Glicemic control in prepubertal and pubertal patients with diabetes type 1 – a one year ambulatory follow-up


Abstract

Objective: to evaluate glycemic control in type 1 diabetes mellitus patients followed in 1998.

Patients and methods: we studied 38 patients [22 males; age = 10.4 ± 4.1 years; 12 (31.6%) prepubertal, 26 (68.4%) pubertal], with diabetes duration of 3.7±3.4 years and age of diagnosis of 7.2 ± 4.7 years. HbA1c was determined using high-performance liquid chromatography (L-9100 Merck Hitachi, reference value =2.6 to 6.2%).

Results: HbA1c was 8.04 ± 2.4%, without association with gender and puberty. In the 27 patients with at least two HbA1c determinations, the level of glycemic control changed in 8 (29.6%) and remained the same in 19 (70.4%). Among the patients with good glycemic control, HbA1c was always within reference values in 4 (25%); 7 (43.75%) had at least one HbA1c measurement within these limits; and in 5 (31.25%), all HbA1c measurements were above the upper limit of the reference range. There was no association between the last glycemic control evaluation and the number of HbA1c determinations. The intraindividual coefficient of variation of HbA1c in the group that had at least three HbA1c determinations (n = 19) was 11.2 ± 5.6% (P = 0.0000).

Conclusion: in our study, although most patients presented satisfactory glycemic control during the follow-up period, only 4 patients (14.8%) maintained normal values of HbA1c. The variability of HbA1c must be evaluated when considering the interrelation between glycemic control and evolution to microvascular complications in diabetes.

Introduction

Currently, it is possible to consider the diabetes mellitus type 1 (DM1) as the most common endocrinopathy that affects infants and adolescents in both developed and developing countries. Recent epidemiological data have indicated a significant increase on the incidence of the disease, predominantly among children up to the age of 5 years in comparison to others. This increase results in a significant number of children and adolescents at risk for presenting diabetes-related chronic and acute complications and, consequently, in early mortality and reduction of the quality of life. In this sense, efficient glycemic control could reduce the risk for evolution to microvascular complications, as demonstrated by the Diabetes Control and Complications Trial (DCCT). The DCCT did not, however, follow-up patients younger than 13 years of age. Conversely, two different studies with DM1 children and adolescents - one that carried out a follow-up in Belgium and the other a cross-sectional non-population-based survey with 22 pediatric departments from 18 countries in Europe, Japan, and North America demonstrated, respectively, that 62%...
and 34% of patients maintained a satisfactory level of glycated hemoglobin (HbA1c) with good glycemic control. Different factors associated to general population of children can cause fluctuations of glycemia and, consequently, affect HbA1c and upset the maintenance of good glycemic control.5 This has been recently described in a retrospective study in England6 that emphasized the need to consider the variability of HbA1c in the relationship between glycemic control and chronic complications of DM1.

Our objective was to analyze the variability of glycemic control and HbA1c in DM1 children during one year of outpatient follow-up.

Patients and methods
Our population included all patients followed-up by a multidisciplinary team at the outpatient diabetes clinic of the Pedro Ernesto Teaching Hospital in Rio de Janeiro, during the year of 1998. The population studied included 38 DM1 patients (16 female; 22 male), classified according to the American Diabetes Association (ADA) criteria,7 aged 10.9 ± 4.1 years, with age at diagnosis of 7.2 ± 4.7 years, and with diabetes duration of 3.7 ± 3.4 years.

Patients were classified for pubertal development according to the criteria presented by Tanner. Due to the reduced size of our sample, we grouped patients into prepubertal (31.6%), or Tanner stage 1, and pubertal (68.4%), or Tanner stage 2 to 4, groups. Groups were paired according to diabetes duration and to sex.8,9

The body mass index (BMI) was calculated according to weight (kg) divided by the height squared (m²) for a value of 18.1 ± 2.1 kg/ m² for the group.

Glycated hemoglobin (HbA1c) was calculated using high-performance liquid chromatography (L-9100 Merck Hitachi; reference value of 2.6 to 6.2%). The intrassay coefficient of variation for lower (4.5%) and higher (10%) values was below 0.1%. During the year of 1998, the total number of chromatography exams for HbA1c carried out per patient included one (n=11), two (n=8), three (n=9), four (n=6), five (n=3), and six (n=1) readings. For statistical analysis of the population, we grouped patients with 2 or more exams (n=27) and computed their average values in comparison to values of the group with only 1 chromatography exam. The coefficient of variation was calculated for patients with 3 or more chromatography exams for HbA1c (n=19). Classification of glycemic control according to good control (glycohemoglobin values within 1.33 times the upper limit of normal), regular control (glycohemoglobin values greater than or equal to 1.33 and less than 1.5 times the upper limit of normal), and poor control (glycohemoglobin values greater than or equal to 1.5 times the upper limit of normal) was based on the criteria presented by Chase (division of the HbA1c value by the upper limit of normal for glycohemoglobin).10

The total dosage of insulin was evaluated at the first and last appointment and the difference between these dosages was calculated.

Statistical analysis was carried out using SPSS (version 7.0) and Epi Info (version 6.0) software. For comparison of the groups we used either the Mann-Whitney or the Kruskal-Wallis test. For analysis of categorical variables we used the chi-square test and Fisher’s exact test. Data are presented in the form of average (+ standard deviation) or median (minimum/maximum). We considered a significance level for P<0.05 (two-tailed).

Results
Clinical characteristics of patients are described in Table 1. The average HbA1c was 8.04 ± 2.4% with no difference between prepubertal and pubertal patients, whose values were, respectively, [7.1 (5.0 - 10.2) vs. 7.9 (4.0 - 15.0)%; P = 0.19], nor between female and male patients, whose values were, respectively, [7.5 (4.7 - 12.6) vs. 7.7 (4.0 - 15.0)%; P = 0.8], nor between patients with > or = 2 years of diabetes duration in comparison to those with < 2 years, whose values were, respectively, [7.75 (4.0 - 12.2) vs. 7.35 (4.7 - 15.0)%; P = 0.54]. The group with diabetes duration < 2 years had a smaller dose of insulin in comparison to the group with diabetes duration > or = 2 years; doses were, respectively, [0.41 (0.04 - 1.42) vs. 0.95 (0.17 - 2.03) U/kg; P = 0.0001].

Twenty-four patients (63.2%) presented good glycemic control at the first appointment, 6 patients (15.8%) presented regular glycemic control, and 8 patients (21.1%) presented poor glycemic control. During follow-up of the 27 patients who had at least two chromatography exams for HbA1c 19 patients (70.4%) presented the same classification for glycemic control at the last appointment, out of which 16 (59.3%) maintained good control and 3 (11.1%) poor

<table>
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<th>Variable</th>
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<tr>
<td>Age (years)</td>
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<td>Sex (M/F)</td>
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<td>Age at diagnosis of diabetes (years)</td>
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<td>Body mass index (kg/m²)</td>
<td>18.1±2.1</td>
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control; in turn, 8 patients (29.6%) presented different classification for glycemic control, out of which 4 presented improvement and 4 worsening of glycemic control. The evaluation of glycemic control at the last appointment was not associated with the number of HbA\textsubscript{lc} readings, puberty, or sex. Comparison of the group that maintained good control with the group that maintained poor control indicated a tendency of patients in the earlier group to present longer diabetes duration; results were, respectively, [2.0 (0.5 - 11.0) vs. 0.8 (0.4 - 2.0); P = 0.09]. Moreover, the group that maintained good control also presented, in comparison with the group that maintained poor control, a smaller increase in the dose of insulin during the 1-year follow-up; results were, respectively, [0.05 (-0.7 - 0.3) vs. 0.3 (0.3 - 0.5) U/kg; P = 0.04]. The other variables analyzed were not significant.

The group that maintained good control presented HbA\textsubscript{lc} levels of 6.4 (5.0 - 7.7) %. In this group, 4 patients (25%) always maintained HbA\textsubscript{lc} levels within the limits for normal glycohemoglobin, 7 patients (43.75%) presented at least one HbA\textsubscript{lc} reading within these limits, and 5 patients (31.35%) always presented HbA\textsubscript{lc} levels higher than the limits for normal for glycohemoglobin. The 4 patients who always maintained HbA\textsubscript{lc} within the limits for normal glycohemoglobin represented 14.8% of the group of 27 patients who had at least 2 HbA\textsubscript{lc} readings during the 1-year follow-up.

The intraindividual coefficient of variation of HbA\textsubscript{lc} in the group of patients who had at least 3 HbA\textsubscript{lc} readings (n=19) was 11.2 + 5.6% (P = 0.0000), for values of 10.5 (2.3 - 16.8) and P =0.0001 for the group that maintained good glycemic control (n=12) and of 11.0 (3.7 - 21.4) and P =0.0006 for the group that presented different classifications of glycemic control (n=6). There were no statistically significant differences between the two groups (P = 0.9).

Discussion

Our study consisted of assessing the variability of glycemic control in children and adolescents with DM1, and with regular medical assistance during the year of 1998 at a Teaching Hospital, in the city of Rio de Janeiro. Due to regionalized characteristics, thus, our data cannot be generalized to the overall population. Moreover, the good conditions for outpatient follow-up at Hospital Pedro Ernesto also do not represent the general conditions of healthcare services offered in our city.

Other aspects that should be considered in the assessment of our results are the size of our sample, especially considering prepubertal patients, and the heterogeneity of the number of HbA\textsubscript{lc} exams carried out per patient. These facts alone could be the reason for our results not presenting differences in metabolic control between the prepubertal and pubertal groups, conversely to results found in the literature.\cite{4}

We employed the classification of glycemic control according to Chase,\cite{10} hose parameters for good control (glycohemoglobin values within 1.33 times the upper limit of normal) are superior to those presented by the ADA,\cite{7} in terms of therapeutic objectives; in other words, the ADA parameter of HbA\textsubscript{lc} values of less than 7% would correspond to values within 1.16 times the upper limit of normal.\cite{11} We chose Chase’s criteria over the ADA’s criteria because the earlier allows for classification of glycemic control according to good, regular, and poor control and for the comparison with other studies that use different methodologies for determining HbA\textsubscript{lc}. It is also important to emphasize that the ADA\cite{7} suggests that, for values greater than 1.33 times the upper limit of normal, additional therapeutic measures should be considered.

We did not find an association between HbA\textsubscript{lc}, sex, and puberty; this result is in accordance with our previous data collected at the same clinic\cite{12} and with that collected at other centers, with respect to data on pubertal groups.\cite{13} In our previous study, HbA\textsubscript{lc} was also not associated with the number of appointments per year, color of skin, nor number of insulin injections per day. Possibly, none of the patients in our sample were in the honeymoon period of DM1, because despite the fact that the group with less than 2 years of diabetes duration used lower doses of insulin, we did not observe differences in HbA\textsubscript{lc} of patients in that group in comparison to others.

In our study, the average HbA\textsubscript{lc} of 8.04\% (1.29 times the upper limit of normal) was similar to that described in Belgium,\cite{3} with values of 6.6\% (1.2 times the upper limit of normal); but lower than that described in a cross-sectional study with children and adolescents in France,\cite{5} with values of 8.97\% (1.42 times the upper limit of normal), and in a cross-sectional, multi-centered study in Europe, Japan, and the United States, with values of 8.6\% (1.36 times the upper limit of normal). The DCCT described patients with over 13 years of age who had intensive treatment and multidisciplinary team support presenting HbA\textsubscript{lc}, at the end of the study, of 7.1\% (1.17 times the upper limit of normal). The comparison of our results with those described above allows for the conclusion that our services are providing satisfactory glycemic control results. While most of our patients maintained good control throughout the year, 5 patients presented worsening of the glycemic control or maintained poor control; this was not associated with the number of HbA\textsubscript{lc} readings. Out of the variables assessed, we observed a smaller increase in the dose of insulin and a longer diabetes duration in patients who maintained good control in comparison to patients who maintained poor control - possibly because 2 patients in the latter group presented diabetes duration shorter than 8 months and were in the adjustment phase of insulin dosage. In the group that maintained good control, only 25\% of patients maintained...
all HbA\textsubscript{lc} readings within normal levels, 43.75% of patients had only one HbA\textsubscript{lc} reading within these parameters, and 31.25% did not have any HbA\textsubscript{lc} reading within normal limits. These findings are similar to those in a 9-year retrospective study in England with DM1 adult patients. In that study, only 3.3% of patients were consistently with HbA\textsubscript{lc} within normal levels (1.14 times the upper limit for normal), 21.3% maintained an average HbA\textsubscript{lc} level, and up to 43% had at least one HbA\textsubscript{lc} reading within normal parameters. These data corroborate our difficulty to maintain glycemic control normal in outpatients and our finding that there is a significant fluctuation of HbA\textsubscript{lc} even in patients with good glycemic control - demonstrated by the significant intraindividual coefficient of variation of HbA\textsubscript{lc} verified in all patients. We did not find differences in the intraindividual coefficient of variation of HbA\textsubscript{lc} among patients consistently with good glycemic control and those with different classification of glycemic control during the study. This finding could be a consequence of the reduced number of patients who were submitted to HbA\textsubscript{lc} chromatography exams during the year of 1998, and of the tendency of patients to present fluctuations in glycemia within the same level of glycemic control. The latter hypothesis is in agreement with our data since most patients (70.4%) consistently presented the same level of glycemic control for the year. The variability of HbA\textsubscript{lc} and, thus, of glycemia, even in patients with good glycemic control, could result in being at risk for development to microvascular complications of diabetes, according to the findings of the DCCT in a group with intensive treatment.  

Our study allows for the conclusion that the service provided at our center, despite all the innate difficulties related to patients of public hospitals and to the institution itself, has been attaining satisfactory results as to what concerns glycemic control and according to the 1-year follow up of DM1 children and adolescents. We feel that it is important that prospective studies be carried out to evaluate the incidence of microvascular complications related to diabetes, while considering both the level and the variability of glycemic control in DM1 patients.

References

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