Lower Basal Insulin Dose is Associated with Better Control in Type 1 Diabetes

David Strich, MD[1,2,*], Lucy Balagour, BMedSc[3,*], Joelle Shenker, MBBS[1], and David Gillis, MD[4]

Objective To test the hypothesis that lower basal insulin doses may be paradoxically associated with better diabetic control, we assessed the association between the basal insulin dose and hemoglobin A1c (HbA1c) level in a group of children and young adults with type 1 diabetes.

Study design This was a retrospective study of 89 patients with type 1 diabetes (mean age, 14.67 ± 4.8 years; range, 3-29 years) treated in a single outpatient clinic. Forty-six of the 89 patients were treated with continuous subcutaneous insulin infusion, and the other 43 were treated with multiple daily injections (glargine as basal insulin). The daily basal insulin dose was taken either as downloaded from the insulin pump or as registered in the chart at the most recent clinic visit. Glucose data were taken from computerized registration of downloaded patient glucometers. The mean time between data download and HbA1c determination was 0.9 ± 0.78 months. HbA1c level and basal insulin dose were entered with other variables in a multivariable linear regression model.

Results There was a significant correlation between injection of less total daily basal insulin and lower HbA1c level (Pearson correlation, 0.441; $P < .001$). Optimal HbA1c level was associated with use of 0.28 ± 0.08 U/kg/day of basal insulin (35 ± 10% basal/total).

Conclusion With lower basal insulin levels, lower HbA1C was achieved despite the same total bolus dose. The optimal basal dose as determined by this study is similar to that found in fasting individuals of similar age. *(J Pediatr 2017;182:133-6).*

The current recommendations for administration of insulin to patients with type 1 diabetes mellitus follow the basal-bolus paradigm, with insulin given for basal coverage either as subcutaneous long-acting insulin or as a continuous subcutaneous infusion of rapid-acting insulin, and prevention or correction of glucose excursions achieved with rapid-acting insulin. Insulin dose adjustments are made based on frequent self-measurement of capillary blood glucose, with the aim of achieving target levels.[1] The optimal starting basal dose is unknown.

Our group recently reported on insulin doses for patients who were fasting for 24 hours.[2] Because the patients received no food and thus no bolus insulin for 24 hours, insulin dose was thought to be a good estimate of their true basal insulin requirements. In that study, patients who received approximately 0.2 U/kg/day were more likely than patients receiving a higher dose to complete a 24-hour fast without clinically significant hypoglycemia.[2] Others have recommended similar basal doses,[3-5] but the documented evidence regarding this issue remains sparse. Although fasting insulin use may be a good measure of basal insulin requirement, the recommendation for nonfasting patients may be more complex. First, fasting in itself is a stressful situation that may affect insulin sensitivity. Second, whether it may be better practice to cover some of the food intake with background insulin for poorly compliant patients to allow for inaccuracies in bolus calculations is unclear. Regarding this latter issue, we held the contrary opinion that because the pharmacodynamics of rapid-acting insulin are better suited for the purpose of dampening glucose excursions, improved control would be better achieved by more careful use of bolus insulin. In fact, this idea is not new, and a recent multicenter study provided evidence that giving more boluses per day (together with more frequent blood glucose testing) correlated with better control.[6] Furthermore, although unnecessarily high basal insulin levels would be expected to initially reduce blood sugar levels, in this case the poorly compliant patient likely would respond with increased food intake, which in turn would induce more hyperglycemia, to which the patient likely would respond insufficiently with bolus insulin. Thus, in the final analysis, more basal insulin would not be expected to improve overall control. In fact, perhaps counterintuitively, injecting less basal insulin may be associated with better overall control.

CSII	Continuous subcutaneous insulin infusion
HbA1c	Hemoglobin A1c
MDI	Multiple daily injections

From the [1]Clalit Health Services, Jerusalem District, Israel; [2]Department of Pediatrics, Shaare Zedek Medical Center, Jerusalem, Israel; [3]Department of Medical Students, Hadassah-Hebrew University School of Medicine, Jerusalem, Israel; and [4]Department of Pediatrics and Pediatric Endocrine Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

*Contributed equally.

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To test this hypothesis in real-life conditions, we performed a retrospective study to evaluate the correlation between basal insulin injection habits and diabetes control among patients in the clinic.

Methods

Eighty-nine patients diagnosed with type 1 diabetes mellitus at least 1 year before the study were enrolled in this retrospective chart review. Demographic and clinical characteristics of the group are presented in the **Table**. The study was approved by the Institutional Review Board of Clalit Health Services.

The basal insulin dose used for the study was recorded as the total daily basal dose registered at the last visit for the continuous subcutaneous insulin infusion (CSII) group and as the most recent glargine dose recorded in the chart for the multiple daily injections (MDI) group. Glucose data downloaded from patient glucometers at the last clinic visit were analyzed and correlated with the most recently recorded hemoglobin A1c (HbA1c) value. The average time between the registration of glucose data and HbA1c measurement was 0.9 ± 0.78 month. For the purpose of this study, hypoglycemic level was defined by whole-blood capillary glucometer-measured glucose as severe at <50 mg/dL and mild at <70 mg/dL.

Statistical Analyses

The Student *t* test was used to compare 2 categories of quantitative variables. Variables that were significantly correlated with dependent quantitative variables were entered in a multivariable linear regression model or ANCOVA to test their simultaneous effect and correct for interfering variables. All statistical tests were 2-way, and $P < .05$ was considered to indicate statistical significance.

Results

HbA1c

There was a significant correlation between HbA1c and basal insulin. With lower total daily doses of basal insulin there was a significant reduction in HbA1c (Pearson correlation, 0.441; $P < .001$). We present the results as quartiles of HbA1c level vs basal insulin. Because the basal insulin level was identical in quartiles 2 and 3 (0.32 U/kg/day or 36.5% basal/total daily insulin), we combined these data into a single column, resulting in a 3-column presentation (**Figure 1**).

To evaluate these recommendations, we looked at a group of patients with optimal control. In this group of 18 patients, the highest HbA1c value was 6.8% (50.8 mmol/mol), and the average value was 6.49 ± 0.34% (47.4 ± 3.7 mmol/mol). The average daily basal insulin dose for this group was 0.28 ± 0.08 U/kg/day (35 ± 10% basal/total). For all other patients (ie, all patients with HbA1c >8.8%; 50.8 mmol/mol), the average basal dose was 0.35 ± 0.1 U/kg/day, or 39 ± 9% of basal/total ($P < .03$).

There was no significant difference among the groups in total daily bolus per kilogram of body weight. The basal insulin dose was significantly higher in patients in the upper quartile of HbA1c compared with those in the second and third quartiles combined ($P = .007$), but the difference between the first quartile and the second and third quartiles was not significant.

Hypoglycemia

Hypoglycemia, defined as serum glucose level <70 mg/dL, was documented in 9.9 ± 7.6% of tests/patients overall, with 10.3 ± 7.7% (range, 0-28.6%) in the CSII group vs 9.5% ± 7.5% (range, 0-31.6%) in the MDI group. Documentation of severe hypoglycemia (<50 mg/dL) occurred in 3.1 ± 4.15% of tests, with no difference between the CSII and MDI groups. The percentage of hypoglycemic tests, defined as self-test results <70 mg/dL, was significantly correlated with basal insulin; that is, a decreasing percentage of hypoglycemia with increasing basal insulin per kilogram of body weight (Pearson correlation, −0.236; $P = .026$). No correlation was found between total daily basal insulin and the number of severe hypoglycemic events, however. Lower HbA1c value was correlated with increasing rate of hypoglycemia (Pearson correlation, −3.00; $P = .004$) (**Figure 2**).

Frequency of Blood Testing

There was great variability in number of tests per day, with 1 patient averaging over 40 daily finger pricks and a large SD for the average number of tests (**Table**). However, in view of the known correlation between number of daily tests and HbA1c,[7] we looked at the average number of daily finger pricks for patients representing each column in **Figure 2**. The average numbers were similar for each group with $P = .54$ (ANOVA).

Age at Study

We used age as a surrogate for puberty because pubertal data were not available. To remove behavior-associated effects that would tend to increase HbA1c and cause poorer control, we compared the basal insulin dose in optimally controlled children aged <10 years vs those aged >10 years. The dose associated with the best control was nominally lower in the younger

Table. Demographic and diabetes-control characteristics by treatment method

Characteristics	All	Pump	MDI	*P* value
Number of patients	89	46	43	
Females/males, n	40/49	20/26	20/23	NS
Age, yr, mean ± SD (range)	14.1 ± 4.8 (3.9-29.9)	14.8 ± 5.6 (3.9-29.9)	14.5 ± 3.8 (5.3-20.9)	NS
Body mass index SDS, mean ± SD (range)	0.43 ± 0.9 (–2.1 to 2.2)	0.39 ± 0.9 (–2.1 to 2.2)	0.48 ± 0.9 (–1.6 to 2.2)	NS
Number of glucose tests/d, mean ± SD (range)	4.3 ± 4.3 (0.8-40.3)	4.9 ± 5.5 (1.9-40.3)	3.5 ± 1.9 (0.8-10.2)	NS
Duration of disease, yr, mean ± SD (range)	5.17 ± 3.21 (1.0-17.3)	5.13 ± 3.58 (1.0-17.3)	5.21 ± 2.82 (1.0-11.8)	NS

NS, not significant.