9-2003

# Beneficial Effects of Flexible Insulin Therapy in Children and Adolescents with Type 1 Diabetes Mellitus

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## Abstract

The purpose of this study was to determine the feasibility of a flexible multiple daily insulin (FMDI) regimen in routine pediatric diabetes care by comparing HbA$_{1c}$, body mass index (BMI), and episodes of severe hypoglycemia (SH) before and after initiation of FMDI therapy. Data from 44 patients (2-16 years old), on a conventional insulin (CI) regimen, were collected during quarterly diabetes clinic visits. These patients were transitioned from CI to FMDI regimen: pre-meal lispro (bolus) and once or twice daily Humulin Ultralente with or without bedtime Humulin NPH as the basal insulin. There was a significant improvement in HbA$_{1c}$ in prepubertal (9.3%+/-1.3% vs. 8.0%+/-1.1%, p<0.002) and pubertal subjects (9.2%+/-1.0% vs. 8.2%+/-0.9%, p<0.001). Pubertal subgroup demonstrated an increase in BMI (21.3+/-3.1 vs. 22.7+/-3.2 kg/m$^2$, p<0.0001) after one year. The rate of SH was decreased in both prepubertal ( p<0.01) and pubertal ( p<0.05) groups of patients on FMDI therapy. The use of FMDI in a general pediatric diabetic population is a feasible therapeutic option for maintenance and possible improvement of glycemic control. It may effectively decrease the HbA$_{1c}$, and reduce hypoglycemic episodes, without producing an abnormal increase in BMI.

## Key words

## Introduction

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin therapy with either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) resulted in dramatic risk reductions for the development and progression of microvascular complications compared with conventional treatment [1]. Data from the adolescent cohort (13-17 years of age at entry) demonstrated the same degree of improvement and the same relationship between the outcome measures of microvascular complications. Intensively treated adolescents had a three-fold greater risk of severe hypoglycemia and a two-fold increased risk for obesity compared to intensively treated adults [2-4]. Other studies of children and adolescents have not documented consistently increased frequency or severity of hypoglycemia with intensive management [5-7].

In recent years, significant changes have occurred in the management of type 1 diabetes mellitus (DM) [8, 9]. Insulin replacement regimens now stress the importance of administering smaller doses of insulin throughout the day based on flexibility in making food choices to fit individual lifestyles while focusing on improved metabolic control [9]. The use of carbohydrate counting has been utilized in a number of diabetic management regimens to aid in this flexibility [10]. Lispro (Humalog) insulin has been shown, for this purpose, to be an ideal mealtime insulin [8, 11-13]. Age-adjusted and individualized insulin to carbohydrate ratios and insulin dosage adjustment algorithms have been developed to normalize elevated blood glucose levels and to compensate for alterations in carbohydrate intake [14]. This has also dramatically changed how insulin replacement is given to toddlers as well as when a flexible meal plan is desired [15].

Intermediate-acting and long-acting insulins, which mimic physiologic low-level basal insulin secretion, are important in intensive glycemic control [16]. They are usually administered once or twice daily independent of carbohydrate content of the specific meal [10, 17].

Though CSII therapy is used increasingly in pediatric patients to achieve meticulous glycemic control [18-20], insulin injection regimens remain the mainstay of diabetes care for the majority of patients. We studied 44 children and adolescents (aged 2-16 years) to determine the feasibility of flexible multiple daily insulin (FMDI) therapy in routine diabetes care. We also evaluated the clinical efficacy, in this selected group, by comparing the $HbA_{1c}$, body mass index (BMI), and frequency of severe hypoglycemic (SH) episodes in these patients before and after initiation of FMDI therapy.

## Materials and methods

### Study subjects

Forty-four Caucasian children and adolescents (aged 2-16 years) were included in the study. All patients were cared for in the Children's Hospital of Wisconsin Diabetes Center (affiliated with Medical College of Wisconsin). Prior to initiation of flexible insulin regimen, all patients were on a split-mixture schedule of 2-3 administrations of lispro and intermediate-acting Humulin NPH insulin. The schedule for 2 administrations was: prc-breakfasl, lispro + NPH; pre-supper, lispro + NPH (n=33). The schedule for 3 administrations was: pre-breakfast, lispro + NPH; pre-supper, lispro; and bedtime, NPH (n=11). Patients were switched to FMDI in an attempt to achieve optimal glycemic control, to reduce hypoglycemic events, and to provide a more flexible lifestyle by allowing mealtime carbohydrate adjustment. Before initiation of FMDI regimen, patients and their parents were evaluated by the diabetes team for ability to manage intensive therapy, which included diabetes self-management and insulin adjustment. They were taught dietary strategies to calculate insulin bolus dosing based on insulin to carbohydrate ratio. They were also taught insulin adjustment strategies that included post-prandial blood glucose determinations. Patients were evaluated at quarterly (every 3 months) Diabetes Clinic visits. Most patients also contacted the team every 6-8 weeks to review blood glucose records.

For each patient, data were collected for one year prior to FMDI initiation and for the first year of FMDI therapy. The following data were collected during the quarterly clinic visits: $HbA_{1c}$, BMI, and Tanner stage. The number of severe hypoglycémie episodes was defined as blood glucose <50 mg/dl (<2.8 mmol/l) associated with unconsciousness with or without seizure (expressed as events per 100 patient-years). The frequency of mild to moderate hypoglycemia, defined as blood glucose <70 mg/dl (<3.9 mmol/l) with or without behavioral impairment, was expressed as hypoglycemic episodes per week. Hypoglycemia data were recorded at each visit for the preceding 3 months. This study was approved by the Institutional Review Board (IRB) of Children's Hospital of Wisconsin in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The IRB approval was obtained for the retrospective review of patients' clinical charts and, therefore, informed consent was not required. The details that might disclose the identity of the subjects under chart review were omitted.

### Nutritional assessment

All patients and their families were already using carbohydrate counting for at least 6 months prior to initiation of flexible insulin therapy. Each subject and family received nutrition and meal planning recommendations and education on the application of carbohydrate counting to flexible insulin regimen, based on established guidelines [21]. Food labels, exchange lists, food models, and restaurant reference guides were used as educational tools. Each patient was evaluated by a nutritionist at quarterly clinic visits. A 24-hour dietary recall with assessment of carbohydrate counting skills was

performed at each clinic visit. If any issues arose regarding accuracy of implementation of these guidelines, they were addressed at the clinic visit or on a separately scheduled visit with the nutritionist.

Growth parameters were assessed at each visit including height, weight, the percentile for age and BMI. According to the National Center for Health Statistics, males and females are considered overweight at a BMI above the 85th percentile for age [22]. This criterion was used to establish the number of children and adolescents who were overweight before and after FMDI treatment.

## Insulin dosage calculations and HbA$_{1c}$ determination

All patients received lispro insulin or lispro (Humalog vial or Humalog Pen Lilly, Indianapolis, USA) before meals. The total daily dose (TDD) of insulin from the conventional regimen was used to calculate bolus and basal doses of FMDI regimen. The lispro insulin dosage for meals was calculated by dividing one-half of TDD of insulin by the total number of carbohydrate exchanges (1 carbohydrate exchange = 15 g), thus estimating lispro insulin to carbohydrate ratio. A correction (supplemental) dose of lispro insulin was based on increasing the dosage of lispro insulin by 0.5 U if the insulin to carbohydrate ratio was 0.5, or by 1 U if the ratio was 1.0. This 0.5 U or 1 U of lispro was added for every 50 mg/dl (2.8 mmol/l) that the blood glucose level was greater than the upper limit of the target range. For children <5 years of age, the target range was 100-200 mg/dl (5.6-11.1 mmol/l); for children > or =5 years of age, it was 80-150 mg/dl (4.4-8.3 mmol/l). However, the insulin dosage algorithm was individualized in some patients because of variable insulin sensitivity. The insulin dosage algorithm instructed the patients to subtract 0.5 U or 1.0 U of lispro insulin if the blood glucose was less than the lower limit of the target range.

Families were instructed to adjust unit per carbohydrate ratio and correction dose based on 2-hour post-prandial blood glucose determinations. For the youngest children, pre-lunch lispro insulin injection was administered by parents, daycare personnel or school nurse. Mealtime lispro insulin was administered at a maximum of 15-20 min after the meal in young children who demonstrated unpredictable eating habits [15|. Independent of lunchtime injections with an insulin pen, adult supervision was encouraged and achieved in most children > or =5 years of age.

The other half of TDD of insulin was given as two equally divided doses of Ultralente insulin (Lilly, Indianapolis, USA) before breakfast and supper. In patients demonstrating prebreakfast hyperglycemia, pre-supper Ultralente was replaced with bedtime Humulin NPH insulin (Lilly, Indianapolis, USA). Families were also given guidelines for adjustment of basal insulin. All insulin dose changes were made through consultation with the clinic at first and then independently by families of patients.

The HbA$_{1c}$ level was determined every day using the Bayer DCA 2000 instrument (Bayer Diagnostics, Tarrytown, USA), with a non-diabetic range of 4.5%-5.7%.

## Statistical analysis

Analyses were performed on the entire group as well as on 2 subgroups that were defined according to the state of pubertal development. Baseline characteristics were compared with $t$ test and chi-square analyses, and when differences were found, they were controlled for in further analyses. The HbA$_{1c}$ data were analyzed using paired $t$ test. The rate of severe hypoglycemia was analyzed using a

generalized estimating equation approach with a Poisson regression. Multiple regression analysis was used to evaluate the relationship between the rate of SH and BMI and duration of diabetes. A value of p<0.05 was considered significant.

Table 1 Characteristics of 44 children and adolescents with type 1 diabetes. Values are mean (SD) unless otherwise indicated

| Characteristic | Prepubertal (n=21) | Pubertal (n=23) | *p* value |
|---|---|---|---|
| Age, years | 7.0 (2.7) | 14.0 (1.7) | <0.001 |
| Female, n (%) | 11 (52) | 12 (52) | NS |
| Age at onset, years | 3.8 (2.6) | 8.2 (3.5) | <0.001 |
| Disease duration, years | 3.2 (1.4) | 5.8 (3.2) | <0.001 |

*NS*, not significant

Table 2 Clinical characteristics of patients before and one year after flexible multiple daily insulin (FMDI) therapy, by study group. Values are mean (SD)

| Parameter | Prepubertal (n=21) | Pubertal (n=23) |
|---|---|---|
| Clinic visits, n/year | | |
|     Conventional therapy | 2.8 (1.0) | 2.9 (0.8) |
|     FMDI therapy | 2.9 (0.9) | 3.1 (0.7) |
| Total daily insulin, U/kg | | |
|     Conventional therapy | 0.72 (0.17) | 1.0 (0.25) |
|     FMDI therapy | 0.73 (0.16)$^{e}$ | 1.0 (0.15)$^{e}$ |
| Bolus-basal ratio | | |
|     Conventional therapy | 0.52 (0.26) | 0.48 (0.35) |
|     FMDI therapy | 1.0 (0.31)$^{f}$ | 0.80 (0.23)$^{e}$ |
| BMI, kg/m$^{2}$ | | |
|     Conventional therapy | 17.2 (1.7) | 21.3 (3.1) |
|     FMDI therapy | 17.4 (2.0) | 22.7 (3.2)$^{f}$ |
| HbA$_{1c}$, % | | |
|     Conventional therapy | 9.3 (1.3) | 9.2 (1.0) |
|     FMDI therapy | 8.0 (1.1)$^{d}$ | 8.2 (0.9)$^{e}$ |
| Severe hypoglycemia, events per 100 patient-years | | |
|     Conventional therapy | 52.3$^{b}$ | 23.7 |
|     FMDI therapy | 19.8$^{b,\ c}$ | 9.1$^{a}$ |

*BMI*, body mass index; [a] *p*<0.05, [b] *p*<0.025, [c] *p*<0.01, [d] *p*<0.002, [e] *p*<0.001, and [f] *p*<0.0001. All *p* values represent comparison of conventional insulin therapy versus FMDI therapy, except for b *p*<0.025, representing comparison of prepubertal versus pubertal groups

## Results

The study enrolled 44 children and adolescents with type 1 diabetes (Table 1). The pubertal patients were significantly older and had longer duration of diabetes compared to prepubertal children (p<0.001).

Table 2 summarizes the results of our study. Thirty-three patients received pre-breakfast and pre-supper Ultralente insulin as basal insulin, and 11 patients (3 prepubertal and 8 pubertal) received pre-breakfast Ultralente insulin with bedtime NPH. There was no significant difference between the number of clinic visits before and during FMDI therapy. The total daily insulin dose was higher in pubertal vs. prepubertal subjects prior to and during FMDI therapy (p<0.001), but did not change in the prepubertal subgroup. However, the bolus to basal insulin ratio increased in both prepubertal (p<0.001) and pubertal (p<0.001) patients.

Figure 1 illustrates the HbA$_{1c}$ values over a one-year period. There was a significant reduction in HbA$_{1c}$ at 6 and 12 months compared to baseline in both subgroups. The HbA$_{1c}$ values decreased significantly for the entire cohort (p<0.0001), for prepubertal (p<0.002) and for pubertal (p<0.0001) patients after one year. Of the total cohort, 39 patients (89%) had a statistically significant decrease in HbA$_{1c}$ from 9.3% to 8.0% (p<0.0001), while 5 patients (11%) had a slight increase in HbA$_{1c}$ from 8.2% to 8.8%, which was not statistically significant. Twenty-five patients (57%) achieved 1% or greater reduction in HbA$_{1c}$, while 18 patients (41%) either maintained or achieved an HbA$_{1c}$ value <8.1% on PMDI treatment.
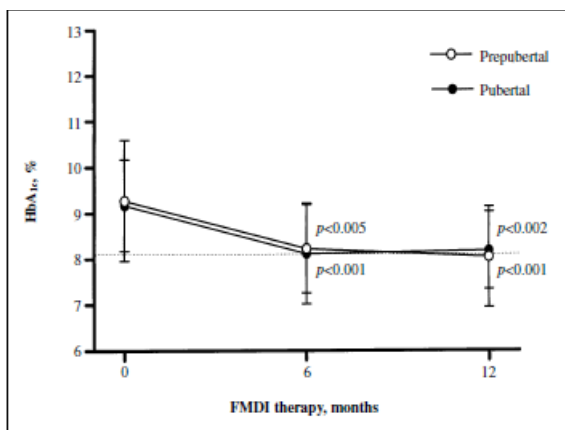


Figure 1 HbA$_{1c}$: values in prepubcrtal and pubertal subgroups over a one-year period of flexible multiple daily insulin (FMDI) therapy. The p values refer to comparisons with baseline values. Horizontal line, mean value for adolescents in the Diabetes Control and Complications Trial (DCCT)

Two pubertal patients in the entire study cohort experienced one episode of diabetic ketoacidosis (DKA) in the year prior to initiation of PMDI therapy. There was no episode of DKA in the entire study population during PMDI therapy.

The prepubertal group had a higher rate of SH than pubertal subjects before and after PMDI therapy (p<0.025). The rate of SH significantly decreased in both prepubertal (p<0.01) and pubertal (p<0.05) groups of patients on PMDI. There was also an inverse relationship between BMl and the rate of SH (r=-0.45, p<0.002). However, longer duration of diabetes was not associated with increased frequency of SH. There was no history of hypoglycemic seizures in any patient prior to or during PMDI therapy.

There was no correlation between frequency of mild to moderate hypoglycemia and BMI or duration of diabetes. During FMDI therapy, hypoglycemia frequency decreased in 52.3% of patients in the entire study group (2.70±0.82 vs. 1.22±0.67 per week, p<0.0001) without a change in 29.5% of the total cohort of patients. However, hypoglycemia frequency increased only among 18.2% of patients (1.5±1.1 vs. 3.1±1.2 per weck, p<0.02), ranging in age from 3.5 to 17.6 years.

While there was no significant change in BMI of the prepubertal subgroup, it increased significantly in the pubertal subgroup (p<0.0001; Table 1). Overall 11 patients (25%, 3 prepubertal and 8 pubertal) were overweight before FMDI therapy, and 11 patients (25%, 2 prepubertal and 9 pubertal) were overweight on FMDI treatment.

## Discussion

For patients with type 1 DM treated with multiple insulin injections, the use of carbohydrate counting and pre-meal insulin per grams of carbohydrate has been shown to offer greater flexibility in choosing foods, portion size, and timing of the meals as well as physical activity [23, 24]. The benefit of this system is supported by the DCCT, which showed better glycemic control for intensively treated patients who adjusted their pre-meal insulin dosages based on carbohydrate content of meals compared to those who did not adjust pre-meal insulin [25]. The use of carbohydrate counting with CSII, in some children and adolescents with type 1 DM, provides greater lifestyle flexibility and improvement in glycemic control [26]. Less has been reported about the use of a flexible insulin regimen utilizing a ratio of short-acting insulin to carbohydrate ratio, based on the content of meal with multiple daily injections.

In our study, there was a significant improvement in glycemic control with FMDI therapy as shown by reduced $HbA_{1c}$. Eleven patients continued to require bedtime intermediate-acting insulin, when they were switched to FMDI, to help lower pre-breakfasl blood glucose rise due to dawn phenomenon [27], a strategy utilized by other investigators [28]. The entire cohort had a statistically significant mean reduction in $HbA_{1c}$. Over half of the patients achieved greater than 1% decrease in $HbA_{1c}$. These findings were clinically significant since the DCCT reported a 21%-49% decreased risk of microvascular complications with a 1 % decrease in $HbA_{1c}$ [29].

Intensive insulin therapy has been commonly associated with excess weight in several studies [1, 3, 18]. In our study population, only pubertal children demonstrated a statistically significant increase in BMI, which was expected among growing children and adolescents. Our patients received ongoing nutritional counseling as glycymic control improved, which may explain the lack of excessive weight gain during the study.

Hypoglycemia has often been regarded as an almost inevitable consequence of good metabolic control, and this view has been underlined by DCCT [2, 4]. Other studies, however, have not reported increased incidence of hypoglycemia during intensive insulin therapy [18-20, 30, 31]. A recent study showed that improved glycemic control and frequent blood glucose monitoring but not intensive insulin therapy were related to frequent hypoglycemia, in contrast to the DCCT findings [32]. In our study cohort, the baseline frequency of severe hypoglycemia was significantly higher among prepubertal as compared to pubertal patients. Subsequently, the rate of severe hypoglycemia decreased significantly in both subgroups on FMDI. While the etiology of severe hypoglycemia in type 1

DM is multifactorial and includes reduced awareness of the symptoms of hypoglycemia and overall level of glucose control [33], it is usually associated with self-management errors, vigorous physical activities, psychosocial stresses, 1 or 2 daily injections, and lower proportion of short-acting insulin out of the total daily dose [7]. In our patient population, institution of FMDI treatment resulted in redistribution of insulin dose throughout the day with higher proportion of short-acting insulin out of the total daily dose. Consistent with other studies [7, 33, 34], we observed that appropriate physiological replacement of insulin with multiple doses, frequent blood glucose monitoring, combined with adequate self-management, and active problem-based training were the likely reasons for decreased severe hypoglycemia.

Janssen et al. [35] recently demonstrated that patients with type 1 DM who have a high blood glucose variability and low average blood glucose concentration, diabetes of long duration, low BMI, self-reported impaired awareness of hypoglycemia and those participating in vigorous physical activities, are at increased risk of frequent mild hypoglycemia. In our patients, there was no correlation between hypoglycemia frequency and BMI or duration of diabetes. However, the rate of hypoglycemia frequency decreased significantly in more than 50% of patients on FMDI treatment. The reasons for this finding likely include motivated families, improved insulin dosing strategies using insulin to carbohydrate ratios allowing for limitations on the amount of required basal insulin.

A number of limitations to this study exist. This study was undertaken to determine the feasibility of use of a flexible insulin regimen in a general pediatric diabetic population. It included patients who were selected for ability to use the flexible insulin regimen and carbohydrate counting principles, similar to the criteria that are used for selection for insulin pump use, results of which have been described in the literature [18, 20]. Bias may be involved in this selected group of patients because of this process. Similar studies evaluating therapeutic interventions in a selected group of patients [20, 36] clearly illustrated the utility of analyzing the feasibility or efficacy of a treatment regimen.

The FMDI therapy may be a desirable option for most pediatric patients who may not elect CSII therapy for intensive glycemic control. The availability of the new long-acting basal insulin glargine (Lantus, Aventis Pharmaceuticals) may further enhance flexibility in insulin delivery and in lifestyle [37]. The introduction of insulin aspart (Novolog, Novo-Nordisk Pharmaceutical) [38, 39], as a new rapid-acting insulin analogue with reportedly longer duration of action will add to the repertoire of insulin types available.

In conclusion, the present study has demonstrated the feasibility of use of this form of flexible insulin management in a selected pediatric population. The FMDI treatment appeared to result in improved glycemic control, decreased rate of severe hypoglycemia and mild hypoglycemia without an abnormal increase in BMI in this selected group of patients. Finally, the philosophy of care developed for and by FMDI treated patients was constantly adjusted toward reaching normal or near normal glycemic goals, while avoiding or minimizing severe episodes of hypoglycemia. Teaching emphasized a proactive (preventive) approach to blood glucose fluctuations with constant readjustment (reactive approach) to counterbalance any high or low blood glucose readings. The present study, like the DCCT, demonstrates the importance of a team approach that focuses on the diabetic child with diabetes and on the family as the prime initiators of ambulatory care.

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