Impaired awareness of hypoglycemia in a population-based sample of children and adolescents with type 1 diabetes

Running title: Impaired hypoglycemia awareness in Type 1 diabetes

Trang T. Ly MBBS\textsuperscript{1} Patricia H. Gallego MD, MSc\textsuperscript{1} Elizabeth A. Davis FRACP\textsuperscript{1,2} Timothy W. Jones FRACP MD\textsuperscript{1,2}

\textsuperscript{1}Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children, Perth, Western Australia, Australia
\textsuperscript{2}Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, Perth, Western Australia, Australia

CORRESPONDING AUTHOR
Associate Professor Timothy W. Jones
Email: Tim.Jones@health.wa.gov.au

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Impaired hypoglycemia awareness in Type 1 diabetes

Objective: To determine the prevalence and clinical associations of impaired awareness of hypoglycemia in a population-based sample of children and adolescents with type 1 diabetes.

Research Design and Methods: A validated questionnaire was administered to 656 patients with type 1 diabetes over a six-month period to determine hypoglycemia awareness status. Case ascertainment was 79% of the clinic population. The rate of severe hypoglycemia (SH) was determined by data collected prospectively in the preceding year.

Results: Impaired awareness of hypoglycemia was present in 29% of patients. Patients with impaired awareness of hypoglycemia had an earlier onset of diabetes (p<0.001), were younger (p<0.001), had lower mean levels of A1C since diabetes onset (p=0.006) and at their last visit (p=0.001). The overall rate of SH was 24.5 episodes/100 patient-years, in the preceding year. The SH rate was higher in those with impaired awareness of hypoglycemia (37.1 vs. 19.3 episodes/100 patient-years, p<0.001). Among patients aged below 6 years (n=46), 59% of care providers reported impaired awareness of hypoglycemia and the rate of SH was significantly higher in those reporting impaired awareness (33.3 vs. 5.2 episodes/100 patient-years, p=0.02). More patients with recurrent hypoglycemia reported impaired awareness of hypoglycemia (47% vs 28%, p=0.03).

Conclusions: A significant proportion of children and adolescents with type 1 diabetes have impaired awareness of hypoglycemia. Screening for impaired awareness is an important component of routine diabetes care and can identify patients at increased risk of a severe hypoglycemic event.
Hypoglycemia is a well-known complication of insulin therapy in children and adolescents with diabetes. The risk of recurrent and severe hypoglycemia causes significant anxiety and emotional morbidity for patients and their families and is a limiting factor in the achievement of tight glycemic control.

Hypoglycemia unawareness is defined as the onset of neuroglycopenia before autonomic activation (1). Patients have defective symptomatic and counterregulatory hormone responses to hypoglycemia and are unable to initiate self-treatment. This impaired awareness has been associated with severe hypoglycemia, accounting for 36% of the hypoglycemia that occurred while subjects were awake during the Diabetes Control and Complications Trial (2).

The neurological consequences of severe hypoglycemia are particularly important in the young child with type 1 diabetes. Hypoglycemia has been associated with a decrease in neurocognitive function in children with type 1 diabetes, particularly those diagnosed before the age of 5-6 years (3-5). Repeated hypoglycemic seizures in young children may also cause structural brain changes, as suggested by the prevalence of mesial temporal sclerosis in 16% of a cohort of children with early-onset type 1 diabetes (6). Severe hypoglycemia adds to the considerable burden of disease in families through increased anxiety, poor sleep, increased hospitalizations, excessive lowering of insulin dose and worsening of glycemic control (7).

For clinical and research purposes, determining the presence of hypoglycemia unawareness in children and adolescents with diabetes is important. Various methods have been applied, including the use of self-reporting symptom questionnaires, to inducing experimental hypoglycemia in the laboratory to determine the symptoms response threshold and counterregulatory hormone response.

The aim of this study is to determine the prevalence of impaired awareness of hypoglycemia in a large, population-based cohort of childhood-onset type 1 diabetes, assessed with a self-reporting questionnaire and to study the relationship between impaired hypoglycemia awareness and severe hypoglycemia.

**RESEARCH DESIGN AND METHODS**

**PATIENTS:** Children and adolescents with type 1 diabetes aged between six months and 19 years, and diabetes duration of at least 6 months, attending paediatric diabetes clinics at Princess Margaret Hospital were eligible to participate in the study. Princess Margaret Hospital is the only paediatric diabetes referral centre for the population of Western Australia and almost all children diagnosed with type 1 diabetes in the state are registered and treated here. Previous studies have shown that this centre has a case ascertainment close to 100% (8; 9). All patients have had ongoing prospective documentation from diagnosis at three monthly intervals, of hypoglycemic events, diabetic ketoacidosis and glycemic control, measured by A1C.

Patients and care providers had undergone extensive diabetes education during their initial inpatient admission at diagnosis, including the recognition and treatment of hypoglycemic episodes. All patients were given glucagon at discharge and care providers had been
instructed on its use. Insulin regimens included a combination of twice daily injections (NPH insulin and analog), through to 4 injections per day with analog insulins and continuous subcutaneous insulin infusion therapy.

**PROTOCOL:** A validated questionnaire to characterize hypoglycaemia unawareness was applied to children and adolescents and/or their care providers. This questionnaire was based on a tool used to assess reduced awareness of hypoglycaemia in an adult population by Clarke et al (10). This questionnaire has been shown to accurately identify patients with impaired awareness of hypoglycaemia for both clinical and research purposes (11). In this study, patients scoring ≤3 were categorised as having normal awareness and patients scoring ≥4 were categorized as having impaired awareness. The original items for scoring severe hypoglycaemia in the previous 12 months and moderate hypoglycaemia in the previous 6 months were not included in our questionnaire as this data was collected prospectively in this clinic population.

For children up to the age of 10 years or those who were unable to fill out the questionnaire, parents or care providers were asked to complete them. For children aged between 10 and 12 years, both care providers and children completed the questionnaire. Children aged greater than 12 years completed the questionnaires independently. The test re-test reliability of this questionnaire was verified by re-testing the first 100 patients and/or care providers.

**DEFINITION OF SEVERE HYPOGLYCEMIA:** For the purposes of this study, severe hypoglycaemia was defined as an event leading to loss of consciousness or seizure. This strict definition was used as it is an unequivocal endpoint rather than the more commonly used definition of severe hypoglycaemia, which is an event requiring help from another individual. This more common definition is difficult to apply to young children, particularly those less than 6 years of age, as all hypoglycaemic episodes may require assistance in this age-group. Patient data were collected prospectively at routine clinic visits every 3 months using a specifically designed data collection form, completed by a limited number of physicians. The details of data collection have been documented previously (9; 12). In summary, both patients and parents were instructed on how to record details of the hypoglycemic event, including blood glucose levels and response to treatment. All care providers were instructed to obtain a blood glucose value at each event once the safety of the child is assured. In our cohort, glucose values were obtained more than 98% of the time. This information was subsequently reviewed by the clinician and if validated, recorded on the data collection form. The physician reviewed the history of the event, the glucose recording and its timing, and the recovery history before judging the event to be hypoglycaemia-related. In addition to the logbooks, most families phoned the diabetes management team to receive advice on event management after a hypoglycemic event of this severity. These calls were recorded. We note that there was a close correlation between recall at clinic through logbooks and calls to the diabetes team, providing further evidence that recall was accurate over this time period.

**DEFINITION OF RECURRENT HYPOGLYCEMIA:** Recurrent hypoglycaemia was defined as the occurrence of two or more episodes of
severe hypoglycemia in the preceding year.

**LABORATORY MEASUREMENTS:** A1C was measured at each 3-monthly visit. A1C was assessed by an agglutination inhibition immunoassay (Ames DCA 2000; Bayer Ltd, Mishawaka, Indiana). The inter- and intra-assay coefficients of variation were 2.5 and 2.3%, respectively.

**STATISTICAL ANALYSIS:** Clinical characteristics of the study groups were compared using Student’s t test (mean ± SD) for variables normally distributed and Mann-Whitney test expressed as median ± SD (interquartile range - IQR) for those with a non-normal distribution.

**RESULTS**

A total of 656 patients and/or care providers (317 male, 339 female) completed the questionnaire over a six-month period. During this period, there were 829 patients attending the clinic, giving a case ascertainment of 79%. The mean age was 12.8 ± 4.0 years with a mean A1C (%) of 8.5 ± 1.0 since diagnosis and 8.1 ± 1.4 at the last visit. During the 12 months prior to the questionnaire visit, data were collected at each 3-monthly visit. The patients had to have had at least 3 visits in the preceding 12 months to be included. Of all subjects, the mean number of visits was 3.7 in the previous year and 92% of patients had 4 visits recorded.

The clinical characteristics of the cohort with impaired and normal awareness are shown in Table 1. Impaired awareness of hypoglycemia was present in 29% of patients. No differences were observed in gender or diabetes duration however patients with impaired hypoglycemia awareness had an earlier onset of diabetes (p<0.001), were younger (p<0.001), had lower levels of mean A1C since diabetes onset and at their last visit (p=0.006 and p=0.001 respectively). Among patients aged below 6 years (n=46), 19 patients (41%) and 27 patients (59%) were observed in the group with impaired and normal awareness respectively (p<0.001). There was no difference observed in hypoglycemia awareness scores between patients on injections compared to those on continuous subcutaneous insulin infusion therapy.

In the preceding year, a total of 161 episodes of severe hypoglycemia were recorded among all patients giving an overall incidence of 24.5 episodes per 100 patient-years. This rate was significantly higher among patients reporting impaired hypoglycemia awareness (37.1 vs. 19.3 episodes/100 patient-years, p<0.001). Among patients aged below 6 years, the rate of severe hypoglycemia was significantly higher in those with reported impaired awareness (33.3 vs. 5.2 episodes/100 patient-years, p=0.02).

Table 2 summarizes the clinical features of patients with recurrent and non-recurrent hypoglycemia in the preceding year. Thirty-eight patients had recurrent hypoglycemia with no differences in gender, age of onset, diabetes duration or A1C between the recurrent and non-recurrent groups. More patients with recurrent hypoglycemia reported impaired awareness of hypoglycemia (47% vs. 28%, p=0.03). As expected, the rate of severe hypoglycemia was much higher in the recurrent group (252.6 vs. 10.5 episodes/100 patient-years).

Table 3 demonstrates the findings in patients with diabetes duration greater than 5 years compared to those with diabetes duration less than 5 years. In
the group with diabetes for greater than 5 years, higher levels of mean A1C since diabetes onset were observed (p<0.001). Even with this higher A1C, a higher rate of severe hypoglycemia (32.6 vs. 17.8 episodes/100 patient years, p<0.001) occurred among those with a diabetes duration of more than 5 years, however no differences in hypoglycemia awareness were observed between the groups.

CONCLUSIONS
In this study, impaired hypoglycemia awareness assessed by a validated, self-reporting questionnaire was reported in 29% of children and adolescents. Overall, the rate of severe hypoglycemia was almost double in the group with impaired awareness. This was even more prominent in children under the age of 6 years with a six-fold increase in the rate of severe hypoglycemia in the group with impaired awareness, as observed by care providers. Care providers of children in this age-group have difficulty recognising hypoglycemia in their children. This group of care-providers reported a change in the pattern of symptoms associated with hypoglycemia in their children. These results suggest that in children as well as adults, screening for impaired awareness of hypoglycemia is an important component of routine diabetes care and can help identify patients at increased risk of having a severe hypoglycemic event.

Our rates of impaired awareness of hypoglycemia are consistent with a previous study reported by Barkai et al. (14). In this prospective study of 130 children and adolescents with type 1 diabetes, impaired awareness was reported by 37% of patients. Patients with impaired awareness had a much greater frequency of hypoglycemia-related coma or seizure (14.6 vs. 1.2 episodes/100 patient-years) and their overall incidence of hypoglycemia-related coma or seizure was 6.2/100 patient-years (14). Clearly despite changes in insulin therapy in the last decade, hypoglycemia unawareness remains common.

Our results are also consistent with several recent studies in adults with type 1 diabetes. The prevalence of impaired awareness is similar to that in adults despite a shorter duration of diabetes in children. There are also differences in treatment regimens and counterregulatory hormone and symptom responses to hypoglycemia (13; 15; 16). Geddes et al. reported the prevalence of impaired awareness of hypoglycemia in approximately 20% of a large, unselected adult population with type 1 diabetes (17). These patients also had a six-fold increase in the frequency of severe hypoglycemia in the preceding year. Similar rates of prevalence of impaired awareness and the association with severe hypoglycemia in adults have been reported by others (18).

Hypoglycemia unawareness has been extensively studied in adult patients. In both adults and adolescents, it is associated with defective counterregulatory hormone response, also known as hypoglycemia-associated autonomic failure (19). In this present study, we found that more children with recurrent hypoglycemia reported impaired awareness of hypoglycemia. This is not surprising given that even short, prior exposure to hypoglycemia can reduce the magnitude of epinephrine and other counterregulatory hormone responses as well as the autonomic symptom responses to a subsequent hypoglycemic episode (20). This shifts the glycemic
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threshold for these responses to a lower level of plasma glucose which further increases the risk of subsequent severe hypoglycemic episodes. Hypoglycemia is more frequent in the young (21) and this may explain the higher frequency of impaired awareness in children and adolescents. In adults, hypoglycemia unawareness is often associated with older age and longer duration of diabetes (17; 22). In our study however, patients with a duration of diabetes greater than 5 years did not have higher rates of impaired hypoglycemia awareness compared to patients with a duration of less than 5 years.

Impaired hypoglycemia awareness is clearly a significant problem for children and adolescents with T1DM and these children are at greater risk of having a hypoglycemia-related coma or seizure. This adds to the considerable burden of disease for families. There is evidence however, that in adults with hypoglycemia unawareness, this phenomenon can be reversed by meticulously avoiding hypoglycemia for 2-3 weeks (23; 24), although this is difficult to accomplish in young children. It is likely that the pathophysiology of the genesis of hypoglycemia unawareness and its associated counterregulatory hormone deficit is similar in the young to adults since attempts to restore responses by strictly avoiding hypoglycemia, at least in preliminary studies, appear to be successful (25).

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Table 1. Characteristics of children and adolescents with type 1 diabetes with normal and impaired hypoglycemia awareness.

|                                   | Total | Normal Awareness | Impaired Awareness | p-value |
|-----------------------------------|-------|------------------|--------------------|---------|
| **n (%)**                         | 656   | 465 (71%)        | 191 (29%)          |         |
| Male/Female                       | 317/339 | 221/244          | 96/95              | NS      |
| Age at diagnosis (years)          | 7.4 ± 4.0 | 8.0 ± 4.0        | 5.9 ± 3.8          | <0.001  |
| Age at questionnaire (years)      | 12.8 ± 4.0 | 13.5 ± 3.6       | 11.0 ± 4.4         | <0.001  |
| Duration of diabetes (years)      | 5.4 ± 3.9 | 5.5 ± 3.9        | 5.2 ± 3.8          | NS      |
| Mean A1C (%) since diagnosis      | 8.5 ± 1.0 | 8.6 ± 1.0        | 8.3 ± 1.0          | 0.006   |
| Mean A1C (%) at last visit        | 8.1 ± 1.4 | 8.2 ± 1.4        | 7.8 ± 1.2          | 0.001   |
| Severe hypoglycemia - episodes in preceding year | 161 | 90 | 71 |         |
| Rate of severe hypoglycemia (episodes/100 patient-years) | 24.5 | 19.3 | 37.1 | <0.001 |
| Patients, age ≤6 years, n=46      | 46    | 41%              | 59%                | <0.001  |
| Rate of severe hypoglycemia in patients aged ≤6 years (episodes/100 patient-years) | 21.7 | 5.2 | 33.3 | 0.02   |

Results expressed in mean ± SD or number (%)
**Table 2.** Characteristics of children and adolescents with type 1 diabetes with recurrent and non-recurrent hypoglycemia in the previous year.

|                          | Recurrent hypoglycemia | Non-recurrent hypoglycemia | p-value |
|--------------------------|------------------------|-----------------------------|---------|
| n (%)                    | 38 (6%)                | 618 (94%)                   |         |
| Male/Female              | 26/12                  | 291/327                     | NS      |
| Age at diagnosis (years) | 6.6 ± 3.6              | 7.4 ± 4.1                   | NS      |
| Age at questionnaire (years) | 12.8 ± 4.1          | 12.8 ± 4.0                  | NS      |
| Duration of diabetes (years) | 6.2 ± 3.6            | 5.4 ± 3.9                   | NS      |
| Mean A1C (%) since diagnosis | 8.5 ± 0.9             | 8.5 ± 1.0                   | NS      |
| Severe hypoglycemia - episodes in preceding year | 96                     | 65                           |         |
| Rate of severe hypoglycemia (episodes/100 patient-years) | 252.6                  | 10.5                         | <0.01   |
| Impaired awareness of hypoglycemia (%) | 47                     | 28                           | 0.031   |

Results expressed in mean ± SD or number (%)
Table 3. Characteristics of children and adolescents with duration of diabetes of more and less than 5 years.

|                          | Duration ≤ 5 years | Duration > 5 years | p-value |
|--------------------------|--------------------|--------------------|---------|
| n (%)                    | 359/656 (55%)      | 297/656 (45%)      |         |
| Male/Female              | 182/177            | 135/162            | NS      |
| Age at diagnosis (years) | 9.1 ± 4.2          | 5.4 ± 3.1          | < 0.001 |
| Age at questionnaire (years) | 11.7 ± 4.2    | 15.0 ± 3.0         | < 0.001 |
| Duration of diabetes (years) | 2.5 ± 1.4       | 8.4 ± 2.9          | < 0.001 |
| Mean A1C (%) since diagnosis | 8.20 ± 1.0       | 8.8 ± 1.0          | < 0.001 |
| Severe hypoglycemia - episodes in preceding year | 64 | 97 |
| Rate of severe hypoglycemia (episodes/100 patient-years) | 17.8 | 32.6 | < 0.001 |
| Impaired awareness of hypoglycemia (%) | 31 | 27 | NS |

Results expressed in mean ± SD or number (%).