Improvement in glycemic control through changes in insulin regimens: findings from a Japanese cohort of children and adolescents with type 1 diabetes

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Objective: Although insulin analogs have dramatically changed diabetes treatment, scarce evidence is available on those effects. We aimed to explore whether glycemic control had improved, the use of insulin analogs had been increased, and hypoglycemic events had decreased over time in Japanese pediatric patients with type 1 diabetes (T1D).

Methods: Glycated hemoglobin A1c (HbA1c) values, proportion of insulin regimens, incidence of severe hypoglycemic events, and pubertal increase in HbA1c were compared in three cohorts of childhood-onset Japanese T1D patients (567 subjects in the 1995 cohort, 754 subjects in the 2000 cohort, and 806 subjects in the 2008 cohort).

Results: Mean HbA1c values tended to decrease [78.5 mmol/mol (9.33%) in the 1995 cohort, 68.2 mmol/mol (8.39%) in the 2000 cohort, and 61.2 mmol/mol (7.75%) in the 2008 cohort; P < .0001]. The proportion of patients who received basal-bolus treatment tended to increase with statistical significance, as did the proportion on insulin analogs. The incidence of severe hypoglycemic events (events/100 patients/y) had decreased (19.1 in the 2000 cohort and 8.7 in the 2008 cohort; P = .02). The pubertal increase in HbA1c were compared in three cohorts of childhood-onset Japanese T1D patients (567 subjects in the 1995 cohort, 754 subjects in the 2000 cohort, and 806 subjects in the 2008 cohort).

Conclusions: Glycemic control and incidence of severe hypoglycemic events were chronologically improved, especially in female adolescents.

KEYWORDS
body mass index, child, diabetes mellitus, glycosylated, hemoglobin A1, hypoglycemia, type 1
against complications,\textsuperscript{3,4} improvement in glycemic control for patients with childhood-onset type 1 diabetes (T1D) is particularly important.

There have been a few studies regarding the long-term efficacy of glycemic control in children with T1D, but these were only cross-sectional analyses\textsuperscript{5,6} or included hospital-based data.\textsuperscript{7} Further, limited cross-sectional data are available on the relation of puberty with worsened glycemic control\textsuperscript{8–11} and the risks to obese and overweight patients.\textsuperscript{12–14} Therefore, a longitudinal study that follows pediatric patients from infancy to adolescence and focuses on the secular trend of HbA1c values is necessary. The aim of this longitudinal study was to explore chronological changes in glycemic control, clinical parameters, insulin regimens, and the incidence of severe hypoglycemic events in three cohorts of Japanese pediatric patients with T1D.

\section{METHODS}

\subsection{Patients}

The subjects were Japanese patients with T1D with an onset age of 16 y or younger, enrolled in three sequential cohorts in the Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes (JSGIT).\textsuperscript{6} Table 1 shows the baseline characteristics of the patients in the three cohorts of the JSGIT. The 1995 cohort consisted of 567 patients in 37 institutions who were followed up from April 1995 to October 1999. The 2000 cohort consisted of 754 patients in 46 institutions who were followed up from March 2000 to February 2008: 225 patients were re-registered from the 1995 cohort. The 2008 cohort consisted of 806 patients in 68 institutions who were followed up from March 2008 to February 2013: 82 patients were re-registered from the 2000 cohort. Data on the patients whose duration of T1D was shorter than 6 mo were excluded from this study to eliminate the effect of early phase treatment. T1D was diagnosed according to the criteria of the Japan Diabetes Society (JDS) and the American Diabetes Association.\textsuperscript{15,16}

\subsection{Data collection and measurements}

To evaluate the trend of glycated hemoglobin (HbA1c) values among patients with T1D, we used the annual data between July and October to eliminate seasonal variations. The annual data included HbA1c value, height, weight, insulin regimen, kind and dose of insulin, and numbers of severe hypoglycemic events. Incidence of severe hypoglycemic events were recorded in the 2000 and 2008 cohorts.

HbA1c values measured in accordance with the JDS values were converted to HbA1c values recommended by the National Glycohemoglobin Standardization Program (NGSP) and the International Federation of Clinical Chemistry (IFCC) according to the following equations: \textit{NGSP (\%) = 1.02 \times JDS (\%) + 0.25},\textsuperscript{17} \textit{IFCC (mmol/mol) = (10.93 \times NGSP) - 23.50}\textsuperscript{18} The HbA1c values of patients at enrollment were measured using a Tosoh Automated Glycohemoglobin Analyzer (HLC-723G8; Tosoh Corp., Tokyo, Japan) in a single clinical testing laboratory (SRL Inc., Tokyo, Japan). In the clinical laboratory, measurement of HbA1c values are always calibrated with the JDS lot 1, 2, or 4.\textsuperscript{19} After enrollment, HbA1c values were followed up at each institution. To ensure accuracy, HbA1c values for four patients at each institution were compared with those in the above-mentioned laboratory. Differences in HbA1c values between each institution and the laboratory were evaluated using absolute relative differences, which is the absolute difference divided by the HbA1c value determined in the laboratory.\textsuperscript{20} The mean ± standard deviation (SD) of the absolute relative differences (SD) was 2.24% ± 0.69% in the 1995 cohort, 2.98% ± 0.42% in the 2000 cohort, and 2.11% ± 0.28% in the 2008 cohort. The accuracy of the differences of measured HbA1c values among the participating institutions was thus judged as acceptable.

According to the consensus guidelines of the International Society for Pediatric and Adolescent Diabetes,\textsuperscript{21} glycemic control was categorized to three ranges of the IFCC and NGSP HbA1c values: (1) an optimal group, with HbA1c values <58 mmol/mol (<7.5%); (2) a suboptimal group, with HbA1c values of 58–75 mmol/mol (7.5–9.0%); and (3) a high-risk group, with HbA1c values >75 mmol/mol (>9.0%). The proportions of these three glycemic control categories were compared among the three cohorts.

Body mass index (BMI) was calculated as the weight in kilograms divided by the height in square meters. Height standard deviation score (SDS) and BMI percentile were calculated using the Japanese population data for each given age and sex, in accordance with the guidelines of the Japanese Society for Pediatric Endocrinology and the National Health and Nutrition Survey.\textsuperscript{22,23} Overweight and obese patients were defined as those with a BMI at the 85th percentile or greater and the 95th percentile or greater, respectively.\textsuperscript{24} Insulin regimens were classified into two groups: regimens of one to three injections per day were included in the "non-basal-bolus treatment group" and regimens including three or more administrations of bolus insulin and basal insulin per day were included in the

\begin{table}
\centering
\caption{Characteristics of the study cohorts}
\begin{tabular}{|l|c|c|}
\hline
 & 1995 cohort & 2000 cohort & 2008 cohort \\
\hline
Numbers (% of male) & 567 (42.0) & 754 (38.3) & 806 (39.0) \\
\hline
Date of birth & January 1, 1975 to December 31, 1988 & January 1, 1982 to December 31, 1999 & January 1, 1990 to December 31, 2007 \\
\hline
Duration of diabetes as of August 1, y; mean ± SD & 6.3 ± 3.6 & 6.0 ± 3.7 & 5.7 ± 3.7 \\
\hline
Age in December (y) & 7.20 (December 31, 1995) & 0.5-17 (December 31, 1999) & 0.5-17 (December 31, 2007) \\
\hline
Follow-up period & April 1995 to October 1999 & March 2000 to February 2008 & March 2008 to February 2013 \\
\hline
\end{tabular}
\end{table}

Abbreviation: SD, standard deviation.
"basal-bolus treatment group." The basal-bolus treatment group was further divided into multiple daily insulin (MDI) and continuous subcutaneous insulin infusion (CSII) groups. The type of insulins was classified as analog or non-analog. The dose of insulin was calculated as the total daily mean insulin amount in units divided by the body weight in kilograms per day (U/kg/d).

We compared longitudinal changes in HbA1c values specific sex and age in each cohort. To compare the degree of increase in the HbA1c values during puberty, pubertal increase in HbA1c was calculated in each patient using the following equation: (pubertal increase in HbA1c) = (maximum HbA1c value at the age between 11 and 15 y) − (HbA1c value at the age of 10 y). The pubertal increases in HbA1c were compared among the three cohorts.

2.3 Statistical analysis

We used Mann-Whitney U test to analyze skewed data and \( \chi^2 \) test to analyze categorical data. The Cochran-Armitage tests or Jonckheere-Terpstra tests was used to access longitudinal trends. Graphs of mean HbA1c values at each age were constructed to compare glycemic control in the three cohorts. All analyses were based on the assumption of missing at random. Descriptive statistics are reported as the mean ± SD. Two-sided probability levels <.05 were considered statistically significant and were corrected using the Bonferroni’s method for multiple comparisons. All statistical tests and descriptive analyses were performed using JMP software (version 11.0; SAS Institute Inc., Cary, NC, USA) or SAS statistical software (version 9.3; SAS Institute Inc.).

### Table 2 HbA1c values and other outcomes in the three cohorts

| Outcomes, mean ± SD or proportions (%) | 1995 cohort | 2000 cohort | 2008 cohort | \( P \) for trend |
|----------------------------------------|-------------|-------------|-------------|-----------------|
| HbA1c, mmol/mol (HbA1c, %)             | 78.5 ± 22.4 | 68.2 ± 17.9 | 61.2 ± 13.0 | <.0001          |
| (9.33 ± 2.05)\(^*\)\(^*\)\(^*\)\(^*\) | (8.39 ± 1.63)\(^*\) | (7.75 ± 1.19) | \( \chi^2 \) test |
| Male                                   | 76.3 ± 20.0 | 66.2 ± 14.8 | 60.1 ± 11.4 | <.0001          |
| (9.13 ± 1.83)\(^*\)\(^*\)\(^*\)\(^*\) | (8.21 ± 1.35)\(^*\) | (7.56 ± 1.35) | \( \chi^2 \) test |
| Female                                 | 80.1 ± 23.9 | 69.4 ± 19.4 | 61.9 ± 14.0 | <.0001          |
| (9.48 ± 2.18)\(^*\)\(^*\)\(^*\)\(^*\) | (8.50 ± 1.77)\(^*\) | (7.81 ± 1.28) | \( \chi^2 \) test |
| Proportion of patients with optimal control for HbA1c < 58 mmol/mol (HbA1c < 7.5%) | 18.5\(^*\)\(^*\)\(^*\)\(^*\) | 30.9\(^*\)\(^*\)\(^*\)\(^*\) | 43.9 | <.0001 |
| Proportion of patients treated with basal-bolus insulin | 34.4\(^*\)\(^*\)\(^*\) | 61.0\(^*\)\(^*\)\(^*\) | 83.5 | <.0001 |
| Proportion of patients using insulin analogs | 0.0 | 14.6 | 94.7 | <.0001 |
| As bolus                               | 0.0 | 14.6 | 88.6 | <.0001 |
| As basal                               | 0.0 | 0.0 | 94.7 | <.0001 |
| Proportion of patients using tea bolus | No data | 1.72\(^*\)\(^*\)\(^*\)\(^*\) | 19.7 | <.0001 |
| Total daily insulin dose per body weight (U/kg/d) | 1.01 ± 0.32\(^*\)\(^*\)\(^*\) | 1.06 ± 0.36 | 1.08 ± 0.34 | .0009 |
| Height SDS                            | -0.19 ± 1.05\(^*\)\(^*\)\(^*\) | -0.17 ± 1.31\(^*\) | 0.05 ± 1.07 | <.0001 |
| BMI (kg/m²)                            | 19.72 ± 3.08 | 20.06 ± 3.40 | 19.67 ± 3.51 | .64 |
| BMI percentile                        | 52.71 ± 25.21\(^*\)\(^*\)\(^*\) | 58.71 ± 26.65 | 58.09 ± 25.79 | .0003 |
| Proportion of overweight patients     | 12.2\(^*\)\(^*\)\(^*\) | 17.2 | 18.0 | <.0001 |
| Proportion of obese patients          | 2.3\(^*\)\(^*\)\(^*\) | 3.9 | 5.0 | <.0001 |
| Incidence rate of severe hypoglycemia, events/100 patients/y | No data | 19.1 ± 16.18 | 8.7 ± 59.6 | .02 |

Overweight patients were at the 85th BMI percentile or higher and obese patients were at the 95th BMI percentile or higher. Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin A1c; SD, standard deviation; SDS, standard deviation score.

\(^*\): \( P < .0001 \) vs 2000 cohort, \(^*\): \( P < .0001 \) vs 2008 cohort, \(^*\): \( P < .05 \) vs 2000 cohort, \(^*\): \( P < .05 \) vs 2008 cohort using the Mann-Whitney U-test or \( \chi^2 \) test. Cochran-Armitage test or Jonckheere-Terpstra test was used to determine \( P \) for trend.

2.4 Ethical approval

This observational study was approved by the review board of each participating institution in accordance with the ethical guidelines and regulations of the Declaration of Helsinki. Written consent was obtained from all patients or their parents.

3 RESULTS

3.1 Changes in glycemic control in the three cohorts

Glycemic control, insulin regimens and doses, height SDS, BMI, proportions of overweight and obese patients, and incidence rate of severe hypoglycemia in the 1995, 2000, and 2008 cohorts are shown in Table 2. A trend of statistically significant improvement in HbA1c values was observed among the three cohorts (\( P \) for trend < .0001). In both sexes, a trend of decreased HbA1c values was observed (\( P \) for trend < .0001). Table 2 and Figure 1 also show the proportions of classified glycemic control (optimal, suboptimal, and high-risk groups). The proportions of optimal glycemic control had increased (\( P \) for trend < .0001). Moreover, the proportion of patients with high-risk HbA1c glycemic control tended to decrease (\( P \) for trend < .0001).

The mean HbA1c values of patients at each age are shown in Figures 2 and 3. The mean numbers of measured HbA1c were 4.2 (SD: 1.4) in the 1995 cohort, 5.6 (SD: 2.4) in the 2000 cohort, and 4.3 (SD: 2.4) in the 2008 cohort.
1.2) in the 2008 cohort. In addition, at the age of 8–19 y, the mean HbA1c values in the 2000 cohort was lower than those in the 1995 cohort (P < .05)

Among female patients, the pubertal increase in HbA1c (mean ± SD) tended to decrease with statistical significance (P for trend =.0003): 14.0 ± 24.9 mmol/mol (1.28 ± 0.31%) in the 1995 cohort, 10.3 ± 19.1 mmol/mol (0.94 ± 0.16%) in the 2000 cohort, and 4.2 ± 9.4 mmol/mol (0.38 ± 0.08%) in the 2008 cohort. The pubertal increase in HbA1c among male patients also tended to decrease, but did not reach statistical significance (P for trend = 0.55): 12.0 ± 23.0 mmol/mol (1.10 ± 2.11%) in the 1995 cohort, 9.4 ± 14.2 mmol/mol (0.85 ± 1.30%) in the 2000 cohort, and 9.4 ± 13.7 mmol/mol (0.86 ± 1.26%) in the 2008 cohort.

3.2 | Other clinical parameters in the three cohorts

Table 2 and Figure 4 show the proportions of the patients with insulin regimens of one, two, and three times a day as well as MDI, and CSII. The frequencies of patients undergoing basal-bolus treatment (MDI or CSII) and the percentage of patients using insulin analogs were significantly increased (P for trend < .0001). The daily insulin dose according to weight tended to increase from the 1995 cohort to the 2008 cohort (P for trend = .0009) (Table 2). Within each cohort, the total daily insulin dose (U/kg/d) in patients who had been receiving basal-bolus treatment was higher than that in patients who had not received this treatment: 1.07 ± 0.30 vs 0.98 ± 0.33 in the 1995 cohort (P = .0045), 1.12 ± 0.33 vs 0.97 ± 0.37 in the 2000 cohort (P < .0001), and 1.09 ± 0.33 vs 1.03 ± 0.03 in the 2008 cohort (P = .043). Although the height SDS tended to increase from the 1995 cohort to the 2008 cohort (P for trend < .0001), the BMI percentiles also tended to increase from in the 1995 cohort to the 2008 cohort (P for trend = .0003). Furthermore, the proportions of overweight and obese patients among the three cohorts significantly increased (P for trend < .0001). Furthermore, the proportions of overweight and obese patients among the three cohorts significantly increased (P for trend < .0001). The incidence rate of severe hypoglycemic events was lower in the 2008 cohort than in the 2000 cohort (P = .02).

4 | DISCUSSION

In this study, glycemic control of pediatric patients with T1D tended to improve among the 1995 to 2008 cohorts. Notably, the pubertal increase in HbA1c values in female patients tended to decrease among the sequential cohorts. The findings of this study also indicated that the improvement in glycemic control and decreased incidence rate of severe hypoglycemic events can be attributed to the increased use of basal-bolus insulin regimens using insulin analogs with sufficient dosages.
4.1 Strengths and limitations

To the best of our knowledge, this is the first multicenter survey of glycemic control and treatments of Japanese childhood-onset T1D. This study is strengthened by several aspects. First, this study from a number of institutions followed up more than 500 patients; thus, it is the largest cohort to date in Japan, where T1D is regarded as a relatively rare disease compared with that in western countries. Second, the measured HbA1c values at each institution were standardized by careful calibrations, which enhanced the accuracy of the present results. Third, it was found that the pubertal increase in HbA1c had improved from 1995 to 2008 in Japan.

Several limitations should be considered when interpreting the results of this study. First, the institutions participating in the present study may not represent the majority of Japanese hospitals. However, because Japanese patients with T1D are usually followed up in specialized institutions, we believe that the three cohorts have registered most T1D patients. As a second limitation, uncontrolled T1D cases may have dropped out. However, we consider that the comparability of the three cohorts would be preserved when the data were missing at random. Third, the measured insulin doses may not be accurate because the information on total daily insulin dose were not from CSII devices but rather self-reports by the patients. Because the variation of day-to-day dose could be large among individual patients, the individual dose were not easily determined. Fourth, this analyses of the three cohorts did not assess ultra-long-acting insulin analogs (eg, degludec), which have been reported as safe and effective for children, and have been covered by the Japanese National Health Insurance Program since 2013. Nonetheless, we consider that we sufficiently evaluated the effects of long-acting insulin analogs.

4.2 Possible mechanism underlying the improvement in glycemic control

The observed improvement in glycemic control may be because of the increased frequency of the basal-bolus insulin regimens using insulin analogs, which mimic the physiological insulin response to glycemic changes in non-diabetic patients. The pediatricians of the JSGIT have been intensively introducing MDI to their patients since 1993. In Japan, rapid-acting insulin analog was introduced in 2001 and the use of a long-acting insulin analog was started in 2003. Blood concentration of rapid-acting insulin analogs (eg, lispro) rises sharply and drops precipitously without increasing the risk of severe hypoglycemic events. On the other hand, the use of long-acting insulin analog (eg, glargine and detemir) enables diabetic patients to maintain peak-less basal insulin levels with fewer hypoglycemic events. The combination of the two above-mentioned insulin analogs enables patients to receive insulin while eating snacks. According to this data, the proportion of basal insulin in the total daily insulin dose among the patients who received basal-bolus treatment was 35% in 2000 and 38% in 2008 (data not shown), and the proportions were similar to that for 27.7% of Japanese adult patients with T1D patients who treated with CSII. In contrast, the proportion of basal insulin is reported to be approximately 50% in western countries. In Japan, such a low proportion of basal insulin requirement may have exerted a favorable effect on glycemic control among Japanese children with T1D.
To assess the efficacy of treatment, the Hvidøre Study Group proposed a new classification for insulin regimens and emphasized the importance of patient education and skill training.\(^3\) In addition, Keller et al. concluded that general health perception was more strongly associated with improvement in glycemic control than insulin regimens and diabetes knowledge. In contrast to these reports, our data suggest that improved glycemic control was associated with progress and development of treatment, especially basal-bolus treatment with insulin analogs.\(^37\) We consider that the observed improvement in glycemic control in this study was also associated with general health perception resulting from safety treatment with rapid- and long-acting insulin analogs without hypoglycemia, particularly in adolescents.

Particularly in Japanese adolescents with T1D, the following factors were considered to contribute to the chronological improvement in glycemic control. First, because most diabetic patients visit a hospital or clinic monthly, they could easily manage their insulin regimens and receive face-to-face medical advice throughout puberty when tailor-made insulin regimens are needed. Because public insurance covers all Japanese residents, patients with T1D are able to frequently visit hospitals or clinics with minimal expense. Second, the well-balanced Japanese diet\(^38\) protects against becoming overweight and may have contributed to the favorable glycemic control. For example, the mean percentage of fat in total energy intake in adolescents aged 15–19 in Japan is reportedly lower (33%) than that in the United States (40\%).\(^38\) Japanese students do not regularly have snack time at schools and receive well-balanced school lunches. Because high-fat diets can prolong postprandial hyperglycemia,\(^39\) plasma glucose from the Japanese low-fat diet may have been more appropriately controlled by newly developed insulin analogs.

4.3 Improvement of clinical parameters

Although the height SDS of the patients in the 1995 cohort was below the average of the Japanese children, the height SDS was significantly increased in the 2000 and 2008 cohorts. BMI percentile had also increased, suggesting that growth of children with T1D had been closer to that of children without T1D. This result may have partially resulted from chronologically developed methods of insulin administration that compensate for the increased need for physiological insulin during childhood. Although the proportion of overweight children (weight >20% over the standard weight adapted to sex and height) in the Japanese general population had not changed from 2003 to 2013 in Japan,\(^40\) the proportion of overweight and obese children with T1D through the present cohorts had slightly increased. This increase in BMI was thought to be partly because of sufficient insulin dosages. Although the levels of BMI in Japanese obese children with T1D is relatively moderate in comparison with that in western countries,\(^1\) it is important to continuously monitor patients to prevent obesity when they approach adulthood.

4.4 Consistency with previous studies

A cross-sectional report on long-term glycemic control in adult Japanese patients with T1D reported mean HbA1c value of 65.9 mmol/mol (8.18%) in 2001 and 63.1 mmol/mol (7.92%) in 2008.\(^41\) Similarly, glycemic control among Japanese children with T1D had improved from 2000 [68.2 mmol/mol (8.39%)] to 2008 [61.2 mmol/mol (7.75%)] in 2008. Other studies reported that glycemic control in female adolescents was poorer and more exacerbated than that in males.\(^9\),\(^42\),\(^43\) These studies agree with the present results that have suggested improved, but worse glycemic control in female adolescents than that in male adolescents in the 1995 and 2000 cohorts\(^42\) (Figures 2 and 3). Although the latest report of American children with T1D showed that the pubertal increase of HbA1c had decreased from 1995 to 2004,\(^42\) the pubertal increase in HbA1c among Japanese children is less than that in western patients.\(^42\),\(^43\) Further, the control of plasma glucose in female adolescents is considered more difficult than that in male adolescents because insulin resistance is greater.\(^44\) The marked improvement in HbA1c values among the female adolescents included in the 2008 cohort was probably because of basal-bolus treatment regimens with insulin analogs, which provided easier glycemic control with less frequent hypoglycemic events.

5 CONCLUSIONS

This study revealed an improvement in glycemic control and a decreased incidence rate of severe hypoglycemic events among Japanese pediatric patients with T1D. This improved glycemic control was probably because of the developed basal-bolus treatment regimens with insulin analogs. The improvement was more pronounced in Japanese pubescent female patients.

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Conflict of interests

The authors declare no potential conflict of interests.

Author Contributions

M.M. and T.K. researched data, equally contributed to the discussion as the first authors and wrote the manuscript. T.U. and N.K. contributed to the discussion. H.Y. contributed to the discussion regarding statistical methodology. T.H. contributed to the standardization of HbA1c values. N.M., N.S., and S.S. were the chairpersons of the first, second, and fourth cohorts, respectively. S.A. was the chairperson of the third cohort, researched data, and wrote the manuscript.
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APPENDIX

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