Prevalence of impaired awareness of hypoglycemia and identification of predictive symptoms in children and adolescents with type 1 diabetes

Running title

Hypoglycemia in children with diabetes

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Title

Prevalence of impaired awareness of hypoglycemia and identification of predictive symptoms in children and adolescents with type 1 diabetes

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Abstract

Background: In children with type 1 diabetes the prevalence of impaired awareness of hypoglycemia (IAH) is uncertain. The present study aimed to ascertain this with greater precision. Secondary aims were to assess symptoms of hypoglycemia and which of these best predict awareness of hypoglycemia in children.

Methods: Questionnaires were completed by 98 children with type 1 diabetes (mean age 10.6 years) and their parent(s); hospital admission data for the previous year were collected. Awareness of hypoglycemia was assessed using two questionnaire-based methods that have been validated in adults. For four weeks, participants performed routine blood glucose measurements and completed questionnaires after each episode of hypoglycemia. Principal components analysis determined how symptoms correlate; multinomial logistic regression models identified which symptom aggregate best predicted awareness status.

Results: The "Gold" questionnaire classified a greater proportion of the participants as having IAH than the "Clarke" questionnaire (68.4% versus 22.4%). Using the "Clarke" method, but not the "Gold" method, children with IAH were younger and more likely to require external assistance or hospital admission. Most aged ≥9 years (98.6%) were able to self-assess awareness status accurately. Puberty and increasing age, augmented symptom scores; duration of diabetes and glycemic control had no effect. In contrast to adults, behavioral symptoms were the best predictors of awareness status.

Conclusions: IAH affects a substantial minority of children and impending hypoglycemia may be heralded by behavioral symptoms. The "Clarke" method was more effective at identifying those at increased risk and could be used as a screening tool.

Key words:

Type 1 diabetes

Hypoglycemia

Impaired awareness of hypoglycemia

Symptom scores

Principal components analysis

Abbreviations:

Impaired awareness of hypoglycemia (IAH)

Type 1 diabetes mellitus (T1DM)

Continuous glucose monitoring (CGM)

Continuous subcutaneous insulin infusion (CSII)

Introduction

Hypoglycemia is the commonest side-effect of insulin therapy and interferes with everyday activities (1). Cognitive impairment associated with hypoglycemia may prevent a child from seeking help, so delaying treatment. Severe hypoglycemia is inversely associated with age (2) and glycemic control (3), but is not strongly associated with duration of diabetes (4, 5). Continuous glucose monitoring (CGM) has suggested that nocturnal hypoglycemia occurs approximately every third night and is associated with strict glycemic control and younger age (6).

In adults, hypoglycemia symptoms show substantial inter-individual variation and can be categorized into autonomic, neuroglycopenic and non-specific groups; children are unable to distinguish autonomic from neuroglycopenic symptoms (7-9). The blood glucose levels at which these symptoms are generated are associated with inter- and intra-individual variation according to factors such as prevailing glycemic control and exposure to antecedent hypoglycemia (10). Symptoms differ in children compared to adults, particularly with respect to age and pubertal status (8, 11). Behavioral changes, such as becoming naughty or irritable, often alert parents to the presence of hypoglycemia (8, 9).

In adults, recurrent hypoglycemia increasingly impairs the normal defenses against hypoglycemia and diminishes the ability to detect hypoglycemia. The glycemic threshold at which autonomic symptoms are triggered is re-set at a lower blood glucose level. Cognitive dysfunction can then precede the onset of autonomic symptoms and interfere with the ability to initiate corrective action (12). Impaired awareness of hypoglycemia (IAH) is a syndrome in which the ability to detect the onset of hypoglycemia is diminished or absent (12).

Counter-regulatory hormonal failure is not the direct cause of IAH as avoidance of hypoglycemia results in improved symptom perception without restoration of the normal counter-regulatory response (13). Nevertheless, the two are closely related, usually co-segregate and probably share a common pathogenesis (14). In adults, IAH carries up to a six fold higher risk of severe hypoglycemia (15, 16).

The prevalence of true IAH is uncertain in children. The recognition of hypoglycemia involves a complex interplay of psychological and physiological factors. Some children may fail to interpret symptoms and react appropriately; this does not mean that they do not experience symptoms of hypoglycemia. The present study investigated the prevalence of IAH in children with T1DM using two methods of assessing awareness status that have good concordance in adults with T1DM (17). Secondary aims were to assess the frequency and symptomatology of hypoglycemia in children and to determine which symptoms best predicts awareness of hypoglycemia.

Methods

Children and adolescents attending pediatric diabetes clinics in the Lothian region of Scotland were recruited; the clinic population was approximately 340 and had a mean DCCT-aligned HbA1c of 71 mmol/mol (8.62%) in the year of survey. Inclusion criteria were T1DM of at least six months duration and measurement of blood glucose three or more times per day with no exclusion criteria. Permission for the study was obtained from the local ethics advisory committee.

Each participant and one of their parents were asked to complete separate baseline questionnaires with a researcher present to answer any queries; the participant completed their questionnaire without assistance from their parent(s). Recognizing that the pediatric population often requires assistance to treat hypoglycemia, severe hypoglycemia was subdivided into events requiring third party assistance and those requiring hospital admission. Awareness of hypoglycemia was assessed using two validated questionnaire-based methods that have been compared in adults, designated the "Clarke" and "Gold" methods, after the first author of each paper (15, 17, 18). The Clarke questionnaire uses eight questions to determine awareness status whereas the Gold questionnaire uses a simple 7-point Likert scale (1 = always aware of hypoglycemia, 7 = never aware of hypoglycemia). American terminology was modified where necessary to reflect British vocabulary. With both methods a score is calculated; a score of 1 or 2 was classified as *aware*, a score of 3 or more classified as *IAH*.

Typical clinical features observed by parents and experienced by children during hypoglycemia were based on a previous study by our group (9); in a similar cohort of

children and parents, good correlation existed between clinical features perceived by the children and observed by their parents (see on line appendix for questionnaires). Because parents cannot directly observe some of the possible symptoms (e.g. headache); they were encouraged to use their own observations and determine which symptoms were present in conversation with their children. Although pallor is a sign, all clinical features in this present paper are referred to as "symptoms" to maintain consistency with previous literature (8, 9). Symptom intensity was estimated using a 7-point Likert scale (1=symptom not present, 7=very intense).

Based on the first few responses of the child to the baseline questionnaire, it was left to the discretion of the parent and the researcher as to whether the participant was likely to understand the remaining questions. If it was evident that they did not understand the questions, then only the parental questionnaire was completed. Participants were asked to record blood glucose at least three times per day, for four weeks. For any blood glucose readings <4 mmol/l, both the parent and participant were asked to complete hypoglycemia questionnaires prospectively, to document blood glucose, hypoglycemia recognition (self, third party or meter), assistance required (self-treated, third party or hospital attendance) and symptoms experienced (using a 7-point Likert scale). This biochemical level was chosen to determine potential hypoglycemic events because 4.0 mmol/L is the alert level for avoidance of hypoglycemia recommended by Diabetes UK, the principal diabetes charity in the UK.

Retrospective review of case records and growth charts were used to determine whether peak height velocity (PHV) or menarche had been achieved. Male participants were classified as pre-pubertal if they were <10.5 years old when surveyed and those aged ≥10.5 years who had not reached PHV within 6 months of survey were considered to be of uncertain pubertal

status. Male participants were considered pubertal if PHV was achieved within six months of survey. Female participants were classified as being pre-pubertal if they were <9.5 years old and those aged ≥9.5 years who had not achieved PHV were considered to be of uncertain pubertal status. Female participants were considered pubertal if they had reached menarche or PHV.

Specimen processing: HbA1c was measured by ion exchange HPLC using a hemoglobin testing system (Bio-Rad Laboratories, Munich, Germany; non-diabetic reference range 31-43 mmol/mol (5.0-6.05%); results were DCCT-aligned.

Statistical analysis: Results were analyzed using SPSS (version 18 for Windows, SPSS, Chicago, IL) and R, version 2.10 (19). Categorical variables were analyzed using Fisher's exact test and continuous variables using an unpaired t-test. Spearman's rank correlation was used to analyze reported symptoms and method of assessing awareness status. Principal Components Analysis was used to examine how symptoms aggregate, the number of factors was determined using a scree plot. A loading of >0.3 was considered significant (a loading is the strength of a given variable's relationship with the underlying factor and may take a value from -1.0 to +1.0). Multinomial logistic regression models were used to predict which aggregate of symptoms best predicts awareness status. Data are shown as median (range) or mean±SD, unless otherwise stated. A p value <0.05 was considered to be significant.

Results

Participant demographics: Ninety-eight participants completed the baseline questionnaire; 57 completed blood glucose diaries prospectively and questionnaires about any episode of hypoglycemia that occurred over the subsequent four weeks. The principal reason given for non-completion was time constraint. No significant baseline differences between completers and non-completers were found. Approximately half of the participants (n=52, 52.5%) were taking a biphasic insulin in the morning followed by a short-acting insulin before their evening meal and a basal (long-acting) insulin in the evening. Most other patients (n=44, 44.4%) used a basal bolus insulin regimen and one used CSII with an insulin pump.

Awareness status: Satisfactory completion of the questionnaire by the child was deemed to have occurred if their awareness status according to the Clarke method could be determined. Awareness status could be determined in 70 children (98.6%) aged nine or over but in only seven (25%) under the age of nine. Table 1 shows baseline demographics by awareness status (Clarke method); both younger age and younger age at diagnosis were significant predictors of IAH. No difference in awareness status was found between different insulin regimens (basal-bolus vs. biphasic, p=0.81, Fisher's) or between those completing versus those not completing the period of blood glucose monitoring (p=0.14, Fisher's).

Clarke and Gold Methods compared: Figure 1 displays a comparison of self-reported or parentally-determined awareness status using both the Gold or Clarke methods. Using the Clarke method, 22 (22.4%) parental responses indicated that IAH was present compared with 67 (68.4%) parental responses using the Gold method. A significant association was observed between the parents' and children's responses when using the Clarke method

(p=<0.001, r_s=0.55, Spearman's) but no positive correlation was found using the Gold method (p=0.28, r_s=0.12, Spearman's). No linear correlation was found between the two methods (p=0.14) with little or no positive correlation (p=0.14, r_s=0.25, Spearman's). Previous studies have demonstrated that young people with IAH have an increased risk of hypoglycemia requiring medical attention (20). While this was evident when participants were classified using the Clarke method (see below), it was not apparent when using the Gold method (Aware vs. IAH, p=1.00, Fisher's). Similarly, no significant increase was observed in hypoglycemia requiring third-party assistance between those with normal awareness or IAH using the Gold method (p=0.08, Fisher's). Therefore the Gold method did not show any of the expected differences in baseline demographics between awareness states. For the reasons outlined above, the Clarke method, assessed using parental responses, was considered a more effective and reliable predictor of awareness status in this pediatric cohort and so was used thereafter to categorize awareness status.

Recognition and frequency of hypoglycemia: Participants completed a mean of 4.4 tests per day over the four week period with mean (±SD) blood glucose 9.7 mmol/l (±4.8) with no difference in testing frequency between awareness states (p=0.67, t-test). Hypoglycemia (defined as blood glucose <4.0mmol/l) was experienced by almost all participants (97%) while more than two thirds (70.2%) had experienced at least one blood glucose <3.0mmol/l. Over the four week period the mean (±SD) number of blood glucose readings <4.0mmol/l and <3.0mmol/l were 10.2 (±7.3) and 2.3 (±2.6) respectively. The number of blood glucose readings less than 3.0mmol/l, per participant, was not affected by insulin regimen (basal-bolus vs. any biphasic, p=0.70, t-test), awareness status (p=0.29, t-test), age (<10 years compared with >12.65 years, p=0.93, t-test), HbA1c <69mmol/mol (8.5%) compared with >78mmol/mol (9.3%), p=0.65, t-test) or duration of diabetes (<2 years compared with ≥5

years, p=0.18, t-test). During the period of prospective monitoring, hypoglycemia questionnaires were completed for 490 of 583 (84.0%) episodes of hypoglycemia recorded in the participants' blood glucose diaries; three of these events required hospital admission. Hypoglycemia was most frequently reported in the late afternoon with 31.8% (n=156) of events occurring between 15:00h and 18:59h, and was least commonly reported overnight with 9.2% (n=45) of episodes between 23:00h and 06:59h. Participants with normal awareness were more likely to recognize hypoglycemia themselves, with 48.2% of hypoglycemic events being recognized by children in the aware group compared with 37.5% in the IAH group (p<0.05, Fisher's). All parents were poor at recognizing hypoglycemia with 3.7% of parents recognizing hypoglycemia in the aware group compared with 6.3% in the IAH group (p=0.29, Fisher's); the remaining episodes were incidental findings on routine biochemical testing.

Hypoglycemia requiring third-party assistance or hospitalization: Third-party assistance was more commonly required in those categorized as having IAH (figure 2) and in younger participants (p=0.0001, t-test). Increasing independence of children as they became older was demonstrated: 82% of the lower age tertile required assistance to treat hypoglycemia in the preceding six months compared with 15% of the upper age tertile (p=0.0001, Fisher's). Hospital data were reviewed for each patient in the 12 months preceding clinic attendance. Seven participants (7.1%) required hospital treatment for hypoglycemia-related events in the 12 months before admission, one patient attended twice. Two of these episodes were associated with seizure and six participants required in-patient admission. A significantly greater proportion of patients with IAH required hospital treatment compared with those with normal awareness (figure 2). Accurate retrospective parental recall of hypoglycemia requiring hospital treatment was demonstrated with eight parents reporting hypoglycemia

requiring hospital attendance in the preceding 12 months; one parent incorrectly attributed the primary cause of the admission to hypoglycemia.

Symptomatology of hypoglycemia: Symptoms are listed in the hypoglycemia questionnaires supplied as an on-line appendix. The most commonly reported symptoms by children were trembling (82.3%) and weakness (70.6%). Parents commonly observed behavioral symptoms including irritability (66.7%) and aggressiveness (46.5%); pallor as a feature of hypoglycemia was reported by 51.5%. Principal components analysis (PCA) was used to identify subgroups of symptoms. Two separate PCAs were performed; scree plots suggested that parentally reported symptom data could be adequately explained by four components and self-reported symptoms by three components. The respective number of components was then extracted using PCA, followed by Varimax rotation with Kaiser Normalization. Using parental reporting the symptoms segregated into "autonomic", "neuroglycopenic", "behavioral" and "non-specific" rotate components and using self-reporting the symptoms segregated into "autonomic/neuroglycopenic", "behavioral" and "non-specific". Once segregated into these components, the loading patterns were used to form symptom scores for each rotated component. Parentally-reported symptom intensity scores were significantly lower in participants with IAH for autonomic symptoms (p=0.006, t-test) but not for neuroglycopenic or behavioral symptoms (p=0.09 and p=0.20 respectively, t-test). Diabetes duration or current age did not affect the likelihood of symptom loss (p=0.10 & p=0.19 respectively, t-test). Participants with IAH were more likely to report symptom loss than those with normal awareness (31.8% vs. 7.9%, p=0.008, Fisher's).

Multinomial logistic regression models were fitted to the data using the "mlogit" library of "R" (19). Parentally-reported symptom subgroups ("behavioral", "neuroglycopenic",

"autonomic" and "non-specific") were compared as predictors of awareness using four models to predict the probability of a particular outcome (i.e. parentally reported awareness of hypoglycemia), from the factor score in each of the four symptom classes. Factor scores for each of the four symptom classes were conventionally derived from factor analysis by regression method. Each model is a multinomial logistic regression model of a symptom subgroup in which the factor score is the predictor of a multinomial outcome consisting of two awareness states; aware and impaired. Consequently each model estimated a slope coefficient representing change in relative risk of choosing aware over impaired for unit increase in the factor score. The model-predicted probability of the particular outcome choice "aware" was obtained from the relative risks over a range of factor scores. Figure 3 shows the model-predicted probability of choosing aware over impaired as a function of the factor score in each of the four symptom groups. The best fitting model used behavioral symptoms as a predictor and was the only model to achieve significance ($p<0.01$), according to the chi-squared likelihood ratio test comparing the full model with an intercept-only model (Nagelkerke R-squared for the behavioral model was 0.18). The behavioral group of symptoms was therefore the best predictor of awareness status. The same procedure was then used to compare how the behavioral symptom group predicted hypoglycemia awareness as determined by the Clarke and Gold methods, either self- or parentally-reported; the two that used the Clarke method were significant ($p<0.05$). The use of behavioral symptoms and the Clarke method, whether obtained from the parent or the child's observations, were better at predicting awareness status than the Gold method.

Effect of puberty on hypoglycemic symptoms: A greater proportion of female participants in the present study had reached puberty in comparison with male participants (62.8% vs. 47.9% of participants respectively). Participants of uncertain pubertal status were excluded

from further analysis (n=9 (9.1%) of whom 5 were male). Total symptom scores increased significantly in participants that had reached puberty (pre-pubertal vs. pubertal or post-pubertal, $p<0.001$ for both parental and self-reporting of symptoms, t-test). Sweating and trembling showed the largest increments in symptom score.

Discussion

In the present study, two questionnaires used in adults to assess hypoglycemia awareness were applied to a pediatric cohort to evaluate their value in assessing awareness status in children and adolescents. In contrast to observations in adults in which these two methods showed good concordance (17), the results correlated poorly in children with T1DM (figure 1). When categorized using the Clarke questionnaire, participants with IAH had a significantly greater risk of requiring third-party assistance or hospital admission to treat hypoglycemia, thus identifying an "at risk" subset of children that was not identified using the Gold method. Children may have difficulty in comprehending the solitary wide-ranging question of the Gold method compared with the closed and specific questions of the Clarke method.

The Clarke method indicated that 22.4% of children with T1DM of relatively short duration (mean 3.9 years) had IAH. An Australian study (mean duration of diabetes, 5.4 years) used the Clarke method and reported a similar prevalence of 29%; in both studies, the participants with IAH were significantly younger (20). The development of IAH was attributed to progressive counter-regulatory hormonal failure, although no relationship was found between IAH and duration of diabetes. As in the present study, IAH was associated with a higher frequency of severe hypoglycemia (37.1 vs. 19.3 episodes per 100 patient years) (20). A Hungarian group used a single question to determine awareness status; the 36.9% of participants who were "sometimes" or "never" aware of hypoglycemia were classified as having impaired awareness (21). The DirecNet study group claimed that Hypoglycemia Associated Autonomic Failure (HAAF) was present in one third (22). Limitations with the DirecNet study design make the results difficult to interpret; the mean blood glucose nadir in

this cohort with good glycemic control, may not have been sufficiently low to provoke a counter-regulatory response (23). While counter-regulatory hormonal failure does co-segregate with IAH in adults with T1DM it is not the cause of IAH *per se* (13, 14). Taken as a whole, the above studies would suggest that the prevalence of impaired awareness is 22-37%.

Hypoglycemia may be difficult to identify in a younger age group due to limited vocabulary and an inability to describe subjective sensations as specific symptoms. In the Australian study only children between the ages of 10-12 years and their parents were both asked to complete the questionnaire; older children completed the questionnaire by themselves while the parents did this on behalf of the younger children (20). The present study demonstrated that children aged 9 years or above can provide sufficient information to allow an accurate assessment of their awareness status and that their assessment closely matched that of their parents. All participants in the present study, but particularly those with IAH, were poor at self-identification of hypoglycemia with most episodes being detected by an observer or by biochemical measurement. This suggests that asymptomatic hypoglycemia is common, and this has been confirmed using CGM (6, 24). Other studies have reported poor recognition of hypoglycemia, with parents and children failing to detect hypoglycemia in >50% and >40% of instances, respectively (25). Surprisingly, parents were poor at recognizing hypoglycemia. Factors that may impair a parent's ability to recognize a hypoglycemic episode in their child might include distraction, educational attainment and the level of independence of the child with regard to self-management of their diabetes. Parents' retrospective recall of hypoglycemia requiring hospital treatment was confirmed to be robust for up to 12 months.

Almost all participants experienced at least one episode of confirmed hypoglycemia (blood glucose <4.0mmol/l) over a 4 week period with two thirds experiencing at least one blood glucose <3.0 mmol/l. This compares with 52% over three months in a previous study (26). The present study reported the lowest frequency of hypoglycemia when children were asleep. However, overnight blood glucose testing was not undertaken routinely, so underestimating the frequency of nocturnal hypoglycemia, as only symptomatic episodes, which would have caused the person to waken, were identified. Catecholamine responses to hypoglycemia are attenuated or absent during sleep and asymptomatic nocturnal hypoglycemia is common (6, 27).

Commonly experienced symptoms during hypoglycemia in children have been documented previously, with strong agreement in terms of symptom intensity being demonstrated between children and their parents. In the present study pallor was observed by 51.5% of parents, consistent with previous reports (8). In a cohort of T1DM adults with a short duration of diabetes (mean 3.9 years), with the exception of glucagon deficiency, the prevalence of counter-regulatory hormonal deficiencies would be anticipated to be low (28). A small proportion of the present study cohort (n=11, 11.1%) had a clear diminution or absence of hypoglycemia symptoms; hormonal responses were not measured so co-existing counter-regulatory failure cannot be excluded. With increasing duration of diabetes and exposure to antecedent hypoglycemia, some reduction in symptom intensity might be expected; this is apparent in adults with T1DM, where the prevalence of IAH rises progressively with duration of diabetes (29).

Principal components analysis (PCA) was used to show the latent structure of hypoglycemic symptoms. As reported previously (8), the children were unable to distinguish between

autonomic and neuroglycopenic symptoms, resulting in three symptom subgroups ("behavioral", "neuroglycopenic/autonomic" and "other") in comparison to four subgroups with parental reporting. Tupola *et* al (1998) did not ascertain the full contribution of behavioral symptoms when assessing episodes of hypoglycemia (26). Multinomial logistic regression showed that autonomic and behavioral symptom groups, whether experienced by the child or perceived by the parent, could be used to predict awareness status using the Clarke method (figure 3). In contrast with the adult population, behavioral symptoms were the most useful in predicting awareness status, which may suggest that a behavioral component may contribute to the development of IAH. Behavioral symptom intensity was not significantly lower in participants with IAH.

When the effect of puberty on hypoglycemia symptomatology was examined previously in a small group of children and adolescents with T1DM, sweating was not observed during hypoglycemia in pre-pubertal children (9). Maturation of sweat glands occurs during puberty, which may augment the sweating response. In the present study symptom intensity increased significantly with puberty in all symptom categories, with scores for trembling and sweating showing the largest increments. The generally higher symptom scores could be attributed to increased physical and emotional maturity. The effect of ageing on symptom scores has been reported previously (26), and with increasing independence and self-treatment, a parent would become less cognizant of the type and intensity of the symptoms experienced by their child.

The main limitations of the present study are the small sample size and completion rate of 58%. Despite these limitations, many findings were highly significant and consistent with those reported previously. The present study was pragmatic, so nocturnal blood glucose

testing was not obligatory and CGM was not utilized as neither are part of routine clinical care. The frequency of asymptomatic hypoglycemia may therefore have been underestimated, particularly during sleep. In retrospect, pubertal assessment using a recognized staging method would have reduced the proportion of participants in whom pubertal status was uncertain (30).

In summary, the recognition of hypoglycemia by children with T1DM is a dynamic process. Various factors, including the distraction of concurrent physical or mental activities can delay recognition of hypoglycemia and corrective action. The underlying pathophysiological mechanisms of IAH include a blunted sympatho-adrenal response combined with altered cognitive and behavioral responses to hypoglycemia. Each factor is modulated by a variety of mechanisms and so may alter in importance with each child as they progress through adolescence into adulthood. Increasing physical and mental maturation may result in improved ability to identify and appreciate the significance of early warning symptoms, allowing earlier corrective action to be taken.

In contrast with the adult population, the ability to predict awareness status is strongest when behavioral symptoms are used. Behavioral patterns are therefore particularly important in the recognition of hypoglycemia in children and introduce the concept of a "voluntary" component to hypoglycemia awareness. Behavioral modification techniques could be used to make a potentially rewarding activity (the child receives increased parental attention and a sugary snack) less attractive. Placing more emphasis on the significance of behavioral symptoms, rather than the traditional autonomic symptoms (e.g. sweating and shaking), may improve the ability of parents and health care professionals to identify hypoglycemia. Clinicians may consider utilizing the Clarke questionnaire to screen for IAH allowing the

identification of an “at risk” cohort within their pediatric clinic population. The awareness status of children may change over time and therefore longitudinal studies are required to characterize any temporal changes associated with hypoglycemia awareness.

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Declaration of competing interests

Nothing to declare

Tables

Table 1: Baseline characteristics of study participants

Awareness status (Clarke method)	Aware	Impaired Awareness of Hypoglycemia	*p* value
n (% female)	76 (52.6%)	22 (45.5%)	*p*=0.63
Current age (years)	12.0 (10.5-13.3)	8.2 (5.7-10.5)	*p*=0.0001
Duration of diabetes (years)	4.1±3.2	3.2±2.0	*p*=0.24
Age at diagnosis (years)	7.4 (4.1-10.1)	4.2 (2.7-6.7)	*p*=0.012
HbA1c at clinic (mmol/mol(%))	74±9 (8.9±1.0)	72±9 (8.7±1.0)	*p*=0.46
Family history of T1DM* (n (%))	8 (10.5%)	3 (13.6%)	*p*=0.71
Data are median (interquartile range) or mean ± SD unless otherwise indicated *parent or sibling with T1DM			

Illustrations

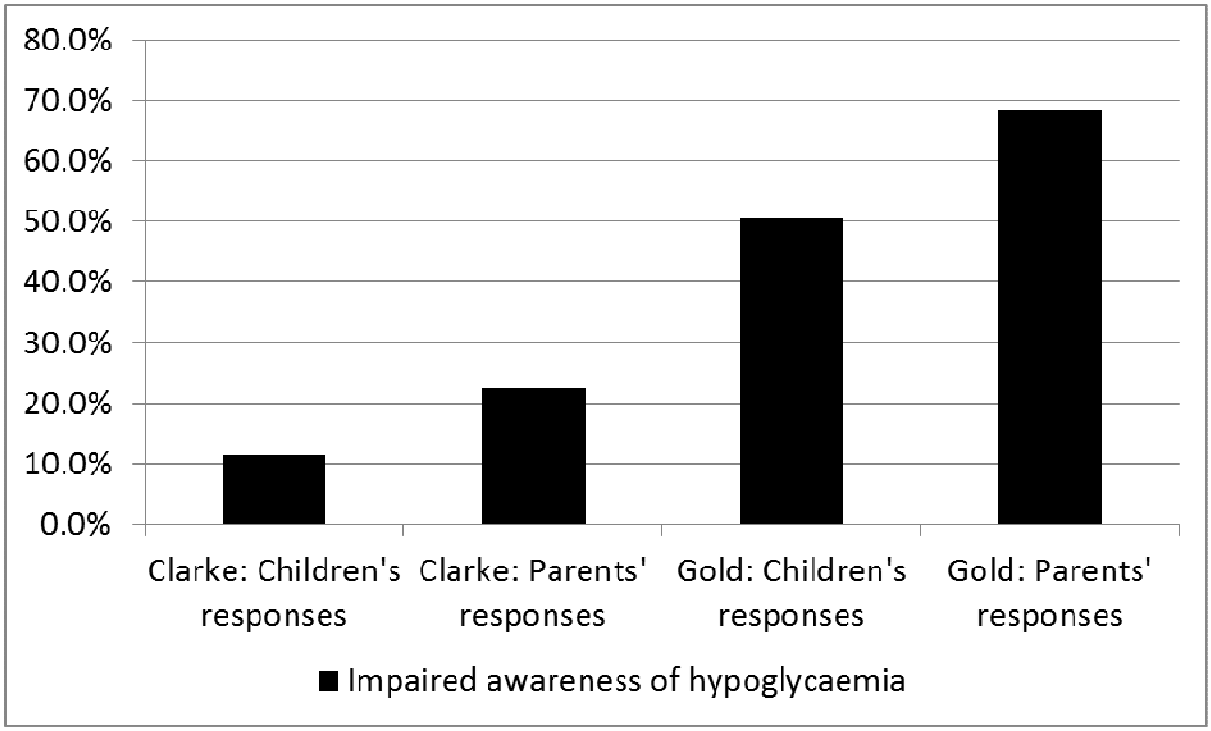

Figure 1: Awareness status according to Clarke or Gold methods using parental or child responses (of those able to answer)

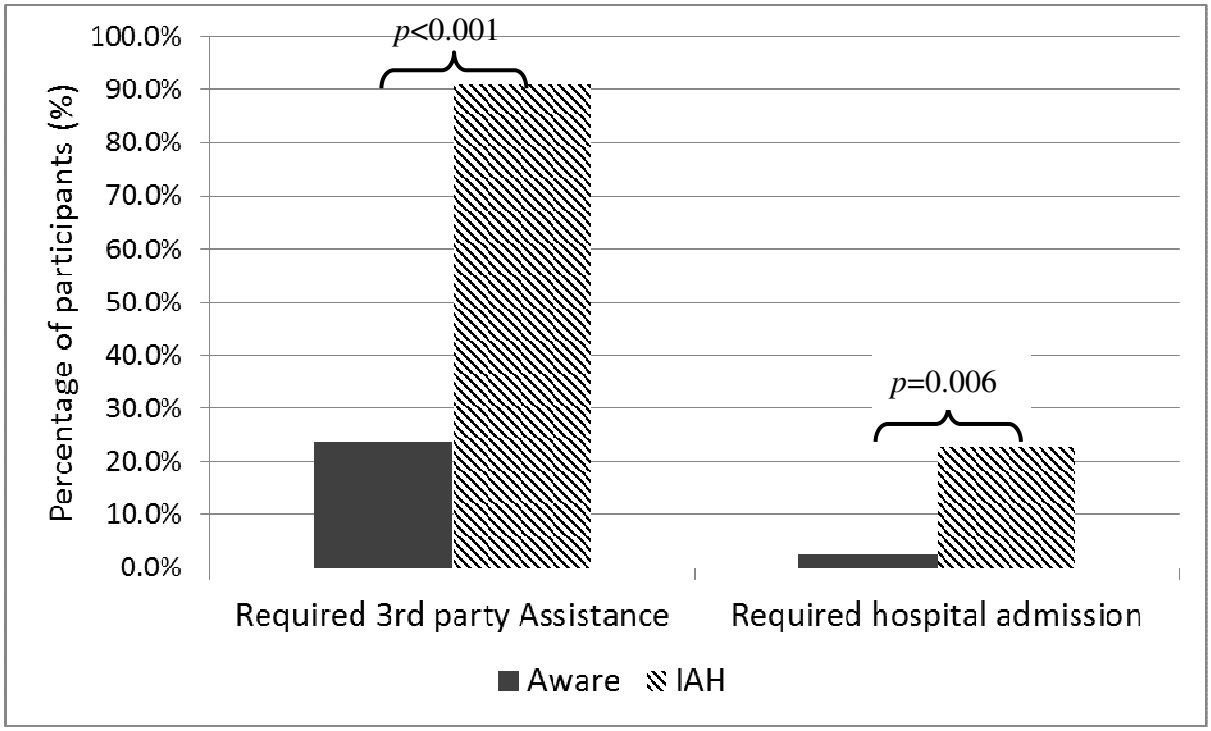

Figure 2: Proportion of participants requiring 3rd party assistance or hospital admission according to awareness status (p values given above, Fisher's)

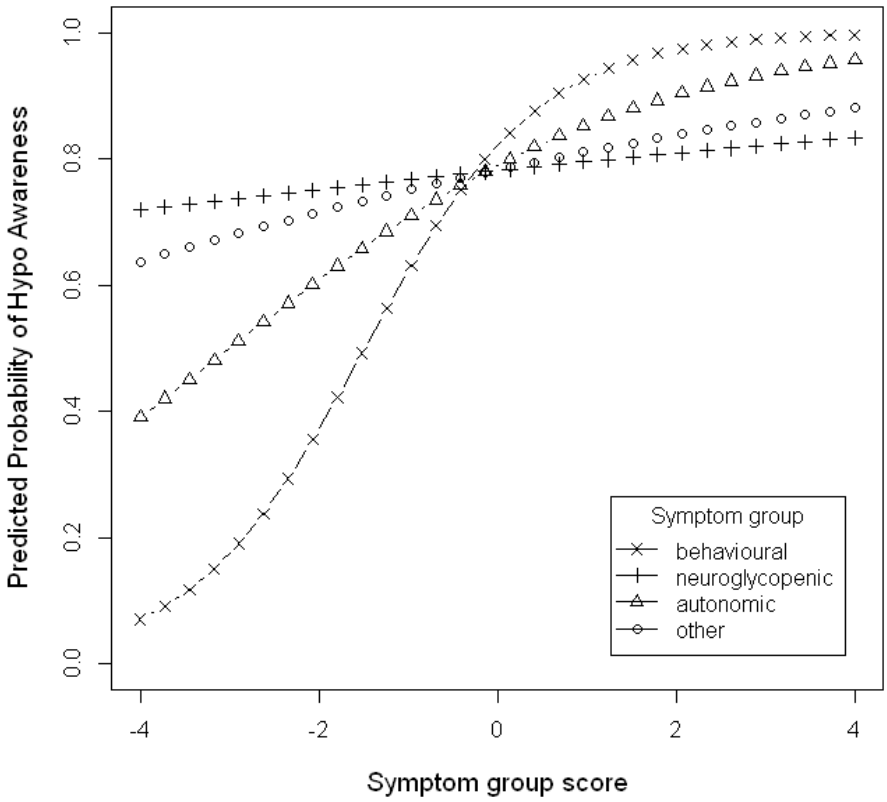

Figure 3: Probability of each symptom group predicting awareness status (Clarke method using parental responses)

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