ORIGINAL ARTICLES

# Impact of improved glycaemic control on rates of hypoglycaemia in insulin dependent diabetes mellitus

E A Davis, B Keating, G C Byrne, M Russell, T W Jones

**Abstract**

**Increased emphasis on strict glycaemic control of insulin dependent diabetes mellitus (IDDM) in young patients may be expected to cause increases in rates of significant hypoglycaemia. To evaluate whether this is the case for a large population based sample of IDDM children and adolescents rates of severe (coma, convulsion) and moderate (requiring assistance for treatment) hypoglycaemia were studied prospectively over a four year period.**

**A total of 709 patients were studied yielding 2027 patient years of data (mean (SD) age: 12.3 (4.4); range 0–18 years, duration IDDM: 4.9 (3.8) years). Details of hypoglycaemia were recorded at clinic visits every three months when glycated haemoglobin ($HbA1_c$) was also measured.**

**Overall the incidence of severe hypoglycaemia was 7.8 and moderate was 15.4 episodes/100 patient years. Over the four years mean (SD) clinic $HbA1_c$ steadily fell from 10.2 (1.6)% in 1992 to 8.8 (1.5)% in 1995. In parallel with this there was a dramatic increase in the rate of hypoglycaemia, especially in the fourth year of the study, when severe hypoglycaemia increased from 4.8 to 15.6 episodes/100 patient years. This increase was particularly marked in younger children (<6 years) in whom severe hypoglycaemia increased from 14.9 to 42.1 episodes/100 patient years in 1995.**

**It is concluded that attempts to achieve improved metabolic control must be accompanied by efforts to minimise the effects of significant hypoglycaemia, particularly in the younger age group.**

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Keywords: hypoglycaemia; insulin dependent diabetes mellitus; glycaemic control

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Hypoglycaemia is the most common acute complication of the treatment of insulin dependent diabetes mellitus (IDDM) and its occurrence often restricts attempts to improve glycaemic control. This is particularly critical for younger patients who may be even more susceptible to severe hypoglycaemia[1] as a result of the interaction of both physiological and behavioural factors. A number of reports have described the incidence and clinical factors associated with significant hypoglycaemia in childhood but many of these have become outdated with recent changes to management goals and practices.[2–5] For example, the greater emphasis on improved metabolic control and intensified treatment after the release of the Diabetes Control and Complications Trial (DCCT) results is likely to have altered the epidemiology of this acute complication of treatment.[6]

We have recently reported results of a study performed over a three year period in which we found a high incidence of significant hypoglycaemia in children and adolescents.[7] Episodes were rare in the first year from diagnosis but were more frequent in children aged <6 years and in those with lower glycated haemoglobin ($HbA1_c$). We now report a continuation of the same study, now completed over four years, and analysed to determine the relationship between glycaemic control and rates of hypoglycaemia. Although the association between lower $HbA1_c$ and the incidence of severe hypoglycaemia has been described in adults and adolescents,[8] the relationship between improved glycaemic control and hypoglycaemia requires further characterisation in children. For instance, it is unknown whether efforts to improve glycaemic control in a large group of children and adolescents will significantly change the overall frequency of hypoglycaemia and whether there is a linear or "threshold" effect of lowered glycaemia. These questions are becoming more relevant now that a central aim of diabetes treatment is to achieve as near normoglycaemia as possible for the individual's circumstances. In this study we have prospectively examined the relationship between glycaemic control and episodes of hypoglycaemia in a large population based sample of adolescents and children with IDDM over a four year time period. During this time there was a significant decrease in the $HbA1_c$ of the patients attending the clinic and an increase in the incidence of hypoglycaemia.

## Patients and methods

### DEFINITIONS

As previously described moderate hypoglycaemia was defined as hypoglycaemia requiring

*Table 1 Clinical characteristics of study group by age*

| | *< 6 years (n=94)* | *6–<12 years (n=262)* | *⩾ 12 years (n=353)* | *Total (n=709)* |
|---|---|---|---|---|
| Mean (SD) age (years) | 4.4 (1.3) | 9.6 (1.4) | 14.8 (1.8) | 12.3 (4.4) |
| Males:females | 49:45 | 137:125 | 183:170 | 369:340 |
| Mean (SD) $HbA1_c$ (%) | 8.8 (1.4) | 8.9 (1.6) | 9.2 (1.5) | 9.0 (1.6) |

*Table 2 Glycaemic control (HbA1) and hypoglycaemia incidence for each year of study*

| | *1992* | *1993* | *1994* | *1995* | *Total* |
|---|---|---|---|---|---|
| Mean (SD) $HbA1_c$ (%) | 10.1 (1.6) | 9.6 (1.4) | 9.1 (1.4) | 8.8 (1.5) | 9.0 (1.6) |
| % Subjects with $HbA1_c$ | | | | | |
| < 8% | 19.4 | 22.1 | 26.1 | 28.2 | |
| 8–10% | 52.0 | 52.6 | 52.7 | 54.7 | |
| > 10% | 28.6 | 25.3 | 21.2 | 17.1 | |
| Hypoglycaemia (episodes/100 patient years) | | | | | |
| Severe | 4.8 | 4.2 | 5.0 | 15.6 | 7.8 |
| Moderate | 6.1 | 8.1 | 11.1 | 21.2 | 15.4 |

the assistance of another person for treatment and severe hypoglycaemia as an event resulting in coma or convulsion.[7] We use the term "significant hypoglycaemia" to describe the combined total of moderate and severe hypoglycaemia. For younger children (<6 years), the definition of moderate hypoglycaemia is troublesome as all symptomatic episodes may be described by this definition as "moderate". As a result, at that age, we counted as moderate only those events with obvious neuroglycopenia manifesting as confusion or drowsiness that required immediate treatment but where the child could be treated with oral carbohydrate and did not need glucagon treatment.

PATIENTS

All diabetic children and adolescents attending the diabetes clinic at Princess Margaret Hospital during the four year period from May 1992 to April 1996, inclusive, were included in the study. Over this time, a total of 709 patients aged 0–18 years were enrolled yielding 2027 patient years of data. A total of 262 children were diagnosed with IDDM during the four years. Clinical characteristics of the subjects are shown in table 1.

Princess Margaret Hospital is the only paediatric referral centre for diabetes servicing Western Australia and almost all children diagnosed aged less than 15 years are registered and treated regularly at that centre as confirmed by the Western Australian Children's Diabetes Register that has a case ascertainment rate >99%.[9]

All patients at school (<17 years) are treated with twice daily insulin. Of the older subjects (>17 years), 14 (46%) were treated using multiple daily injections.

Treatment goals included the achievement of optimal metabolic control and to this end all parents and patients had undergone extensive diabetes education including details concerning the recognition and treatment of hypoglycaemia as well as insulin adjustment. All parents/patients were seen at least every three months by the diabetes care team that included nurse educator, dietitian, social worker, and specialist physician. Parents and patients were encouraged routinely to adjust insulin according to home glucose levels to allow for exercise patterns and food intake. All caregivers had access to glucagon and had been instructed in its use.

PROTOCOL

Data were collected prospectively over a period of four years. Patients and/or parents and caregivers were asked to record any moderate and severe episode when they occurred along with details of the event. A standardised data collection form was used and completed by one of the physicians. In addition, patients/parents were asked to contact a diabetes team member after a severe episode.

Patients were seen in clinic every three months and on each attendance a detailed history was obtained by the physician about any episode of moderate or severe hypoglycaemia since the previous visit. The patients were questioned about the circumstances surrounding the event. The mode of treatment was also recorded. Over the four years of the study, 97% of all subjects attended a minimum of four visits per year. For all patients, $HbA1_c$ was determined at each three monthly visit. This was measured by agglutination inhibition immunoassay (Ames DCA 2000, non-IDDM ref <6.2%) and the result was available at the time of the clinic appointment.

STATISTICAL ANALYSIS AND PROCEDURES

Demographic data are expressed as mean (SD). The data were analysed using generalised estimating equation models[10 11] that were fitted with the exchange correlation structure. These models are an extension of multivariate logistic regression analysis that are designed to account for multiple or repeated measures on the same subject; p values <0.05 were considered significant. Factors analysed included: sex, IDDM duration (<1, 1–<5 , 5–<9, ⩾9 years), $HbA1_c$ (<7%, 7%–<8%, etc), age (<6, 6–<12, ⩾12 years,) and year of study (1992, 1993, 1994, 1995).

## Results

GLYCAEMIC CONTROL

The mean $HbA1_c$ of the clinic for each of the four years is shown in table 2. As shown there was a gradual reduction for each year in $HbA1_c$ values ($p<0.01$). Consistent with the decrease in $HbA1_c$ the proportion of those with $HbA1_c$ <8% increased from 19.4% in 1992 to 28.2% in 1995. This improvement in glycaemic control was seen in all age groups. Table 2 shows that the decrease in mean $HbA1_c$ was a consequence of fewer children falling into the >10% range and more into the <8%. In 1992 twice as many children had mean $HbA1_c$ >10% than they did <8%. In 1995 this was reversed with twice as many having mean $HbA1_c$ <8% than >10%. The percentage in the 8–10% range stayed the same at about 52%.

HYPOGLYCAEMIA INCIDENCE

During the four years of the study, a total of 152 severe and 319 moderate hypoglycaemic episodes were recorded. This yielded an overall incidence of severe episodes of 7.8/100 patient

*Table 3 Rates of severe and moderate hypoglycaemia according to HbA1$_c$ (%) closest to the event*

| | *6–< 7* | *7– < 8* | *8– < 9* | *9– < 10* | *10– < 11* | *⩾ 11* |
|---|---|---|---|---|---|---|
| Hypoglycaemia (episodes/100 patient years) | | | | | | |
| Severe | 18.7 | 15.3 | 7.3 | 6.1 | 2.8 | 2.0 |
| Moderate | 34.5 | 30.6 | 16.2 | 10.2 | 7.4 | 4.9 |

years and of moderate episodes of 15.4/100 patient years (that is total incidence of significant hypoglycaemia of 23.2/100 patient years).

During the total study period, 14.9% of the children experienced at least one significant episode per year and of these 4.7% per year experienced coma/convulsion. A total of 35.1% of patients who experienced a severe episode had a further episode over the four years. No significant differences were noted between males and females in overall rates of hypoglycaemia but of those with repeat episodes males predominated (2:1, males:females).

As reported previously, children who had diabetes for <1 year had a reduced incidence of severe hypoglycaemia (1.9 *v* 8.8 episodes/100 patient years: diabetes duration <1 year *v* duration >1 year, p<0.001). Thereafter, duration of diabetes was unrelated to the incidence of hypoglycaemia.

The incidence of hypoglycaemia was analysed in three age groups: <6, 6–12, and >12 years. The youngest group had the highest incidence of hypoglycaemia with a total of 53.1 episodes/100 patient years in comparison with the rates in those >6 years of 21.5 episodes/100 patient years. In the youngest group, the rate of severe hypoglycaemia was approximately 50% higher than in older children (14.9 *v* 7.2 episodes/100 patient years, <6 *v* >6 years, p<0.05). The effect of younger age was independent of diabetes duration and HbA1$_c$ however within each age group those with lower HbA1$_c$ were more likely to develop significant hypoglycaemia.

As expected, there was a strong relationship between the HbA1$_c$ closest to the event and the incidence of hypoglycaemia. As shown in table 3, the incidence of both severe and moderate hypoglycaemic episodes increased sharply at a HbA1$_c$ below 8% (for example significant hypoglycaemia incidence 45.9 *v* 23.5 episodes/100 patient years, HbA1$_c$ 7–8% *v* 8–9%, p<0.01). In those children with HbA1$_c$ <7%, the incidence of hypoglycaemia increased further to almost threefold greater than the mean (for example severe episodes 18.7 *v* 7.8/100 patient years, HbA1$_c$ <7% *v* overall group). This effect was independent of age, duration of diabetes, or method of insulin treatment and was even more pronounced when subjects with duration <1 year were excluded from analysis, for example at HbA1$_c$ <7% the rate of severe episodes is 20.7/100 patient years (*v* 18.7/100 with those duration <1 year included).

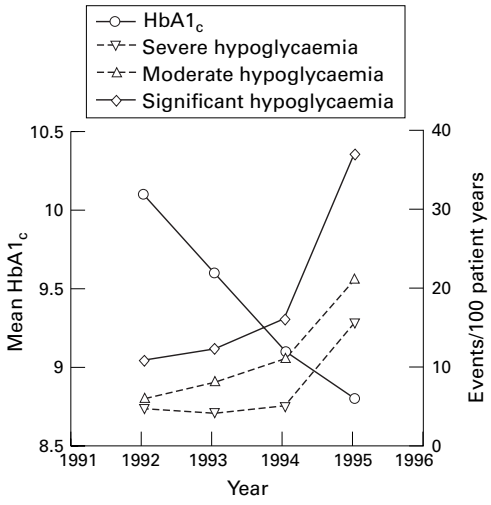


*Figure 1 Rates of severe, moderate, and significant hypoglycaemia contrasted with the change in mean HbA1$_c$ over the four year period.*

Analysis of rates of hypoglycaemia for each year of the study is shown in table 2 and fig 1. As shown the incidence of both severe and moderate episodes increased sharply in the final year of the study (for example for severe episodes: 4.8 *v* 15.6 episodes/100 patient years, 1992 *v* 1995, p<0.01). During the final year 12.1% of the patients experienced a severe episode and 25.2% a moderate episode. This increase in 1995 was seen in all ages but was particularly pronounced in the younger age group (<6 years) in whom the rate of severe episodes increased to 42.1 events/100 patient years (*v* an overall rate of 14.9 at this age over the four year study period).

## Discussion

The care of children with diabetes has undergone many changes recently with an increased emphasis on metabolic control having a pivotal role in management practices. Consistently better control has become a more realistic goal with the availability of new insulins, portable and more accurate home glucose monitors, and the facility to perform HbA1$_c$ assays at the time of medical review. The emphasis on better glycaemic control has been launched by evidence[6] that long term complications can be delayed and diminished by such measures. With these changes however, it has become even more important to maintain surveillance on the negative aspects of improved glycaemic control, in particular, hypoglycaemia. This information is becoming more available for adults,[8 12 13] but is unfortunately still limited for children. The epidemiology of hypoglycaemia has recently been described in a large prospective study[7] and the current report was provoked by the necessity to examine in detail the relationship between glycaemic control and hypoglycaemia in children and adolescents at this critical time when changes in accepted metabolic control were being made.

Our study was designed to minimise the confounding factors that have limited interpretation of other surveys. The prospective nature and at least three monthly review of patients reduce the likelihood of over reporting of hypoglycaemia. Indeed other studies suggest that our reported incidence of hypoglycaemia is likely to be an underestimate since episodes

may go unrecognised particularly at night.[14 15] The decision as to how to define moderate hypoglycaemia is always difficult in the younger age group. The use of the definition "needing help to treat their hypoglycaemia" risks including mild episodes in young children who are too small to help themselves. To avoid this we modified the definition in this age group to include only those episodes accompanied by obvious neuroglycopenia. We were reasssured that between each of the age groups analysed in our study, the proportion of moderate to severe hypoglycaemia is consistent.

A central aim of this study was to examine the important question as to the relationship between improvements in diabetes control in a group of patients and the occurrence of hypoglycaemia and to characterise this relationship. Our results identify an increase in moderate and severe hypoglycaemia as the mean $HbA1_c$ of the group decreased. The question of whether there is a threshold at which hypoglycaemia becomes a greater risk remains, although there was a dramatic rise in the final year of the study. Certainly, when hypoglycaemia is considered with respect to the most recent $HbA1_c$ measurement we confirmed previous observations and found that when the $HbA1_c$ moves down from the 8–9% category to the 7–8% category the incidence of hypoglycaemia doubled.

We found that when mean clinic $HbA1_c$ decreased from 9.1% in 1994 to 8.8% in 1995 the incidence of significant hypoglycaemia doubled. This along with the data relating to the $HbA1_c$ closest to the hypoglycaemic event suggests that a $HbA1_c$ of about 8–9% is a critical level at which significantly increased rates of hypoglycaemia are seen. Recent literature from the DCCT assessing adults and adolescents found that the relative increase in risk of hypoglycaemia as the $HbA1_c$ decreased was less for those with $HbA1_c$ <8% than in those >8%.[16] Although our data are not analysed to answer this specific question and are presented grouped, it can be seen that there was little difference between risk of hypoglycaemia for those in the 6–7% and 7–8% group but the risk decreased significantly for those whose rates are >8%, an observation that is consistent with those findings.

Increased rates of hypoglycaemia have to be evaluated in the light of the potential for adverse effects at that age as well as the potential benefits. What the gain is in decreased long term complications with a 1% improvement in $HbA1_c$ at this level, remains unknown for the younger individual. It is not yet clear whether prepubertal glycaemic control plays as important a part in the complication risk as post pubertal metabolic control. For this reason we feel it is important to draw attention to the high rates in younger children particularly in 1995 when $HbA1_c$ was lowest. Current evidence suggests that severe hypoglycaemia in young children, particularly those less than 5 years old may have long term adverse effects on cognitive function.[17–19] As this is the age group at which parental attitude rather than patient attitude tends to dictate the level of metabolic control many young children have $HbA1_c$ in the lower range. The high rates of hypoglycaemia in this age group suggest these patients may need to be targeted and parents further educated about the high risk and possible adverse effects of tight control as well as to detect and prevent hypoglycaemia. In addition, higher $HbA1_c$ levels may need to be set as goals.

When monitoring hypoglycaemia in a clinic setting it may be important to separate out the children with recurrent hypoglycaemia. Wertlieb *et al* reported that recurrent hypoglycaemia over eight years of follow up occurred almost exclusively in boys and had no relationship with the mean $HbA1_c$ during the year of the episode or mean $HbA1_c$ for the eight years of follow up.[20] They found this was independent of most psychosocial factors but tended to occur in boys whose defence mechanisms were more immature. We also found recurrent hypoglycaemia to be significantly more prevalent in boys compared with girls.

The normal insulin regimen in our clinic is a twice daily mixture of intermediate and short acting preparations. It has been suggested that a three times daily regimen may have less hypoglycaemic consequences but this remains to be confirmed. An extra daily dose of insulin carries with it a considerable extra burden for families with school age children so this is an issue which needs to be clarified by further studies. New insulins such as the rapid acting insulin analogues are reported to have less propensity to hypoglycaemia in well controlled type 1 diabetics and its use may have a future impact. In view of such potential changes, this and other reports[21] are reminders of the importance of continually monitoring the frequency of hypoglycaemia in patients with IDDM as management changes. This is particularly critical with the increasing emphasis to maintain and improve metabolic control. Furthermore, as the case is not yet made for the advantages of improved glycaemic control in prepubertal patients we recommend being aware of the potential for unacceptably high rates of hypoglycaemia in the very young patient especially during tight glycaemic control.

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1 The DCCT Research Group. Effect of intensive diabetes treatment on the development and progression of long term complications in adolescents with insulin dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 1994;**125**:177–88.
2 Goldstein D, England JD, Hess R, *et al.* A prospective study of symptomatic hypoglycaemia in young diabetic patients. *Diabetes Care* 1981;**4**:601–5.
3 Daneman D, Perlman K, Ehrlich R. Severe hypoglycaemia in children with insulin dependent diabetes-mellitus: Frequency and predisposing factors. *J Pediatr* 1989;**115**: 681–5.
4 Bergada I, Suissa S, Dufresne J, *et al.* Severe hypoglycaemia in IDDM children. *Diabetes Care* 1989;**12**:239–44.
5 Bhatia V, Wolfsdorf J. Severe hypoglycaemia in youth with insulin-dependent diabetes mellitus: frequency and causative factors. *Pediatrics* 1991;**88**:1187–92.
6 The Diabetes Control and Complications Trial. The effect of intensive treatment of diabetes on the development and progression of longterm complications in insulin dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
7 Davis EA, Keating B, Byrne GC, *et al.* Hypoglycaemia: incidence and clinical predictors in a large population based sample of children and adolescents with IDDM. *Diabetes Care* 1997;**20**:20–5.
8 The DCCT Research Group. Epidemiology of severe hypoglycaemia in the Diabetes Control and Complications Trial. *Am J Med* 1991;**90**:450–9.

9 Kelly HA, Byrne GC. Incidence of IDDM in Western Australia in children aged 0–14 yr from 1985 to 1989. *Diabetes Care* 1992;**15**:515–7.
10 Liang KY, Zeger S. Longitudinal data analysis using generalized line models. *Biomedica* 1986;**73**:13–22.
11 Zeger S, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1987;**42**:121–30.
12 The DCCT Research Group. Adverse events and their association with treatment regimens in the diabetes control and complications trial. *Diabetes Care* 1995;**18**:1415–27.
13 MacLeod KM, Hepburn DA, Frier BM. Frequency and morbidity of severe hypoglycemia in insulin treated diabetic patients. *Diabet Med* 1993;**10**:238–245.
14 Simell T, Simell O, Lammi EM, *et al.* Glucose profiles in children two years after the onset of type 1 diabetes. *Diabet Med* 1993;**10**:524–9.
15 Porter P, Byrne GC, Stick S, *et al.* Nocturnal hypoglycaemia and sleep disturbances in young teenagers with insulin dependent diabetes mellitus. *Arch Dis Child* 1996;**75**:120–3.
16 The DCCT Research Group. The absence of a glycaemic threshold for the development of long term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes* 1996;**45**:1289–98.
17 Ryan C, Vega A, Drash A. Cognitive deficits in adolescents who developed diabetes early in life. *Pediatrics* 1985;**75**: 921–7.
18 Rovet J, Ehrlich RM, Hoppe M. Intellectual deficits associated with early onset of insulin dependent diabetes mellitus in children. *Diabetes Care* 1987;**10**:510–5.
19 Golden MP, Ingersoll GM, Brack CJ, *et al.* Longitudinal relationship of asymptomatic hypoglycemia to cognitive function in IDDM. *Diabetes Care* 1989;**12**:89–93.
20 Herskowitz Dumont R, Jacobson AM, Cole C, *et al.* Psychosocial predictors of acute complications in youth. *Diabet Med* 1995;**12**:612–8.
21 Egger M, Gschwend S, Smith GD, *et al.* Increasing incidence of hypoglycemic coma in children with IDDM. *Diabetes Care* 1991;**14**:1001–5.