

## New options in insulin therapy

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### Abstract

**Objective:** To review the new options in insulin therapy for controlling diabetes mellitus in children and adolescents.

**Sources:** Articles indexed in PubMed were located using the search terms insulin analogs in children and adolescents and reviewed. Information was also obtained from American Diabetes Association and Sociedade Brasileira de Diabetes consensus documents.

**Summary of the findings:** Information is presented on new analogs of insulin and, for purposes of comparison, the other insulin modalities currently available are also reviewed, focusing on insulin therapies which attempt to approximate basal-bolus treatment strategies to physiology. With the objective of obtaining improved metabolic control, more and more children are being put on multiple daily injection regimes or using continuous subcutaneous insulin infusion. It is difficult to achieve optimum glycemic control in children due to the increased risk of hypoglycemia resulting from the great variability in dietary intake habits and in physical activity levels. With diabetes type 1, if rapid-acting analogs are given subcutaneously in bolus, they generally reduce hypoglycemia episodes and postprandial glycemia levels, compared with regular human insulin, while basal analogs tend to reduce particularly the number of episodes of nocturnal hypoglycemia.

**Conclusions:** Although the benefits to individual metabolic and clinical outcomes appear modest, the majority of studies demonstrate benefits when insulin analogs are used in the treatment of diabetes type 1 or 2.

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### Introduction

In 1993, the results of the Diabetes Control and Complications Trial (DCCT)<sup>1,2</sup> revolutionized the treatment of diabetes mellitus type 1 (T1DM), demonstrating the importance of aiming at lower glycemic levels than those generally obtained and of maintaining glycosylated hemoglobin (HbA1c) levels as close as possible to normal. The study proved that intensive treatment of T1DM, with three or more doses of different types of insulin with differing actions, is effective for controlling the chronic complications of diabetes mellitus (DM), since it detected a 76% reduction in cases of retinopathy, 60% fewer cases of neuropathy and 39% less nephropathies among patients treated intensively in relation to those treated conventionally. Since there was this difference in the incidence rate of the chronic microangiopathic complications of DM, this was interpreted as being caused by better metabolic control,

since these patients' glycosylated hemoglobin levels were statistically lower (8.05%) than those of patients treated conventionally (9.76%). For this reason, when the DCCT was completed, it was suggested that all patients should continue in another study, named Epidemiology of Diabetes Interventions and Complications (EDIC). In this study, all patients were given intensive treatment and, specifically in the subset of adolescents (13 to 17 years), the degree of metabolic control did not vary statistically when those who had been intensively treated on the DCCT and those who had received conventional treatment were compared (HbA1c of 8.38% vs. 8.45%). When the frequency of progression to diabetic retinopathy and nephropathy was evaluated, it was observed that the group that had been treated intensively for longer (since the start of the DCCT) continued to have a lower frequency of progression to diabetic retinopathy and nephropathy, suggesting that the attempts to achieve better glycemic control

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must begin early on in the course of T1DM.<sup>2</sup> Furthermore, 12 years after the end of the DCCT, the results of the EDIC demonstrated a reduction of 40 to 60% in macrovascular events among the intensively treated cohort compared with the less intensively treated group.<sup>3</sup> Both studies had evidence level 1 and recommendation grade A for intensive insulin treatment in T1DM. Intensive treatment with insulin is therefore recommended for all children, but successfully carrying out this treatment remains a challenge: if factors relating to compliance with treatment and with inadequate family support are excluded, hypoglycemia continues to be the factor limiting the attainment of ideal glycemic control.<sup>4,5</sup>

More recent advances in insulin therapy help us to meet the challenge of carrying out the intensive diabetes treatments recommended by the results of the DCCT, EDIC and other similar studies. In this review article we present the types of insulin available and the methods for administering them in order to provide this intensive treatment in accordance with the requirements of each child or adolescent.

On the other hand, several different studies have consistently demonstrated that the frequency of glycemic self-monitoring has an inverse relationship with HbA1c, i.e., a positive relationship with better glycemic control.

Target glucose and HbA1c levels recommended by the American Diabetes Association<sup>4</sup> should be established for children and adolescents according to age group (Table 1). The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends that glycated hemoglobin should be kept below 7.6%.<sup>3</sup>

Since monitoring of blood glucose is an essential component of intensive insulin treatment, we will also present new technological advances in the field of continuous glycemia monitoring, which will improve intensive diabetes treatment and will probably also support the development of a closed-loop insulin delivery system.

### Types of insulin and their uses with children being treated intensively

#### Rapid-acting analogs and regular insulin

Rapid-acting types of insulin (soluble and regular), in combination with intermediate-action insulin, administered in two,

or preferably three, daily doses are still used today as essential components of the majority of insulin replacement regimes in many parts of the world (Table 2).

Short-acting insulin reaches peak activity later than do the new rapid-acting analogs and to achieve optimal activity it must be administered at least 30 minutes before meals. It is, consequently, inflexible and inconvenient to use, especially with children. On the other hand, compared with the new analogs, its action is longer lasting: this allows a patient to eat a snack in the middle of the morning or afternoon, without an additional injection, making it a more attractive option in some circumstances, where the aim is to intensify treatment. It is, however, important to remember that this advantage of regular insulin must be balanced against the finding that there is an increased risk of hypoglycemia.

Rapid-acting analogs insulin lispro (ILis; HumaLog1, Eli Lilly) and insulin aspart (IAsp; NovoRapid1, Novo Nordisk) were the first to be used. More recently, a third rapid-acting analog was cleared for use in the United States – insulin glulisine (IGlu; Apidra™, Sanofi-Aventis). In relation to human insulin, rapid-acting analogs break down in the subcutaneous tissues immediately after injection so that their onset of action is also faster, with a higher peak level in serum (Table 2).

The first rapid-acting insulin analog became available in 1996 and other rapid-acting analogs have been developed since then. They have been created by a variety of modifications to the chemical structure of the human insulin protein, substituting several amino acids in different positions, with the intention of bringing forward onset and shortening duration of action when compared with regular/soluble insulin. Analogues have this effect because, after injection into subcutaneous tissue, the proportion that is bound in the form of dimers and hexamers is lower, which means that the monomeric analog molecule can be absorbed at the point of injection more quickly. Although they have different chemical structures, no significant differences have been reported between them in terms of onset or duration of action. Administration 5-15 minutes before a meal has a greater impact on increase in post-prandial glucose (PPG), when compared with regular human insulin, with patients on analogs having levels

**Table 1** - Target glucose and HbA1c levels in plasma for T1DM patients, by age group

Values by age group	Plasma glucose (mg/dL)		HbA1c
	Before meals	Before going to bed	
Toddlers and preschool aged children	100-180	110-200	< 8.5 and > 7.5%
School aged children	90-180	100-180	< 8%
Adolescents and young adults	90-130	90-150	< 7.5%

Adapted from American Diabetes Association.<sup>4</sup>

**Table 2** - Types of insulin and their actions

Type of insulin	Onset of action	Peak of action	Total duration
Short and rapid action			
Regular	30-60 minutes	2-4 h	6-9 h
Aspart, lispro, glulisine	10-15 minutes	30-90 minutes	3-4 h
Intermediate action			
NPH	1-2 h	3-8 h	12-15 h
Basal insulin			
Glargine	1-2 h	no peak	24 h
Detemir	1-2 h	no peak	24 h
Premixed insulin			
70/30 NPH/regular	30-60 minutes	3-8 h	12-15 h
75/25 NPH/lispro	10-15 minutes	30 min-8 h	12-15 h

NPH = neutral protamine Hagedorn.<sup>6</sup>

that are lower by 0.6 to 2.0 mmol/L.<sup>4,5</sup> Another advantage of rapid-acting analogs that has been found by some studies is a reduction in the number of episodes of hypoglycemia.<sup>7,8</sup> Several studies undertaken with adults have demonstrated a mild reduction in HbA1c (20.1 to 20.2%) for all three analogs when compared with regular insulin, but studies undertaken with children did not detect significant differences.<sup>9</sup>

With small children the quantity of food that will be ingested at each meal is often highly unpredictable, which makes the use of preprandial rapid-acting insulin a cause for concern, whenever the child does not consume the quantity that was calculated for that dose of insulin. Therefore, in certain situations it is safer to administer ultra-rapid insulin after the meal, when the quantity that the child has consumed is already known. Jovanovic studied the glycemic profile when aspart insulin was given before or soon after meals and concluded that it was better when administered before the meal.<sup>10</sup> Nevertheless, each case should be assessed individually and, very often, children whose feeding habits are highly unpredictable will benefit from post-prandial insulin.

Although a recent meta-analysis suggested that short-acting analogs offer only a small advantages in terms of HbA1c and no advantages in terms of hypoglycemia, it is important to take into consideration that the majority of the studies included in the meta-analysis were not designed to demonstrate the superiority of insulin analogs over human insulin, but their equivalence and that, in some of these studies, HbA1c was a secondary outcome. Furthermore, there was a great variation between the studies in terms of the populations investigated, patient follow-up and therapeutic strategies.<sup>8</sup>

There is strong evidence that PPG is a direct and independent risk factor for cardiovascular disease, irrespective of fasting plasma glucose and HbA1c. A prospective study has suggested that, in T2DM, a reduction in PPG is associated with a reduction in cardiovascular risk. Therefore, the reductions in PPG observed with the use of rapid-acting analogs may offer significant benefits in terms of future morbidity and mortality.<sup>10</sup>

### ***Intermediate-acting insulin***

The action profile of intermediate-acting insulin makes this type appropriate for regimes where basal insulin is given once to three times a day. The principal preparation currently used with children is neutral protamine Hagedorn (NPH) (Table 2). It has been used at night as nighttime basal insulin. It is more effective for treating diabetes type 2 (T2DM) than for treating children with T1DM. With peak activity occurring 3-8 h after injection, one dose in the morning may allow children to avoid having to take another insulin injection at lunchtime. However, in order to utilize NPH, a rigid daily nutrition program is needed, including relatively fixed times for meals and snacks with consistent carbohydrate levels. The greatest disadvantages of NPH are the wide daily inter-individual and intra-individual variations in synchronization and duration of peaks, which, when compared with long-acting analogs, may result in less than optimum metabolic control and increased risk of nocturnal hypoglycemia. Lente insulin was used as an intermediate-acting insulin for many years, with a profile of activities similar to that of NPH.

### ***Basal insulin analogs***

Basal insulin analogs have a different mode of action when compared with insulin that exhibits peaks. Two basal insulin

analogs, glargine insulin (IGlarg; Lantus1, Sanofi-Aventis) and detemir insulin (IDet; Levemir1, Novo Nordisk) are available on the Brazilian and North-American markets. Insulin glargine (IG) is a clear insulin that precipitates in the subcutaneous tissues, after injection, while detemir is an acylated insulin that binds to albumin (Table 1). Although these two basal analogs have not been formally approved in the United States for use with children less than 6 years old, many pediatric diabetes centers have used them with success in these cases.<sup>9,11</sup> The majority of studies using IG and detemir found reductions in hypoglycemic episodes, particularly of nocturnal hypoglycemia.<sup>9,12</sup> Basal analogs exhibit a more predictable insulin effect, with lower glycemic variation from one day to another, when compared with NPH insulin.<sup>13</sup> Glargine insulin became available in 2000. This is a long-acting analog which has a very low peak of activity, with approximately 24 hour duration. The time at which IG is administered does not appear to have any impact whatsoever on its efficacy.<sup>14</sup> Furthermore, it has proven effective with children and adolescents with poorly controlled T1DM and for reducing hypoglycemic episodes and improving HbA1c levels.<sup>15</sup> Insulin glargine should be administered at approximately the same time each day in order to maintain its efficacy as a non-peaking basal insulin. If one dose is missed, 50% of that day's insulin will be lacking.

Due to its pH and the solubility properties of IG preparations, the manufacturer's current recommendations require that IG be injected separately from all other insulin preparations, although there is evidence that it can be mixed with lispro and aspart without affecting its effects on glycemia or HbA1c.<sup>16,17</sup>

Insulin Detemir is the newest long-acting analog, with an action that lasts approximately 6-23 h according to studies undertaken in adults.<sup>18</sup> The duration of action is dose-dependent. If used twice a day, injections offer excellent control, however, one injection per day can be used if the doses are high. Acylation of detemir allows bonding with albumin, which in turn permits the prolonged action. After the injection, insulin detemir forms a liquid deposit in the subcutaneous tissues and then binds with albumin.<sup>19</sup> Although insulin detemir is soluble at neutral pH, it cannot be mixed with the rapid analogs. Several studies of detemir have demonstrated potential benefits in terms of weight, with weight loss or reduced weight gain in adults<sup>19</sup> and also in children and adolescents.<sup>20</sup>

## **Other types of insulin**

### ***Premixed insulin***

Premixed insulin preparations containing a fixed proportion of rapid and intermediate insulin (Table 1). Different proportions of rapid acting insulin and NPH are available in several countries from multiple manufacturers. Although the use of

premixed insulin may reduce potential errors preparing insulin syringes, it also removes the flexibility to adjust each type of insulin separately. Premixed insulin does not therefore allow for easy adjustment to account for glycemic variability as foods are absorbed or physical activity carried out; important factors when treating children with T1DM. Premixed insulin can be useful for patients with T2DM, patients who are incapable of learning a more intensive treatment regime or when compliance to insulin treatment is a problem.<sup>21</sup>

### ***Lente, ultralente, and semilente insulin***

The principle manufacturers of lente, ultralente and semilente insulin have recently reduced production, anticipating total discontinuation in the near future. They are not currently available in North America or the majority of Europe and availability is limited in the rest of the world.

Insulin lente has an intermediate action, similar to NPH; semilente is a short-acting insulin and ultralente is a basal insulin, but it is not free from peaks. Ultralente insulin can have an unpredictable activity curve, resulting in unexpected and prolonged hypoglycemia and its use as basal insulin cannot be encouraged.<sup>21</sup>

### **New methods of insulin administration**

Insulin can be obtained in disposable pens and rechargeable pens, with replacement cartridges. The dose is set by twisting or pressing a button, providing a more convenient administration system and also a system which allows for more exact doses for children, most especially when the dose must be given by people with little knowledge of the problems involved in administering insulin. Some individuals have reported that injections are less painful when pens are used, which may improve compliance with a multiple injection regime. The precision and convenience of these pen devices for injecting insulin have improved the quality of life of patients with T1DM. Insulin pens offer advantages of simplicity, convenience, and, for some patients, increased independence. Some of the most modern pens are capable of storing information on the time of injection and quantity of each insulin dose. The fact that these devices provide a record of insulin doses makes them useful for use with adolescents, who rarely record this information.<sup>21</sup>

### ***Inhaled human insulin***

Inhaled human insulin was recently approved for preprandial use with adult diabetes mellitus patients, but it has not been approved for use with children. This insulin formulation has more rapid onset, but the duration is similar in terms of the glycemic levels obtained with regular insulin given subcutaneously. A meta-analysis carried out by Ceglia et al.<sup>22</sup> demonstrated a small reduction in HbA1c, favoring subcutaneous insulin when compared with inhaled.

Principal notable side-effects were increased incidence rates of smooth dry nonprogressive coughing and a mild

reduction in pulmonary function test results [forced expiratory volume in one second (FEV1) and lung carbon monoxide diffusing capacity (DLco)], which did not deteriorate over 2 years.<sup>23</sup> However, no long term safety data is available from adults with relation to altered pulmonary function. Approval for use with children will need to wait for this information. The fact that it is available as a dry preparation, which does not require a refrigerator, may offer great advantages in tropical parts of the world if cost-effective preparations can be prepared.<sup>21</sup>

### **Intensive diabetes treatment**

Intensive management of diabetes includes administering insulin calculated to meet basal and mealtime requirements and frequent blood glucose measurements in order to adjust insulin doses, also offering the possibility of making adjustments to account for the rate at which the carbohydrates from meals and snacks are consumed during physical exercise. This type of management is known as basal-bolus dosing and is currently the most recommended strategy.<sup>21</sup>

### **Basal-bolus regime**

The models which best provide for insulin delivery in a basal-bolus dosing scheme are those treatment regimes that employ insulin infusion pumps, although basal-bolus treatment can also be given using injections. They are best when employing a long-acting analog as basal insulin and a rapid or short-acting insulin for mealtimes (bolus). Other regimes of basal insulin include multiple doses of NPH/lente or NPH/lente administered before sleep, combined with daytime bolus of rapid or short-acting insulin. In basal-bolus regimes the insulin dosage calculation varies according to age, weight and duration of diabetes. In general, the distribution of the total daily dose is close to 50% basal and 50% prandial. The most flexible and most physiological means of covering mealtimes is to use the carbohydrate-insulin ratio, which is a calculation that is based on the insulin sensitivity of each individual. The majority of individuals require a carbohydrate to insulin ratio of 10-15 g per unit of insulin, but often prepubescent children require less and adolescents require a greater number of units per gram of carbohydrate. Prandial insulin can be adjusted testing blood glucose levels 2-3 h after meals and comparing this with the preprandial level. The difference between the preprandial glucose and the PPG should be less than 20-30 mg/dL (1-1.5 mmol/L) if the insulin dosage is correct. Basal insulin dosage is best adjusted by means of frequent glycemia assays (every 2 h) during a period of fasting of at least 6 h.

Injection-based basal-bolus regimes allow greater flexibility in terms of the times of meals, but the regime often results in an increased number of injections per day. Furthermore, basal-bolus treatment can be complicated for children who are reluctant to inject themselves at school because it sets them apart from their peers.<sup>21</sup>

In addition to the mealtime bolus, individuals on basal-bolus insulin regimes can also apply a corrective bolus when their blood glucose level is above the target recommended by their physician. The American Diabetes Association (ADA) and other international organizations have published guidelines for target glycemic ranges by age.<sup>4</sup> The corrective bolus is based on the number of units (mmol/L or mg/dL) by which glycemia is reduced after administering one unit of rapid-acting insulin. This depends on insulin sensitivity. One method of calculating the correction dose for a patient is known as the 1500 rule. According to this rule, the correction dose can be calculated by dividing 1500 (or 83 in the SI system) by the total daily dose (TDD) of insulin. This rule works best for people using regular insulin as their bolus insulin. More recently, 1800 (100 SI) was proposed as being the ideal numerator to be used with this rule when the individual is using a rapid-acting insulin analog. Numerators between 1600 (89 SI) and 2200 (122 SI) were proposed for use when the basal-bolus ratio is greater than or equal to 1. Numerators below 1800 (100 SI) are recommended when basal insulin makes up less than 50% of the total daily dose and numerators greater than 1800 (100 SI) are recommended when basal insulin accounts for more than 50% of the total daily dose.<sup>24</sup> Except during disease, an interval of 2-3 h should be allowed between each correction bolus in order to avoid summation of the insulin doses, which could result in hypoglycemia.

Irrespective of the insulin regime, physical exercise calls for adjustments to insulin dosage and/or additional carbohydrate doses. The dose of insulin and carbohydrate intake before, during and after exercise, are heavily dependent on the type, intensity and duration of physical activity. If the blood glucose level prior to exercise is below 130 mg/dL (7.2 mmol/L), a snack containing 15-30 g of carbohydrates will reduce the risk of hypoglycemia in a period of 1 to 2 h of moderate exercise.<sup>25</sup> For users of insulin pumps, suspending the basal rate during exercise for up to 120 min reduces the risk of hypoglycemia during exercise.<sup>26</sup> For those who use injection regimes, the risk of nocturnal hypoglycemia can be reduced if low blood glucose levels during exercise are treated with 30 g of carbohydrates, the bolus dose is reduced for the meal after exercise and the evening snack is increased if blood glucose levels before going to sleep are below 130 mg/dL (7.2 mmol/L).<sup>27</sup> Greater adjustments are necessary for highly active young athletes, who may need to reduce their insulin regime by as much as 50% on days of much physical activity.

### **Continuous subcutaneous insulin infusion pumps**

Continuous subcutaneous insulin infusion (CSII) pumps offer a more physiological insulin delivery because, in comparison with the other options currently available, they most closely simulate insulin production by the pancreatic beta cells, with prandial bolus superimposed on the continuous feed (Figure 1). The CSII system has been shown to improve the glycemic control of children and adolescents with T1DM, with



a concomitant reduction in severe hypoglycemic episodes.<sup>28,29</sup>

Using rapid acting analogs is superior to regular insulin for CSII, with reduced rates of postprandial hyperglycemia and nocturnal hypoglycemia.<sup>30,31</sup> Insulin lispro, aspart, and glulisine are all approved for use with CSII in the United States and many other countries.<sup>32</sup> Interrupting the basal insulin rate (pausing or disconnecting the pump) during physical exercise has proven effective for reducing hypoglycemia in children with T1DM.<sup>26</sup> Although there is no evidence that treatment with insulin pumps results in sustained improvements in glycemic control with young children less than 6 years old,<sup>30</sup> the risks are low<sup>33</sup> and parental satisfaction with the increased flexibility appears to be elevated, making CSII a useful option for younger children.<sup>34</sup>

The newest generation of smart pumps can preprogram prandial or correctional bolus doses based on the insulin-to-carbohydrate ratio, maintaining the bolus insulin and insulin sensitivity useable. Smart pumps also offer the option of delivering the prandial bolus in a square or extended wave or in combined bolus to better cover mixed meals, which may take longer to absorb, or for diabetes patients who suffer from gastroparesis. This increases the convenience of more sophisticated insulin profiles for all CSII users and increases CSII treatment safety with younger children. The variability of basal infusion rate profiles, in combination with the ability to make very small adjustments (0.025-0.05 U/h of insulin), make it possible to reduce hypoglycemia episodes, particularly during the night. The standard hourly tests of basal levels and prandial insulin demands vary with age and the time of day; young children require lower basal rates.<sup>21</sup> The ratio of insulin to carbohydrates (the quantity of insulin per gram of carbohydrates) is generally most elevated in the morning and lower at a lunch and dinner. Adolescents have reduced

insulin sensitivity in the early morning (the dawn phenomenon), while younger children require basal insulin frequently during the night, before midnight.<sup>29,35</sup> Not administering the mealtime bolus appears to be the major cause of less than ideal glycemic control among children and adolescents with T1DM on CSII treatment.<sup>36</sup>

### Continuous glucose control by subcutaneous monitoring

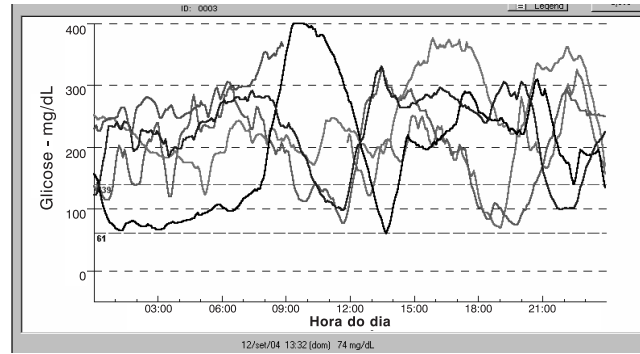
The continuous glucose monitoring system (CGMS) is a powerful tool for improving the intensive management of diabetes (Figure 2). Despite the results of the DCCT, around 70% of young T1DM patients continue to be incapable of achieving their recommended glycemic targets.<sup>37-39</sup> Hypoglycemia is more common among children than adults<sup>2</sup> and continues to be the principal impediment to achieving the glycemic control that is aimed at. Continuous sensors may be of a type which provide glycemic data when the patient returns to the laboratory where the monitor was installed or they can be real time. Real-time continuous glycemia sensors (not yet available in Brazil) have the potential of revolutionizing T1DM treatment, providing patients with information which relates to PPG and nocturnal glycemia, which is rarely available with conventional capillary glycemia monitoring. There are currently three instruments approved for use in the United States by the FDA and which provide hundreds of glycemia readings per day and display the information in real-time.

However, just one device is approved to use with children less than 18 years old.<sup>40</sup> Devices are equipped with alarms to warn of glycemic levels outside of the target range and also of hypoglycemia and hyperglycemia. These CGMS devices provide patients with an immediate breakdown of their response to nutrition, exercise and insulin doses, often resulting in behavioral changes.<sup>41</sup> Several insulin pumps of the most recent generation have incorporated programming compatible with continual glycemia monitoring, and it is anticipated that eventually they will have internal algorithms that automatically adjust the insulin infusion rate, based on the glycemia level and rates of change. Such closed-loop devices would probably reduce user error, making treatment with pumps a safe and viable option in a larger proportion of the population.

Furthermore, the information obtained from the use of continuous glycemia monitoring in research studies can be applied to general practice even if this technology does not become widely available for many years. For example, the clinical experience of some authors with continuous glucose sensors has demonstrated that, in children, postprandial hyperglycemia often lasts for 2-3 h after the meal and that peak activity of a rapid-analog can be combined with the meal when the dose is administered 20-30 minutes before eating. Clinical experience with CGMS has also led to the recommendation of more frequent use of quadruple one double bolus



**Figure 1** - Insulin infusion pump fitted to the waist of an 11-year-old girl. The subcutaneous cannula can be observed on the left above the belt



**Figure 2** - Records of subcutaneous glucose monitored over 4 days (MINIMED) in an 11-year old child. Postprandial hyperglycemia can be observed at several points

with mixed meals for children who use CSII, in order to greater reduce glycemc increases.<sup>21</sup>

### Future insulin treatments

Other routes of insulin administration are being investigated, including dermal, buccal and oral insulin. Buccal insulin is sprayed into the cheek where it is absorbed by the buccal mucosa and may be an alternative route to subcutaneous or inhaled insulin to control PPG increases.<sup>21</sup>

Oral insulin is another alternative method of insulin administration that is still in the early stages of development. The oral route of insulin delivery has advantages due to the portal-hepatic absorption route. To our knowledge, only clinical experiments with prevention (but no therapeutic experiments) have been published on human beings to date. The challenge will be to develop a formulation that is stable for oral insulin delivery. Potential carriers for oral route insulin delivery are being studied with promising results in diabetic rats.<sup>21</sup>

### Conclusions

The DCCT demonstrated the efficacy of intensive management of diabetes mellitus for reducing microvascular complications of T1DM. However, the DCCT also reported a clear inverse correlation between HbA1c levels and the occurrence of severe hypoglycemia. Currently, the majority of national and international diabetes organizations recommend the use of basal-bolus insulin regimes. The more widespread use of insulin pump treatments and the introduction of insulin analogs have provided a more physiological approximation to insulin replacement in children and adolescents with T1DM. In January 2005, the ADA published age-specific guidelines on HbA1c and new glycemc targets for children similar to those in other guidelines published by the association and the diabetes society. However, it is estimated that just approximately 30% of diabetic children in the United States achieve

these new ADA objectives. Hypoglycemia is the principal limiting factor to maintaining intensive glycemc control, especially in young children who are at risk of developing compromised cognitive functions if they suffer repeated hypoglycemic episodes. The effective application of new technologies to diabetes, such as continuous subcutaneous glucose monitoring and the closed-loop system, offer hope that the lower glycemc targets can be met without increasing the number of episodes of hypoglycemia.

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