypoglycemia prevalence (%) in relation to time of night and morning. *P = 0.005; **P < 0.001. ■, BID; □, TID.

We found hypoglycemia to be more prevalent at night, when episodes were prolonged and largely asymptomatic. Of our cohort, 43% demonstrated hypoglycemia on at least two of three nights. The effects of recurrent, nocturnal hypoglycemia have not yet been fully evaluated. However, when compared with healthy control subjects, evidence shows children with type 1 diabetes have a range of cognitive defects, particularly in those with early-onset diabetes and with previous severe hypoglycemic episodes (7,26). Other studies show alterations in mood that could affect school performance the fol-

lowing day (27) and that, in the longer term, altered cognition in younger children (26) and persisting electroencephalogram abnormalities in older children (28). There is clear evidence for a blunted counter-regulatory response (3) and, in adolescents, nocturnal hypoglycemia has been linked to cardiac arrhythmias and sudden death (29). However, further investigation is required to determine the consequences of nocturnal hypoglycemia in this age group.

Previous reports of risk factors for hypoglycemia vary among studies, and this is in part related to differences in populations, ascertainment of data, definitions of outcome, and statistical analysis, thus making comparisons among studies difficult. Furthermore, these studies are limited by being reliant on conventional finger-prick glucose measurements (6,9,12), reporting of only moderate or severe hypoglycemia (6,7,9,10,12,14–18), and retrospective patient recall of hypoglycemic events (6,9,13).

The prolonged and asymptomatic nocturnal hypoglycemic episodes compared with daytime may be explained by the patients' actions against symptomatic hypoglycemia while awake that result in quicker recovery from hypoglycemia. However, there is clear evidence of blunted counter-regulation in association with recurrent nocturnal hypoglycemia (3,30). In addition, unlike previous studies (14,31), our results show that use of standard insulin regimens contribute to nocturnal hypoglycemia risk, independent of other covariates. The kinetics of medium and short-acting insulin used in

Table 3—Conditional logistic regression model, with presence or absence of hypoglycemia (either >24 h or overnight only) as the dependent variable and independent covariates as listed (see text for detailed explanation)

	β	P	Exp (β)	95% CI for Exp (β)
Over 24 h				
HbA _{1c} (%)	-0.5	0.06	0.6	0.3–1.0
Duration of diabetes (years)	0.1	0.2	1.2	0.9–1.4
Age (years)	-0.6	0.001	0.5	0.4–0.8
Daily insulin dose (units · kg ⁻¹ · day ⁻¹)	0.4	0.007	1.5	1.1–1.9
Insulin regimen	-0.03	0.9	0.9	0.3–3.4
Weight SDS	0.7	0.04	1.9	1.0–3.6
Overnight				
HbA _{1c} (%)	-0.5	0.1	0.6	0.3–1.1
Duration of diabetes (years)	-0.1	0.5	0.9	0.7–1.2
Age (years)	-0.6	0.005	0.6	0.4–0.8
Daily insulin dose (units · kg ⁻¹ · day ⁻¹)	0.5	0.003	1.6	1.2–2.2
Insulin regimen	-1.8	0.03	0.2	0.1–0.9
Weight SDS	1.0	0.02	2.7	1.2–6.3

T1D and BID regimens result in periods of high free insulin levels (31,32). As duration of action of NPH insulin is up to 10 h (33), on a T1D regimen free insulin levels tend to be higher in the morning as compared with those on a BID regimen (4). Free insulin levels may also be affected by exercise, site of injection, temperature, and day-to-day intraindividual variation in rate of insulin absorption, which may vary by up to 50% (5). Together, these factors may induce a shift in timing of over-insulinization to between 0400 and 0730 h on a BID regimen and 0730 and 1200 h on a T1D regimen. This, together with blunted counter-regulatory responses (3) and lack of balance between carbohydrate supplementation and insulin therapy, may influence the timing of hypoglycemia on one regimen compared with the other, rather than indicate the benefit of one regimen over the other.

In keeping with other studies, nocturnal hypoglycemia risk was associated with younger age (9,14). This may reflect difficulties in achieving adequate control at this age together with differing levels of patient education, attitudes of the diabetes team to young diabetic subjects, and blunted counter-regulation in the young (3). Furthermore, the patterns of growth hormone (GH) secretion may vary with age and affect nocturnal glucose levels, such that in adolescence GH hypersecretion may account for the dawn rise in glucose levels (31), whereas in prepubertal children GH secretion may be similar to nondiabetic control subjects.

Similar to previous studies (7,18), hypoglycemia risk was associated with increasing insulin dose, possibly as a result of attempts at improving glycemic control; however, this was not accompanied by a lowering in HbA_{1c}. One consequence of this management strategy may be the strong association of hypoglycemia risk with weight SDS, which has not previously been described. A similar lack of association of hypoglycemia risk to glycemic control has been reported in some studies (7,12,13,17,18) but not in others (9,14,16). In the Diabetes Control and Complications Trial (DCCT), those clinics with highest median HbA_{1c} (>7.3%) had similar rates of hypoglycemia as those with lowest median HbA_{1c} (<6.8%) (34). These important findings suggest that management aimed at reducing hypoglycemia prevalence need not adversely affect prevailing HbA_{1c} levels. Clearly, the

causes of hypoglycemia are multifactorial, and confounding factors such as exercise, previous hypoglycemia, and poor injection technique have not been included in our study.

Strategies to alleviate prevalence of hypoglycemia include alterations in the bedtime carbohydrate intake and content and reductions in overnight insulin dose, possibly at the expense of increased hyperglycemia. However, the balance between over- and under-insulinization using these types of insulin and frequency of injections is difficult to achieve, although studies show it is possible to achieve good control without increasing hypoglycemia while on multiple injection therapy and receiving active psychological support and education (13). Reports of use of insulin pumps show improved glycemic control while reducing hypoglycemia (35), and new medium-acting insulin analogs show improved pharmacokinetic profiles (36). However, randomized controlled trials are lacking.

In summary, use of CGMS has confirmed the disturbingly high hypoglycemia prevalence in prepubertal diabetic children on standard insulin regimens, particularly at night, when episodes are prolonged and asymptomatic. Nocturnal hypoglycemia risk was associated with younger age, increasing insulin dose, insulin regimen, and increased weight, but not HbA_{1c} or duration of diabetes. The timing of hypoglycemic episodes on one insulin regimen compared with the other may reflect differences in insulin kinetics, together with defective counter-regulatory mechanisms and inadequate carbohydrate intake. The significance of such findings needs to be established before intensification of insulin therapy becomes commonly adopted in this age group.

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