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Original Article

Association between Sex, Age, Insulin Regimens and Glycemic Control in Children and Adolescents with Type 1 Diabetes

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Abstract. We examined the association between sex, age, insulin regimens and glycemic control in 133 Japanese children and adolescents, 42 males and 61 females aged 16.8 ± 7.0 yr, with type 1 diabetes mellitus (T1DM). The patients were divided into 5 age groups and were also classified according to the insulin regimen. The annual median HbA1c level in males (7.3 ± 0.2%) was similar to that in females (7.2 ± 0.2%). In regard to the age of the patients, the median HbA1c levels in patients aged 15–19 yr (7.9 ± 0.4%) was significantly higher than those aged 5–9 yr (7.2 ± 0.1%) and those aged 20≤ yr (6.6 ± 0.4%, $p<0.05$, respectively). On the other hand, there were no significant relationships between the HbA1c values and the insulin regimens. In conclusion, difficulty in management of diabetes due to emotional issues and endocrinological factors during adolescence may play a possible role in the deterioration of diabetes control. On the other hand, the insulin regimen does not seem to have a major impact on the metabolic outcome in young people with T1DM.

Key words: type 1 diabetes, insulin regimen, glycemic control

Introduction

In recent years, a variety of insulin regimens have been used for the treatment of type 1 diabetes mellitus (T1DM) in children and adolescents (1). Multiple daily injections (MDI) of rapid- (Ra) and long-acting (L) insulin analogues have been used widely in these patients. Moreover, use of continuous subcutaneous insulin infusion (CSII) has been extended to those in whom MDI is either impractical or ineffective. These measures have been reported to improve hyperglycemia with reducing the occurrence of severe hypoglycemia in the young patients (1–4). On the other hand, the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends a target range for HbA1c of less than 7.5% in pediatric patients of all ages with T1DM in its Clinical Practice Consensus Guidelines (5). Several studies have demonstrated that the recent HbA1c levels of young patients with T1DM on an intensive insulin treatment using newer insulins are still higher than the goal (6–8). In addition, it is known that optimization of metabolic outcome in females and adolescent patients is more difficult despite intensification

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of insulin therapy (6, 7).

We examined the annual mean HbA1c levels during 2008 in Japanese children and adolescents with T1DM and compared them in relation to the sex and age of the patients and the insulin regimens employed to identify the factors associated with glycemic control.

Methods

One hundred and three patients, 42 males and 61 females aged 16.8 ± 7.0 yr, with a duration of diabetes of at least one year were enrolled in this study. The patients were divided into 5 age groups: group A, 1–4 yr (n=6); group B, 5–9 yr (n=17); group C, 10–14 yr (n=18); group D, 15–19 yr (n=26); and group E, ≥20 yr (n=36). They were also classified according to the insulin regimens used as follows: twice daily insulin injections, n=10; thrice daily insulin injections, n=14; four times daily insulin injections, n=49; five times daily insulin injections, n=15; and CSII, n=15.

In regard to the insulin preparations used, 8 patients used premixed insulin analogue (aspart+NPH or lispro+NPH), and 2 used twice-daily injections of a mixture of regular (R) and neutral protamine Hagedorn (NPH) insulins. Six patients used varying combinations of premixed insulin analogue, Ra (aspart or lispro) and L (detemir or glargine), 5 used premixed insulin analogue, Ra or L, and one used thrice-daily injections of premixed insulin analogue and Ra. In the 49 patients taking 4 injections daily, 42 (85.7%) used Ra as bolus insulin and L as basal insulin, 3 used Ra as bolus insulin and NPH as basal insulin and 4 used Ra and R as bolus insulin and L as basal insulin. In the 15 patients taking 5 injections daily, 12 (80.0%) used Ra as bolus insulin and twice-daily injections of L as basal insulin, 2 used Ra as bolus insulin and NPH and L as basal insulin and one used Ra and/or R as bolus insulin depending on their daily schedule and twice-daily injections of L as basal insulin. All of the 15 patients on CSII used Ra.

All the patients were instructed to self-monitor their blood glucose levels at home. Determination of the insulin regimens and adjustments of the insulin dose were performed by one pediatrician, who was mainly involved in treatment of the patients at an outpatient clinic on the basis of the blood glucose profiles determined by self-monitoring and the lifestyles and daily activity schedules of the patients. The patients visited the outpatient clinic each month or at least every two or three months.

The HbA1c level was measured at each visit. We compared the annual mean HbA1c levels from January to December 2008 in relation to the sex and age of the patients and the insulin regimens employed. The HbA1c level was determined by an HPLC method (normal reference range, 3.3–5.8%).

Statistical analysis

The results were expressed as medians ± SE. The statistical significance of differences between groups was analyzed by the Mann-Whitney U test and Kruskal-Wallis test (*Dr. SPSS*II). p values <0.05 were regarded as denoting statistical significance.

Results

The overall mean annual HbA1c level in 2008 was 7.2 ± 1.1% (4.5–9.7%). In the 103 patients, the mean HbA1c level was <7.5%, which is defined as optimal in the ISPAD Clinical Practice Consensus Guidelines (5), in 59.2% of the patients, while it was >9.0%, which is considered to be predictor of poor outcome in the same guidelines, in 6.8% of the patients.

Differences in the HbA1c level in relation to sex and age at the time of the study

There was no significant difference in the median HbA1c level between the male and female patients (7.3 ± 0.2% vs. 7.2 ± 0.2%).

In regard to the relation with age, the median HbA1c level in group D was significantly higher

Table 1 Differences in the HbA1c level in relation to age at the time of the study

Age group	N	HbA1c (%)[#]
Group A (1–4 yr)	6	7.6 ± 0.2
Group B (5–9 yr)	17	7.2 ± 0.1
Group C (10–14 yr)	18	7.3 ± 0.3
Group D (15–19 yr)	26	7.9 ± 0.4*
Group E (≥20 yr)	36	6.6 ± 0.4

*vs. groups B and E, $p<0.05$, respectively (Kruskal-Wallis test). [#]The results were expressed as medians ± SE.

Table 2 Differences in the HbA1c level in relation to the insulin regimens employed

Insulin regimens	N	HbA1c (%)[#]
Twice-daily injections	10	7.1 ± 0.2
Thrice-daily injections	14	7.6 ± 0.3
Injections 4 times daily	49	7.2 ± 0.1
Injections 5 times daily	15	7.0 ± 0.2
CSII	15	7.3 ± 0.5

There were no significant relationships between the HbA1c values and the insulin regimens (Kruskal-Wallis test). [#]The results were expressed as medians ± SE.

than the levels in groups B and E (7.9 ± 0.4% vs. 7.2 ± 0.1% and 6.6 ± 0.4%, $p<0.05$, respectively; Table 1). There were no significant differences in median HbA1c level among groups A, B, C and E. In group D, HbA1c levels of <7.5% were achieved in only 8 (29.6%) patients; conversely, 6 (22.2%) patients showed poor glycemic control with HbA1c levels of >9.0%.

Differences in the HbA1c level in relation to the insulin regimens employed

In regard to the frequency of insulin regimens, of the 103 patients, 70 (72.8%) received three or more injections of insulin, and 15 (14.6%) received CSII. Among the 26 patients in group D, 22 (84.6%) used multiple injections of insulin or CSII. In addition, all the young children in group A received either multiple injections or CSII.

Table 2 shows the distribution of the median HbA1c levels among the various insulin regimens. We could not find any statistically significant differences in relation to the insulin regimens employed.

Discussion

Good glycemic control is critical in patients with T1DM. A target range of <7.5% is recommended in the Clinical Practice Consensus Guidelines of the ISPAD for all pediatric age groups (5). The long-term microvascular and macrovascular complications of diabetes mellitus, the sequelae of acute hypoglycemia and the central nervous system alterations associated with hyper- and hypoglycemia are considered to be avoidable if this glycemic goal can be achieved. Nevertheless, it still appears to be difficult to achieve this glycemic goal in young people with T1DM, even when intensive insulin therapy using the newer insulins is adopted (6–9). Danne *et al.* of the Hvidoere Study Group on Childhood Diabetes (7) reported that the mean HbA1c level in 1998 of 2,780 children and adolescents with T1DM aged 0–18 yr from 21 international pediatric diabetes centers in 17 countries was 8.62 ± 0.03%, which was not different from that in 1995 of 2,101 patients aged 11–18 yr from the same centers, despite adoption of intensive insulin regimens. De Beaufort et al. of the same study group (8) reported that the mean HbA1c level in 2005 among 2,062 patients with T1DM aged 11–18 yr was 8.2 ± 1.4%. They concluded that even intensive insulin regimens with increased use of CSII were not effective for improving the HbA1c levels in this large cohort of adolescents with T1DM. These results suggest that it might be difficult to obtain significant improvement of the glycemic outcome in young patients with T1DM despite substantial changes in the therapeutic approaches.

Some studies have shown an association of

Table 3 Factors in deterioration of glycemic control during adolescence

1) Decreased peripheral insulin sensitivity, perhaps caused by hypersecretion of growth hormone
2) Corrupted lifestyles including irregular daily diets and activity patterns
3) Spread of psychological and/or familiar problems
4) Inequality between demand for greater independence and responsibility for diabetes management
5) Difficulties in motivation for diabetes management

poor glycemic control with the female gender and adolescent age (6–8). Endocrinological factors play a possible role in aggravating glycemic control in females as compared to males, especially in the pubertal age group. In addition, females at this age suffer more frequently from behavioral problems, including eating disorders and subthreshold disorders, as compared with males (10, 11). Moreover, the practice of insulin omission to control body weight is frequently used by females of mid-teen age, which induces poor glycemic control (12). Nonetheless, we did not find any significant differences in the median HbA1c levels in relation to gender, even during adolescence, in the present study. On the other hand, we found the highest median HbA1c levels among the patients in group E. Most of the patients with an HbA1c >9.0% were adolescents. Some studies have suggested that decreased peripheral insulin sensitivity during adolescence, perhaps caused by hypersecretion of growth hormone, is the major reason for deterioration of glycemic control at this age (13, 14). Moreover, the majority of adolescent patients with poor glycemic control had psychological and/or familiar problems in the present study. They displayed corrupted lifestyles, including irregular daily diets and activity patterns. Adolescence is a period in which young people try to gain independence from the family, but the demand for greater independence may not be equaled by the need to take greater responsibility for diabetes management (15). It may be difficult to motivate proper diabetes management during this period, but it is important for diabetes teams to elicit it by providing continual mental support and diabetes education (Table 3).

There was no significant relationship between the HbA1c levels and the insulin regimens used in the present study; thus, the insulin regimen does not seem to have a major impact on the metabolic outcome in young people with T1DM. Nevertheless, we consider this to be one of the reasons why our patients were treated with optimal insulin regimens taking into consideration the patients' lifestyles, customs and daily activity schedules, as well as the glucose profiles for the individual patients. Patients who achieved satisfactory glycemic control even though they received twice-daily injections of insulin did not need either MDI or CSII. For some reason, such as their lifestyles and daily activity schedules, they could not be treated with MDI; however, the twice-daily injections seemed to be more optimal for their treatment. Patients who were treated with thrice-daily injections sometimes missed their bolus injections at lunchtime during school hours while on MDI with injections a times daily. This was the major reason why they chose the regimen of thrice-daily injections of insulin. On the other hand, patients on MDI or CSII eventually required further intensification of the insulin regimens to improve glycemic control when the optimal glycemic outcome could not be accomplished by conventional insulin therapy. Some patients who were treated with injections 5 times daily subsequently required twice-daily injections of basal insulin to attain stable glucose levels throughout the day. MDI and CSII should

be introduced in motivated patients of any age, including very young children, if they fail to achieve optimal glycemic control with twice- or thrice-daily injections of insulin (16, 17). Consequently, the insulin regimen should be individualized for each patient, and an optimal insulin regimen should yield satisfactory metabolic outcomes. In addition, diabetic education and a team approach by the diabetes care team is indispensable to achieve good glycemic control.

Conclusions

Adolescents with T1DM showed significant higher annual serum HbA1c levels than patients from the other age groups. Difficulty of diabetes management due to emotional issues and endocrinological factors during puberty may play a possible role in deterioration of diabetes control in this age group. On the other hand, the insulin regimen does not seem to have a major impact on the metabolic outcome in young people with T1DM.

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