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Original Article

Improved glycemic control and lower frequency of severe hypoglycemia with insulin detemir; long-term experience in 105 children and adolescents with type 1 diabetes

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Objective: To assess the effect of the insulin analog detemir on glycemic control and severe hypoglycemia in children and adolescents with type 1 diabetes.
Research design and methods: A retrospective chart analysis was performed in 105 patients with type 1 diabetes after switching to insulin detemir between 2004 and 2007. In children below 12 yr of age (n = 53), evening neutral protomin hagedorn (NPH) insulin was replaced by insulin detemir if therapeutic goals were not reached and blood glucose levels were unpredictable or hardly controllable. In adolescents above 12 yr of age (n = 52), insulin detemir was started when changing to intensified insulin therapy.
Results: In children below 12 yr of age, hemoglobin A1c (HbA1c) at start was 8.3 ± 0.8% and after 12 months of treatment with insulin detemir significantly lowered (7.6 ± 0.6%, $p < 0.001$). In the age-group above 12 yr of age at the start of the study, the improvement of HbA1c after 12 months of treatment was less pronounced (8.0 ± 1.2 vs. 7.6 ± 1.0%) but still significant ($p < 0.01$). The risk for severe hypoglycemia was significantly decreased compared with patients attending the outpatient clinic between 1995 and 2003 (4.8/100 patient years vs. 7.6/100 patient years, $p = 0.003$). From the beginning to the end of the follow-up period, body mass index dropped significantly in children below 12 yr of age but no effect was observed in adolescents.
Conclusions: Use of insulin detemir allows a safe nocturnal glycemic control in children and adolescents with type 1 diabetes and is associated with significantly improved HbA1c levels and fewer severe hypoglycemic events. This makes insulin detemir a most valuable new tool for the treatment of children and adolescents with type 1 diabetes.

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Type 1 diabetes in children and adolescents is a demanding disease, both for parents and involved health professionals. Therapeutic goals are long-term average hemoglobin A1c (HbA1c) levels in the range of 7.5% to prevent the well-known complications of diabetes (1–5) and avoidance of severe hypoglycemia. However, in many children below 8–10 yr of age, such goals are more wishful thinking than realistic as they are usually hampered by hardly controllable and sometimes erratic ups and downs of blood glucose concentrations. A main contributor to blood glucose irregularities is the widely used neutral protomin hagedorn (NPH) insulin, an intermediate insulin, which is well known for its intra-individual and day-to-day variations in the absorption from the subcutaneous injection sites, especially in young children. Whereas unexpected blood glucose deviations during the day can be corrected immediately, they cause a stressing uncertainty for parents during

nights. Therefore, pediatric diabetologists eagerly awaited new long-acting insulin analogs with reproducible and predictable absorption characteristics.

Recently, the new insulin analog detemir (Levemir®; Novo Nordisk A/S, Bagsvaerd, Denmark) became available (6, 7). Switzerland was the first country worldwide where this new insulin was officially introduced in early 2004. With the experience of earlier phase III studies (8, 9), we started using this new insulin after its commercial availability as a basal night insulin in children of any age in whom night blood glucose concentrations were poorly controllable with NPH insulin. This early introduction especially in young children provides us with an accumulated experience of the use of detemir for up to 36 months. The aim of this publication is not the comparison of insulin detemir with other widely used long-acting insulins [e.g., glargine (Lantus®), Sanofi-Aventis Groupe, Paris, France] but is to share our clinical experience with the new insulin analog insulin detemir in 105 children and adolescents. We would like to state that this observational investigation is independent and not supported or influenced in any way by the insulin-producing pharmaceutical company.

Research design and methods

Subjects

Children and adolescents attending the Diabetes Center of the University Children's Hospital in Zurich, Switzerland, represent about 20% of all Swiss children and adolescents with type 1 diabetes. In the outpatient clinic, approximately 300 patients with type 1 diabetes up to 20 yr of age are followed. Diabetes management has been described in detail in earlier publications (10). Young children, usually younger than 12 yr of age, are initially treated with two injections per day using individual mixtures of short-acting normal and intermediate-acting NPH insulin. Only if therapeutic goals are not reached or if children have unpredictable blood glucose control or nocturnal hypoglycemic events, evening NPH insulin is replaced by insulin detemir. In older children and adolescents, an intensified insulin therapy scheme with four to five injections per day is used, and insulin detemir is used as long-acting basal insulin with one or two injections per day. This difference in insulin therapy led us to split the study population into two groups, those below 12 yr of age at the time of introducing detemir and those above 12 yr of age.

So far, 105 patients are treated with insulin detemir for at least 30 months, the time point of the retrospective analysis of the data shown here. At the time of starting detemir, 22 girls and 31 boys were below and 19 girls and 33 boys were above 12 yr of age (Table 1).

All patients were seen at least every 3 months in the outpatient clinic at the Children's Hospital in Zurich. Patients with a serious lack of compliance were excluded from the chart analysis (n = 8) because they would not contribute to enhance our experience with the new insulin. The same is true in newly diagnosed adolescents treated with insulin detemir from the very beginning because blood glucose control is usually unproblematic.

Design

Chart analysis was performed on 105 of 146 patients with type 1 diabetes whose treatment was changed to insulin detemir. The follow-up time per subject was 30 months. Patients with a follow-up of less than 30 months (n = 41) were not analyzed.

Charts were reviewed for the following variables: age and duration of diabetes at start with insulin detemir, HbA1c, length, weight, body mass index (BMI), and the occurrence of severe hypoglycemic events. Episodes of severe hypoglycemia are defined as attacks of unconsciousness with or without seizures and were carefully recorded as described (10). HbA1c was measured in capillary whole blood by a DCA 2000+ analyzer (Bayer, Leverkusen, Germany), normal range 5.0 ± 0.8% (mean ± 2 SD).

Statistical analysis

Data were analyzed for differences between the time point of switching to insulin detemir and every

Table 1. Clinical data of 105 patients with type 1 diabetes treated with insulin detemir for 30 months

Age-group at change (yr)	Number of patients	Age at insulin change to detemir (yr)			Duration of diabetes at insulin change to detemir (yr)		
			Range			Range	
		Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
<12	53	8.4 ± 2.6	1.6	11.7	3.4 ± 2.2	0.3	8.7
Girls	22	8.3 ± 3.0	1.6	11.5	3.4 ± 2.1	0.3	8.1
Boys	31	8.4 ± 2.4	3.1	11.5	3.4 ± 2.3	0.6	8.7
>12	52	14.1 ± 1.6	12.0	18.0	6.0 ± 3.8	0.4	16.3
Girls	19	13.6 ± 1.2	12.0	16.3	6.1 ± 3.2	0.4	12.6
Boys	33	14.5 ± 1.7	12.1	18.0	5.9 ± 4.1	0.6	16.3

3 months thereafter. Differences in mean values between groups were analyzed with a paired *t*-test. Data are reported as mean ± SD.

Results

The relevant characteristics of the study population are shown in Table 1. In children younger than 12 yr of age (n = 53), the mean HbA1c levels improved significantly after switching to insulin detemir (Fig. 1B). HbA1c at start of detemir was 8.3 ± 0.8% (n = 53), and it dropped significantly to 7.6 ± 0.6% ($p < 0.001$) after 12 months of treatment with detemir and thereafter remained at this level over the entire observation period of 30 months (7.7 ± 0.9%). Figure 1A shows the data for the subgroup of children younger than 8 yr in whom the drop of the HbA1c levels after 12 months was even more pronounced (8.6 ± 06 vs. 7.6 ± 0.6%, n = 19, and $p < 0.001$) and remained at this level until the end of the observation period (7.6 ± 0.7%). The biggest benefit of insulin detemir was seen in the small group of children younger than 5 yr of age at switching. Their HbA1c levels decreased from 8.8 ± 0.7 to 7.6 ± 0.5% (n = 8 and $p = 0.02$) after 12 months of treatment, and it stabilized at this level with an HbA1c of 8.0 ± 0.8% at 30 months of treatment ($p = 0.03$, paired *t*-test against 0 months). Up to 12 yr of age, no differences could be observed between girls and boys.

In adolescents (age-group >12 yr at the start of the study), the improvement of HbA1c after 12 months of treatment was less pronounced (8.0 ± 1.2 vs. 7.6 ± 1.0%) but still significant (n = 52 and $p = 0.004$; Fig. 1C). Thereafter, HbA1c levels remained between 7.5 and 7.7% for the rest of the observation period. Also, in this age-group, we did not find a difference between girls and boys.

A decrease of the risk for severe hypoglycemia was found in children and adolescents treated with insulin detemir (4.8/100 patient years) compared with all children and adolescents treated at the outpatient clinic between 1995 and 2003 (7.6/100 patient years). This comparison with our own 'historical' frequency was necessary because of the rather short duration between diagnosis of type 1 diabetes and switching to insulin detemir in many children – especially in the younger age-group – making an intra-individual comparison of the frequency of severe hypoglycemia impossible and meaningless. However, the comparison is possible as the therapeutical approach remained the same with the new insulin. The difference was significant (chi-squared test: $p = 0.003$ and odds ratio: 2.49). In children below 12 yr of age, the frequency of severe hypoglycemia was even lower (4.0/100 patient years). Overall, only two episodes (0.8/100 patient years) were reported during the night.

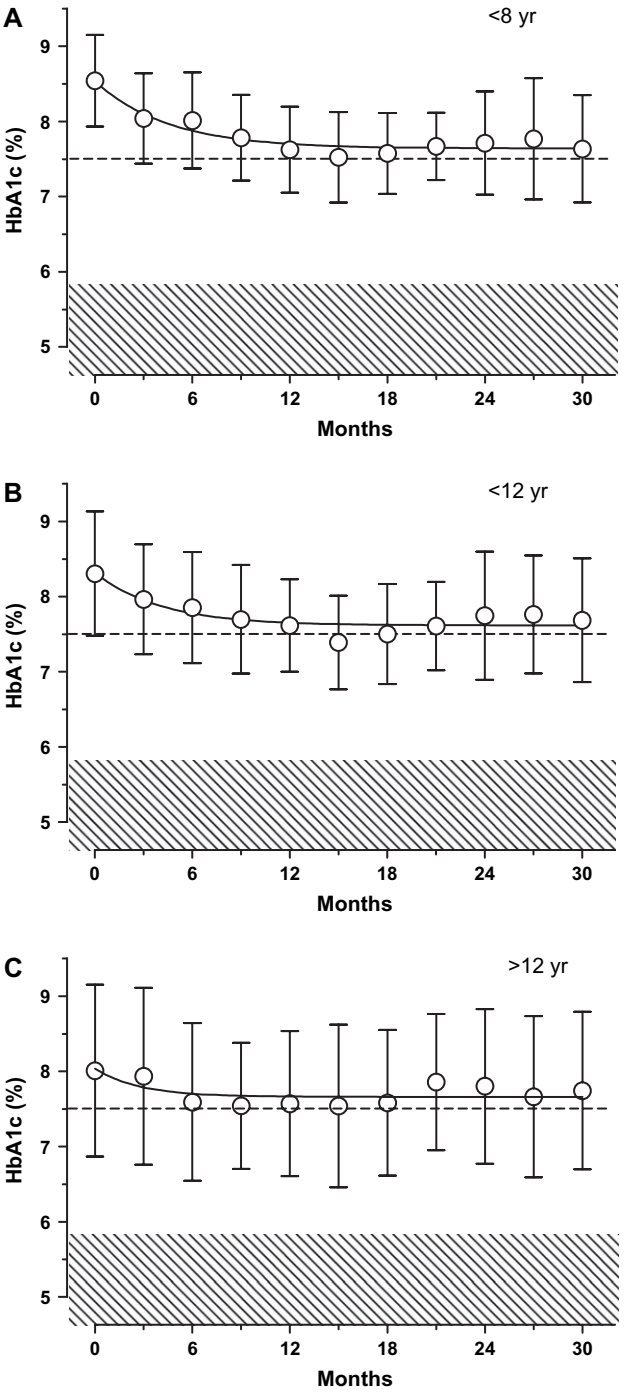

Fig. 1. HbA1c levels measured every 3 months over a period of 30 months in children and adolescents with type 1 diabetes after switching to insulin detemir below 8 yr of age (n = 19; A), below 12 yr of age (n = 53; B), and above 12 yr of age (n = 52; C) after switching to insulin detemir. Mean ± SD are shown. The shaded area shows normal range, and the dotted line shows the 'target' HbA1c of 7.5%. HbA1c, hemoglobin A1c.

Figure 2 shows that the insulin dose per kilogram body weight did not change in the age-group younger than 8 yr of age at 12 months after switching to detemir ($p = 0.20$) and between 12 and 30 months ($p = 0.10$). This was different in the age-group above 12 yr of age.

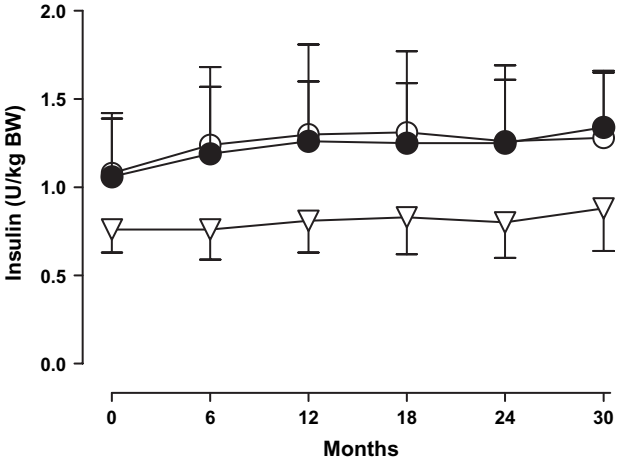

Fig. 2. Average total insulin dose in units per kilogram body weight (mean ± SEM) after switching to insulin detemir in children below 8 yr (∇) of age and above 12 yr of age (● = boys and ○ = girls). BW, body weight.

A significant increase in the amount of total insulin was recorded at 12 months after switching to detemir in girls ($p < 0.05$) and boys ($p < 0.01$) but no longer between 12 and 30 months ($p = 0.80$ in girls and $p = 0.51$ in boys). We did not find a difference of the insulin dose per kilogram body weight between girls and boys ($p = 0.96$ at 0 months, $p = 0.71$ at 12 months, and $p = 0.60$ at 30 months). There was a tendency toward an increase in the ratio of short-acting to long-acting insulin in the younger age-group after 12 months ($p = 0.06$) but no longer thereafter ($p = 0.77$) until 30 months. This increase was significant in the older age-group ($p = 0.02$ at 12 months) and did not change afterward ($p = 0.15$). The ratio was not different between girls and boys of the older age-group ($p = 0.53$).

BMI dropped significantly in children below 12 yr of age, both in boys ($p < 0.001$) and in girls ($p < 0.01$) during the observation period. In contrast, such effect was not seen in adolescents (Fig. 3).

Discussion

Insulin detemir significantly improved glycemic control in children and adolescents with type 1 diabetes. The younger the child, the more pronounced was its lowering effect on HbA1c levels. As described, the younger children were switched to detemir because of the impossibility to control blood glucose concentration during the night using NPH insulin. With detemir as night insulin, the parents were clearly advised to aim for a morning fasting blood glucose concentration of 5 mmol/L. To aim for this rather aggressive blood glucose concentration target is possible without risking a higher frequency of severe hypoglycemia as the absorption of detemir is much more stable and thus its effect much more predictable. Indeed, we found a lower occurrence of severe hypoglycemia using detemir, especially in children younger than 12 yr of age. However, the comparison of the frequency of severe hypoglycemia was not done in the same patients (Results). It rather compared patients of the same center with the same therapeutical approach but a different night insulin. Similar results are published for adults (11, 12).

We believe that targeting for a normal or near-normal fasting morning blood glucose concentration (in our hands) is the clue for improving HbA1c. However, parents and adolescents initially hesitated to follow this advice and first had to get used to the new night insulin. Insulin detemir has an initial slightly faster activity (13–15). Therefore, our recommendation was to aim for higher bedtime glucose concentrations of 7–8 mmol/L by reducing the short-acting dinner insulin to be able to administer a sufficient amount of detemir to achieve near-normal fasting glucose concentrations during the night and in the morning.

The use of insulin detemir seems to be more successful in younger children than in adolescents. This observation is primarily explained by the fact that the parents are responsible for diabetes management in younger children, and compliance is not a problem. After the initial learning, better predictability of

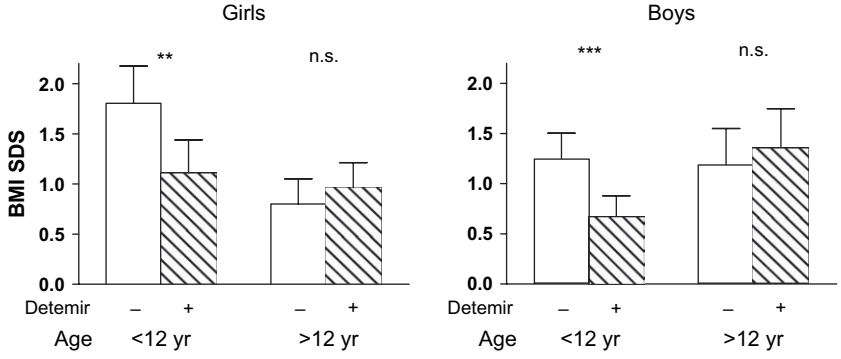

Fig. 3. BMI before and 30 months after switching to insulin detemir in girls and boys below 12 yr of age and above 12 yr of age. The numbers of patients are as reported in Table 1. p values: **$p < 0.01$, ***$p < 0.001$. BMI, body mass index; n.s., not significant (paired *t*-test); SDS, standard deviation score.

detemir compared with NPH insulin (9, 15) was also observed in younger children (<8 yr) and even in very young children below 5 yr of age. The experience of the better predictability of the morning target blood glucose and the lower risk of severe hypoglycemia during the night unanimously led to a relief and decline of stress in all families. This confirms findings from the literature (16–18).

Adolescents tend to be less compliant than parents caring for their children with type 1 diabetes (19). However, adolescents using insulin detemir also experienced and reported similar advantages of the new insulin analog. It has to be mentioned that adolescents were selected to participate in this study according to their compliance, i.e., a few (n = 8) noncompliant adolescents were excluded from this analysis. Therefore, adolescents were starting with a HbA1c level already quite low compared with international experiences (20, 21) and thus the improvement of HbA1c levels among this group was less pronounced, albeit still significant.

Both in the younger age-group and in the adolescents, the improvement of HbA1c levels lasted over the whole observation period, i.e., 30 onths and therefore has not to be attributed to a study effect that usually might influence the first 6–12 months. This further is the evidence for easier management of diabetes with insulin detemir, especially in younger children.

Usually, children have to dramatically increase their insulin dose after entering puberty, which probably explains the increase in the total insulin dose per kilogram body weight in the older age-group. In clearly prepubertal children (below 8 yr of age at the time of switching to insulin detemir), the total insulin dose did not change at all. In all children and adolescents, we recorded a slight increase in the short-acting portion of the insulin, which was more pronounced in the older groups (Fig. 2).

BMI dropped significantly in children younger than 12 yr but not in adolescents. This finding is in marked contrast to the reported experience of weight gain depending on number of injections, increased daily amount of insulin, and good metabolic control as measured by HbA1c (22). A possible explanation could be the lower frequency of hypoglycemia and consequently lower intake of carbohydrates, but this is not proven as the frequency of common (not severe) hypoglycemia was not recorded by the patients. As shown in Fig. 3, the average BMI in children and adolescents was 1–2 SDS above normal, thus an early use of insulin detemir might be able to prevent overweight.

Adolescents, especially females, with type 1 diabetes are at risk to gain weight exceedingly, resulting in a higher BMI (22, 23). Our findings support an earlier report that insulin detemir seems to prevent such development (9).

There are minor drawbacks in the use of insulin detemir. First, although prepared in a neutral solution, it is not mixable with short-acting insulin. Initially, we mixed short-acting insulin (for dinner) with detemir (for the night) in a syringe as usually done with NPH insulin in young children. However, after a few patients, the fast-occurring insulin peak of the short-acting insulin completely disappeared. Separate injections of the short-acting and the long-acting insulin solved this problem but meant one additional injection for the child. In addition, lipohypertrophy at the injection sites occurred in many children using detemir for more than 18 months. This led to absorption irregularities with consecutive fluctuations of blood glucose concentrations during the night, loosing the most important advantage of detemir, its stability and predictability. Careful control of injection sites and clear instructions to change injections sites could solve this problem.

In conclusion, in our long-term experience of 30 months, the administration of insulin detemir even in very young children with type 1 diabetes is safe, well tolerated, and effective regarding glycemic control but needs careful instruction. Thus, insulin detemir is a most valuable new tool for the treatment of children and adolescents with type 1 diabetes.

Acknowledgement

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