RESEARCH

Predictors of glycaemic control and hypoglycaemia in children and adolescents with type 1 diabetes from NSW and the ACT

Maria E Craig, Penny Handelsman, Kim C Donaghue, Albert Chan, Barbara Blades, Rosetta Laina, Darna Bradford, Angela Middlehurst, Geoffrey Ambler, Charles F Verge, Patricia Crock, Patrick Moore, Martin Silink, for the NSW/ACT HbA_{1c} Study Group

ABSTRACT

Objectives: To audit glycaemic control and incidence of severe hypoglycaemia in children and adolescents with type 1 diabetes in New South Wales (NSW) and the Australian Capital Territory (ACT).

Design: A multicentre, population-based, cross-sectional study from 1 September to 31 December, 1999.

Participants: 1190 children and adolescents aged 1.2–15.8 years with type 1 diabetes, identified from three hospital-based paediatric diabetes units, four private city-based paediatric practices and 18 regional outreach clinics in NSW and the ACT.

Main outcome measures: HbA_{1c} level and incidence of severe hypoglycaemia (defined by unconsciousness or seizures).

Results: The response rate was 67% (1190 of a target group of 1765). The median HbA_{1c} level was 8.2% (interquartile range, 7.6%–9.1%). Significant predictors of HbA_{1c} level in a multiple regression model were duration (b = 0.05; 95% CI, 0.02–0.07) and insulin dose/kg (b = 0.46; 95% CI, 0.27–0.66). At least one episode of severe hypoglycaemia in the previous three months was reported in 6.7%, and the rate of severe hypoglycaemia was 36/100 patient-years. Significant predictors of hypoglycaemia in a Poisson regression model were younger age ($P = 0.03$), male sex ($P = 0.04$), longer diabetes duration ($P = 0.02$), and > 3 daily insulin injections ($P = 0.02$), but not HbA_{1c} level. Children with diabetes had higher BMI standard deviation scores compared with population standards, and those in the highest quartile of BMI standard deviation score were younger, had shorter diabetes duration and had higher HbA_{1c} level.

Conclusions: Many children and adolescents with type 1 diabetes have suboptimal glycaemic control, placing them at high risk of developing microvascular complications. Those with longer diabetes duration are at increased risk of suboptimal glycaemic control and severe hypoglycaemia and should be targeted for interventional strategies.

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TYPE 1 DIABETES is the most common chronic disease of childhood, with about 300 new cases diagnosed each year in New South Wales (NSW) and the Australian Capital Territory (ACT).[1] The assessment of glycaemic control in children and adolescents with diabetes, as for adults, is based on measurement of glycosylated haemoglobin (HbA_{1c}). The Diabetes Control and Complications Trial (DCCT), a multicentre study of 1441 patients (195 of whom were adolescents), showed a positive benefit of improved glycaemic control, with a reduction in long-term risk of microvascular complications.[2] However, this was associated with a twofold to threefold increase in the rate of severe hypoglycaemia and weight gain. The applicability of the DCCT findings to managing diabetes in children is not known. Surveys of glycaemic control have shown that many children with type 1 diabetes are not achieving optimal diabetes control (HbA_{1c} level, < 8%), and yet rates of hypoglycaemia are unacceptably high.[3,4] The risk of severe hypoglycaemia, particularly in preschool children, and fear of weight gain in adolescents may be potential impediments to achieving targets for glycaemic control.

The predictors of glycaemic control are likely to be multifactorial in young people with diabetes. In NSW and ACT children with type 1 diabetes, we have previously reported that variation in public versus private care, socioeconomic background and urban versus rural location were not predictors of glycaemic control.[5] In contrast, a recent survey of young people from Scotland proposed strategies of medical care and clinic organisation as factors contributing to between-centre variation in HbA_{1c} level,[6] and an audit from France found better glycaemic control in university-affiliated hospitals and centres following more than 50 patients.[4] The

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Department of Paediatrics, St George Hospital, Kogarah, NSW.
Maria E Craig, PhD, FRACP, Paediatric Endocrinologist (also at The Children's Hospital at Westmead).
The Children's Hospital at Westmead, Sydney, NSW.
Penny Handelsman, MPH, Study Co-ordinator; **Kim C Donaghue,** PhD, FRACP, Paediatric Endocrinologist; **Albert Chan,** MAppStat, Statistician; **Barbara Blades,** BSc(Hons), PhD, Laboratory Manager; **Rosetta Laina,** MSc, Laboratory Scientist; **Darna Bradford,** BSc(Hons), Laboratory Scientist; **Angela Middlehurst,** RN, Diabetes Centre Manager; **Geoffrey Ambler,** MD, FRACP, Paediatric Endocrinologist; **Martin Silink,** MD, FRACP, Director, Ray Williams Institute of Endocrinology.
Sydney Children's Hospital, Randwick, NSW.
Charles F Verge, PhD, FRACP, Paediatric Endocrinologist.
John Hunter Children's Hospital, Newcastle, NSW.
Patricia Crock, MB BS, FRACP, Paediatric Endocrinologist.
The Canberra Hospital, Canberra, ACT.
Patrick Moore, MB BS, FRACP, Paediatrician.
Reprints will not be available from the authors. Correspondence: Dr Maria E Craig, Department of Paediatrics, St George Hospital, Gray Street, Kogarah, NSW 2217. m.craig@unsw.edu.au

aim of our study was to further explore the relationship between glycaemic control, hypoglycaemia and body mass index (BMI) in a large population-based cohort of children with type 1 diabetes in NSW and the ACT.

METHODS

Children with type 1 diabetes aged 15 years or younger were recruited from 1 September to 31 December 1999 from three hospital-based paediatric diabetes units, four private city-based paediatric practices and 18 regional outreach clinics in NSW and the ACT. Those with no scheduled visit during the study period were invited to participate by mail. Written informed consent was obtained. Ethical approval was obtained from participating hospitals and regional health authorities.

The NSW/ACT type 1 diabetes incidence register[1,7] and clinic data were used to compare study participants and non-participants.

Date of diagnosis (defined as date of first insulin injection), number of injections per day, number of units of insulin per day, number of severe episodes of hypoglycaemia (defined by unconsciousness or seizures) over the previous three months, sex, height, weight and residential postcode were recorded on the day of HbA_{1c} estimation. Standard deviation scores (z scores) for height, weight and BMI were derived from published standards,[8] with a score of zero being the mean for the population.

HbA_{1c} estimation

A 5 μL fingerprick blood sample was collected by means of the Bio-Rad HbA_{1c} Capillary Collection System (Bio-Rad Laboratories, GmbH, Munich, Germany). Samples were stored at 4°C until transported, within one week of collection, to the central laboratory for analysis.

HbA_{1c} level was analysed by ion-exchange high performance liquid chromatography (HPLC) at the Institute of Endocrinology, The Children's Hospital at Westmead, by means of the Bio-Rad Variant Haemoglobin Testing System (Bio-Rad Laboratories, Diagnostics Group, Hercules, CA, USA). Level II laboratory certification of traceability to the DCCT Reference Method was obtained through the National Glycohemoglobin Standardization Program (established to standardise glycohaemoglobin test results to those reported in the DCCT) with the University of Missouri Secondary Reference Laboratory #1. The interassay coefficient of variation was 1.1% and 1.2% at mean variant HbA_{1c} levels of 5.95% and 9.76%, respectively. With the regression equation $y = 1.045x - 0.767$, variant HbA_{1c} values (x) were converted to and are reported as DCCT Reference Method values (y). The variant HbA_{1c} normal range was 4.2%–5.9% (mean, 5.1%).

Statistical analysis

Results are expressed as mean (95% CIs) or median [interquartile range (IQR)] for skewed data. Continuous variables were compared by t tests or the Wilcoxon rank sum test, as appropriate. Multiple linear regression was used to examine the relationship between HbA_{1c} level and age, sex, duration of diabetes, number of injections, insulin dose per kg, BMI standard deviation score and number of hypoglycaemic episodes.

Participants were divided into quartiles of BMI standard deviation score, and multiple logistic regression was used to explore the predictors of being in the highest quartile of BMI standard deviation score compared with the lower three quartiles.

Poisson regression was used to examine the effect of age, sex, duration of diabetes, number of injections and HbA_{1c} level on the incidence of hypoglycaemia. For the regression models, assumptions were satisfied and diagnostics checks showed no obvious lack of fit for the data. Statistical analysis was performed with SPSS[9] and SAS[10] statistical software.

1: Predictors of being in the highest quartile of BMI standard deviation score in children with type 1 diabetes, determined by logistic regression

Variable	Odds ratio (95% CI)		*P*
Age	0.82	(0.78–0.86)	< 0.001
HbA_{1c}	1.14	(1.01–1.29)	0.03
Diabetes duration	0.86	(0.75–0.98)	0.03
Insulin dose/kg	0.81	(0.45–1.49)	0.50
Interaction (insulin dose/kg x duration)	1.15	(1.02–1.30)	0.02

2: Predictors of hypoglycaemia in children with type 1 diabetes, determined by Poisson regression

Variable	Incidence density ratio (95% CI)		*P*
Age	0.93	(0.88–0.99)	0.03
Male sex	1.49	(1.01–2.19)	0.04
More than 3 injections daily	1.83	(1.08–3.11)	0.02
Diabetes duration	1.08	(1.01–1.15)	0.02

RESULTS

Of a total target group of 1765, 1190 children and adolescents (67.4%) participated in the study. There were more females (649) than males (541), reflecting the higher incidence of type 1 diabetes in females in this population.[1] Median age was 11 years (range, 1.2–15.8 years) and median diabetes duration was three years (range, 0.2–14.2 years). Comparing the 1190 participants with the 571 non-participants, the former were younger (11 years [IQR, 8.1–13.2] v 12.7 years [IQR, 9.1–14.4]; $P < 0.0001$) and had shorter diabetes duration (3 years [IQR, 1.3–5.5] v 4.5 years [IQR, 2.9–6.9]; $P < 0.0001$), but did not differ in sex distribution or urban versus rural location.

Insulin regimens

Most children (730 [61.3%]) were treated with two insulin injections daily; 38 (3.2%) received one, 274 (23.1%) received three and 144 (12.1%) received four or more injections daily.

Two children were managed with continuous subcutaneous pump therapy and two were not receiving insulin (diabetes duration less than one year), and these children were excluded from all analyses.

Glycaemic control

Significant predictors of higher HbA_{1c} in the multiple regression model were longer duration (b = 0.05; 95% CI, 0.02–0.07; $P = 0.0001$) and insulin dose per kg (b = 0.46; 95% CI, 0.27–0.66; $P = 0.0001$). Age, sex, number of injections, BMI standard deviation score (upper compared with lower three quartiles), severe hypoglycaemia and interaction terms were not significant in the model.

Anthropometry

Standard deviation scores for height, weight and BMI were significantly higher in both boys and girls, compared with reference standards[8] ($P < 0.001$ for all three variables). Children in the upper quartile of BMI standard deviation score (> 1.04) were younger, had a higher HbA_{1c} level and a shorter duration of diabetes (Box 1). There was no effect of sex, number of severe episodes of hypoglycaemia or number of injections on BMI.

Hypoglycaemic events

Severe hypoglycaemia in the previous three months was reported in 73 children (6.7%). A single episode occurred in 50 (4.2%), two in 17 (1.4%) and three or more in six (0.5%). The incidence of severe hypoglycaemia was 36 events per 100 patient-years. Significant predictors of hypoglycaemia, determined by Poisson regression, are shown in Box 2. HbA_{1c} level was not significant in the model.

DISCUSSION

The outlook for preventing long-term complications remains a challenge in children and adolescents with type 1 diabetes. In our audit of 1190 children, longer diabetes duration was a predictor of higher HbA_{1c} level, and an elevated HbA_{1c} level (> 8%) is a known risk factor for microvascular complications.[2] Our participants' median HbA_{1c} level of 8.2%, with a median duration of diabetes of three years, is comparable to that found in the multicentre Hvidore Study[3] (DCCT equivalent, 8.3%) and in a Brisbane clinic-based study[11] (mean HbA_{1c} level, 8.6%, determined by several assay methods). However, six years after diagnosis of type 1 diabetes in childhood, early microvascular complications were found in 34% of an incident cohort from NSW, whose median HbA_{1c} level was 8.7%.[12]

Our response rate of 67.4% compares favourably with other surveys. However, we cannot exclude the possibility of selection bias. The children identified from the diabetes register who did not participate in the study were older and had longer diabetes duration. Adolescents are at greatest risk of non-compliance and worse glycaemic control, so our participants may represent the better-controlled two-thirds of the population.

The relationship between higher insulin dose and higher HbA_{1c} level was initially surprising. There was no difference in insulin dose per kg between the conventionally and intensively treated cohorts in the DCCT,[13] but the same positive relationship between suboptimal glycaemic control and higher insulin dose has been reported in several studies.[4,5] The cross-sectional design of these studies clearly limits the conclusions that can be drawn from these data and further investigation of these findings is required. It may be that the insulin dose had recently been increased in children with worse glycaemic control in an attempt to improve control. Also, higher HbA_{1c} levels may have resulted from non-compliance with prescribed doses in our cohort. Adolescent girls with diabetes are at increased risk of eating disorders,[14] are worried about the risk of weight gain,[15] and have been found to manipulate or omit insulin therapy as a means of weight control.[16,17]

Children in the highest quartile of BMI standard deviation score, who were all overweight (BMI, > 85th percentile) had higher levels of HbA_{1c}, were younger and had shorter diabetes duration. Parental fear of hypoglycaemia has been shown to be an impediment to improved glycaemic control,[15] particularly in young children. Parents may respond by overfeeding their young children, but obesity itself is a growing problem in Australian children.[18] Therefore, the heaviest children may have a combination of type 1 and type 2 diabetes or insulin resistance.[19]

It is of concern that, while children in our study had a relatively high rate of severe hypoglycaemia, there was no association with glycaemic control. The incidence of severe hypoglycaemia (36 per 100 patient-years) is higher than that in the Hvidore study (22 per 100 patient-years)[3] and the DCCT intensively treated adolescent cohort (26.7 per 100 patient-years),[13] but lower than that in the French study (42 per 100 patient-years).[4] A regimen of four injections per day was also a significant risk factor for hypoglycaemia in the Poisson regression model. Subjects in the intensively treated DCCT cohort, who were on a regimen of at least three daily insulin injections, had a higher rate of hypoglycaemia, but lower HbA_{1c} level, than those receiving conventional therapy. An increase in severe hypoglycaemia was associated with improved glycaemic control in a Western Australian study, although all children aged less than 17 years in that cohort were treated with two injections per day.[20]

In conclusion, children with longer duration of diabetes and those receiving higher doses of insulin provide a challenge for healthcare providers to determine how best to improve glycaemic control and prevent severe hypoglycaemia. Younger children are at particular risk of hypoglycaemia and being overweight. Investigation into the quality of life, fears and coping skills of children and their parents is needed to better understand the barriers to improving glycaemic control.

COMPETING INTERESTS

None identified.

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