

The Effect of Insulin Detemir on the Metabolic Control in Children and Adolescents with Type 1 Diabetes Mellitus

Tip 1 Diyabetes Mellituslu Çocuk ve Adolesanlarda İnsülin Detemirin Metabolik Kontrol Üzerine Etkisi

Tolga Ünüvar¹, Ayhan Abacı¹, Ali Ataş¹, Ece Böber¹, Atilla Büyükgebiz²

¹Acıbadem Hastanesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Endokrin ve Adölesan Bölümü
²Dokuz Eylül Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Endokrin ve Adölesan Bölümü

Aim: Since there is limited number of studies in medical literature regarding the efficiency of insulin detemir, decrease in number of night hypoglycemia, weight changes and the improvement the lipid profile in pediatric and adolescent age group, we planned a prospective study to analyze abovementioned issues.

Material and Method: 15 diabetic patients (10 male) with insufficient metabolic control and/or morning hyperglycemia were included in to the study. The average age of the patients was 13.41±3.68 years and the average duration of diabetes was 5.03±1.74 years. Hemoglobin A1c levels, lipid levels and home glucose monitoring profiles were measured before and 32±2.32 months after substitution with insulin detemir.

Results: After insulin detemir administration as basal insulin, the mean HbA1c values decreased from 9.08 % to 8.31 %. Total and LDL cholesterol values decreased significantly after detemir. The mean four point blood glucose profiles showed a significant decrease after the substitution with detemir. There was a decrease in the nocturnal hypoglycemia frequency and the rates were statistically significant differ before and after detemir. Daily insulin doses, bolus/basal rates and body mass index SDS of patients were not changed significantly before and after detemir.

Conclusion: In pediatric diabetic patients, insulin detemir as basal insulin is safe and significantly lowers glucose levels compared with NPH insulin. This pilot study showed that the substitution of NPH with detemir provides a better glycemic control without increased hypoglycemic events.

Key Words: **Detemir, NPH, Type 1 diabetes mellitus**

Amaç: Literatürde çocuk ve adolesan yaş grubunda insülin detemirin etkinliği, gece hipoglisemi sıklığındaki azalma ve kilo değişiklikleri hakkında sınırlı sayıda çalışma olması nedeniyle bu prospektif çalışmayı planladık.

Materyal Metod: Kötü metabolik kontrollü ve/veya sabah hiperglisemileri olan 15 diyabetik hasta (10 erkek) çalışmaya dahil edildi. Hastaların ortalama yaşı 13.41±3.68 yıl ve ortalama diyabet süresi 5.03±1.74 yıldır. Hemogloblin A1c ve lipid düzeyleri, kan şekeri profilleri ve vücut kitle indeksleri başlangıçta ve detemir kullanımından 32±2.32 ay sonra değerlendirildi.

Bulgular: Bazal insülin olarak insülin detemir uygulanmasından sonra ortalama HbA1c değerleri %9.08'den %8.31'e geriledi. Total ve LDL kolesterol düzeylerinde detemir sonrası istatistiksel olarak anlamlı azalma görüldü. Detemire geçildikten sonra ortalama günlük kan şekeri profillerinde anlamlı azalma saptandı. Gece hipoglisemi sıklıklarında detemire geçiş sonrası anlamlı azalma saptandı. Hastaların günlük insülin dozları, bolus/bazal oranları ve BMI SDS değerlerinde anlamlı bir değişiklik olmadı.

Sonuç: Bu çalışma, bazal – bolus rejimde günde tek doz detemir tedavisinin NPH ile karşılaştırıldığında özellikle dislipidemi riskinin azaltılmasında ve daha iyi metabolik kontrol sağlanmasında gece hipoglisemi riskini arttırmaksızın, etkin ve iyi tolere edilebilir olduğunu desteklemektedir.

Anahtar Kelimeler: **Detemir, NPH, Tip 1 Diyabetes Mellitus**

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Corresponding author

Yrd. Doç. Dr. Tolga Ünüvar
Acıbadem Hastanesi

Phone : +90 (505) 728 41 11 - +90 (256) 444 12 56/588

Fax : (256) 214 64 95

E-mail address : tunuvar@gmail.com

Insulin detemir (Levemir[®], Novo Nordisk) is a novel, biologically engineered analogue of human insulin that has been successfully developed for clinical use in diabetes as

a basal insulin1. Insulin detemir is a soluble long-acting human insulin analogue acylated with a 14-carbon fatty acid. The fatty acid modification allows insulin detemir to

reversibly bind to albumin, thereby providing slow absorption and a prolonged and consistent metabolic effect of up to 24 hours in patients with type 1 diabetes mellitus (2,3). The soluble formulation ensures a homogenous concentration, with no need for agitation before administration. Insulin detemir has a less-pronounced peak of action and lower intrasubject variation in pharmacokinetic parameters compared with neutral protamine Hagedorn (NPH). Thus, it may provide more consistent insulin levels and more predictable, protracted and consistent effect on blood glucose than NPH because of lower absorption variability (4,5).

Traditional basal insulin preparations such as NPH insulin and ultralente do not accurately reproduce physiological serum insulin levels and are characterized by peaks in plasma concentration 3–8 h after administration that may result in hypoglycemia during the night (6). Furthermore, differences in crystal size and inadequate resuspension make absorption kinetics and dosing precision with NPH insulin variable and result in unpredictable glucose levels (6,7).

This study compared the glucose lowering effect of insulin detemir with NPH insulin given bedtime in type 1 diabetic patients on four doses insulin injection regime.

Material – Method

15 diabetic patients (10 male, 5 female) with insufficient metabolic control and/or morning hyperglycemia were included in to the study. The average age of the patients was 13.41 ± 3.68 years and the average duration of diabetes was 5.03 ± 1.74 years. All of the pa-

tients used insulin aspart before meals and single dose NPH at bed time. The metabolic and clinical parameters of the patients such as hemoglobin A1c levels, lipid levels, hypoglycemia frequency, home glucose monitoring profiles and body mass index SDS were measured before and 32 ± 2.32 months after substitution with insulin detemir. HbA1c levels were measured two times, at the beginning and end of insulin detemir treatment. At home, blood glucose measurements were performed with glucose test strips before meals and at 10 pm and 3 am, which was obtained to detect nocturnal hypoglycemia. Informed consent was obtained prior to the change in treatment modality. Wilcoxon test was used to compare the metabolic and clinical parameters. Statistically significant value was defined as $p < 0.05$.

Results

After insulin detemir administration as basal insulin, the mean HbA1c

values decreased from 9.08 % to 8.31 %. This decreased was not statistically significant ($p=0.061$). Before and after the Detemir administration, a statistically significant difference was not observed between the triglyceride and HDL cholesterol values ($p=0.615$, $p=0.887$). However, total and LDL cholesterol values decreased significantly after detemir (171 ± 44.23 vs 151 ± 20.41 mg/dl, $p=0.011$; 89 ± 22.59 vs 73 ± 20.67 mg/dl, $p=0.005$ respectively). The mean four – point blood glucose profiles showed a significant decrease after the substitution with detemir (10 ± 1.95 vs 8 ± 1.95 mmol/L, $p=0.004$). There was a decrease in the nocturnal hypoglycemia frequency and the rates were statistically significant differ before and after detemir ($p=0.036$). Although there was a decrease in the day hypoglycemia frequency, the rates did not statistically significant differ before and after detemir ($p=0.115$). Daily insulin doses, bolus/basal rates and body mass index SDS of patients were not changed significantly before and after detemir (Table 1).

Table 1. Summary of variables before and after detemir therapy

	Before Detemir Therapy**	After Detemir Therapy**	p*
Weight SDS	0.17±1.59	0.13±1.48	0.778
BMI SDS	0.19±1.01	0.29±0.76	0.300
Hb A1c (%)	9.08±1.90	8.31±1.29	0.061
Triglyceride (mg/dl)	132±148.36	95±30.78	0.615
Cholesterol (mg/dl)	171±44.23	151±20.41	0.011
HDL (mg/dl)	58±14.79	58±13.18	0.887
LDL (mg/dl)	89±22.59	73±20.67	0.005
Hypoglycemia frequency (day)	7±4.30	5±3.75	0.115
Hypoglycemia frequency (night)	2±2.59	1±0.99	0.036
Mean glucose values (mmol/L)	10±1.95	8±1.95	0.004
Total insulin doses (IU/kg/day)	0.91±0.24	0.97±0.21	0.211
Bolus (IU/kg)	0.50±0.13	0.61±0.15	0.044
Basal (IU/kg)	0.38±0.22	0.33±0.10	0.432
Bolus/basal rate	1.71±0.94	2±0.76	0.173

* Wilcoxon test, **The datas are provided as \pm SD

Conclusion

This study compared the glucose lowering effect of insulin detemir with NPH insulin given bedtime in type 1 diabetic patients on four doses insulin injection regime. Large-scale intervention and outcome studies have shown that intensified treatment aimed at tight glycemic control helps to delay onset and slow progression of diabetes complications in children and adolescents and adults (7,8). However, intensive insulin therapy is associated with increased risk of daytime and nocturnal hypoglycemia, which has been attributed to the pharmacodynamic properties of traditional human insulin preparations (9).

In most comparative studies of insulin detemir, no statistically significant between-group differences are reported for HbA1c, despite the reduced risk of hypoglycaemia seen with insulin detemir (10-13). This is also true for some of the most recently reported studies (13). However, in the study by Home et al (15), an analysis that combined data for the two insulin detemir groups did show a statistically significantly lower HbA1c, in comparison with NPH insulin (-0.18%; 95% CI -0.34,-0.02), but the effect size is clinically small. In the same study the authors concluded that decrement in the levels of HbA1c will result in the decrement of future microvascular complications (15). In our study, although the decrement of HbA1c levels was not statistically significant, the decrease of HbA1c levels by 0.77% may result in decreased future vascular complications. Based on the DCCT study, Pickup et al. (16) calculated that the absolute risk reduction for sustained progression in retinopathy associated with a difference in HbA1c of 0.5% was approximately 0.5 cas-

es per 100 patient - years. We consider that the decrement of HbA1c will increase when patients show good compliance with insulin detemir. Additionally, it has been considered that the decrease in HbA1c would reach significance with better adherence to diet in these patients.

The lower and more predictable fasting plasma glucose observed with insulin detemir are clinically significant advances compared to NPH insulin (14). Administration of insulin detemir resulted in more predictable blood glucose levels, with significantly lower day-to-day within-subject variation in fasting self-measured blood glucose profiles than with NPH insulin. This finding is consistent with findings from other trials in patients with type 1 diabetes (10,17). In the study of Home et al. (15), self-monitored prebreakfast levels at end point were significantly improved on detemir regimens. Russell-Jones et al. (18), have found that both fasting plasma glucose and fasting self-measured blood glucose were significantly reduced with insulin detemir compared with NPH. Prolonged duration of action complements findings from kinetic studies showing that insulin detemir has a flatter time-action profile than NPH, reaching a peak effect almost 90 min later than NPH5. From these profiles, the duration of action of insulin detemir appears to be long enough to cover nighttime basal insulin requirements. The effect of insulin detemir was most pronounced during the early morning hours, reflected in the lower FPG levels with insulin detemir compared with NPH insulin. In our study, the mean four - point blood glucose profiles showed a significant decrease after the substitution with detemir. It is likely that further optimization of the bas-

al insulin regimen would be possible using insulin detemir, which would hopefully provide superior glycemic control. The authors considered that once-daily administration of insulin detemir provided flatter and more stable nocturnal glucose profiles than NPH insulin, with the glucose-lowering action of insulin detemir being more persistent than that of NPH insulin, which seemed to wane in the early morning (1).

The earliest insulin detemir study did suggest a significantly reduction in overall hypoglycaemia rate compared with NPH insulin (17). Previously published 6-month trial, using insulin aspart as mealtime insulin, showed statistically significant 22% and 34% risk reductions for overall and nocturnal hypoglycemia, respectively, comparing insulin detemir with NPH insulin (A). Russell-Jones et al. (18) reported a 26% reduction in risk of nocturnal hypoglycaemia ($p = 0.003$). Other hand, Home et al. (15) reported on a highly significant reduction in the risk of nocturnal hypoglycemia in the detemir given in the morning and at bedtime group compared with the NPH insulin group. De Leeuw et al. (12) reported that the overall risk of hypoglycaemia in their study was not statistically significant insulin detemir and NPH insulin treatments. They found that between-group difference over 12 months was only statistically significant for nocturnal hypoglycaemia. Also, in our study, there was a decrease in the nocturnal hypoglycemia frequency and the rates were statistically significant differ before and after detemir. On the other hand, although there was a decrease in the day hypoglycemia frequency, the rates did not statistically significant differ before and after detemir. We consider that this difference will be more signif-

icant with prolonged insulin detemir treatment.

The mean requirement for insulin detemir was 2.35 times higher than that for NPH to obtain comparable blood glucose levels was evaluated (17). The impact of the difference in administered volume is not known, and in general it is difficult to compare the absorption of the two insulins because of their different modes of protraction (3,5). Vague et al. (11) reported that the mean daily basal dose was 30.7 units in the detemir group compared with 26.0 units in the NPH insulin group. In our study, daily insulin doses, bolus/basal rates of patients were not changed significantly before and after detemir. After detemir treatment, although not statistically significant basal insulin doses decreased compared to increased bolus insulin doses. Vague et al. considered that this finding may be related to additional evening time boluses which is used to prevent nocturnal hypoglycemia.

A significant difference in body weight was observed in the insulin detemir group compared with the NPH group during multiple adult trials. Adult patients treated with insulin detemir gained significantly less weight during the treatment period compared with those receiving NPH insulin (10,11,12,15,18,19). Robertson et al. (14) showed that BMI decreased significantly after insulin detemir treatment in childhood.

The mechanisms behind this reduced weight gain are currently unknown. We have thought that the lower weight gain associated with insulin detemir may result from a decreased need to counteract hypoglycemia through defensive, between meal snacking. We showed that although it was not significant, patients gained weight after insulin detemir treatment. This weight gain is thought to be related to the pubertal stage of the patients.

On the other hand, coronary artery disease is a leading cause mortality in adult patients in type 1 diabetes. Because coronary artery disease prevalence has recently been shown to be associated with dyslipidemia (20). In our study total and LDL cholesterol values decreased significantly after the Detemir administration. This finding indicates that insulin detemir treatment will result in good metabolic control in a short time. The improvement the lipid profile will decrease coronary artery disease related to dyslipidemia.

These study suggest that once-daily insulin detemir is effective and well tolerated as the basal component of long term basal - bolus therapy and compares favorably with NPH insulin, as demonstrated by a trend toward reduced risk of nocturnal hypoglycemia and better metabolic control.

REFERENCES

1. Home P, Kurtzhals P. Insulin detemir: From concept to clinical experience. *Expert opinion pharmacother.* (2006) 7 (3).
2. Kurtzhals P, Havelund S, Jonassen Ib et al. Albumin binding of insulins acylated with fatty acids: characterization of the ligand protein interaction and correlation between binding affinity and timing of the insulin effect in vivo. *Biochemistry J* (1995) 312, 725-731.
3. Whittingham JL, Havelund S, Jonassen Ib. Crystal structure of a prolonged - acting insulin with albumin - binding properties. *Biochemistry* (1997) 36, 2826-2831.
4. Chapman TM, Perry CM. Insulin detemir, a review of its use in the management of type 1 and 2 diabetes mellitus. *Drugs* 2004; 64 (22): 2577-2595.
5. Heinemann L, Sinha K, Weyer C et al. Time - action profile of the soluble, fatty acid acylated, long - acting insulin analogue NN304. *British diabetic association. Diabetic medicine* (1999); 16: 332-338.
6. Jehle PM, Micheler C, Jehle DR et al. Inadequate suspension of neutral protamine Hagedorn (NPH) insulin in pens. *The Lancet.* (1999); 354: 1604-1607.
7. Danne T, Lüpke K, Walte K et al. Insulin detemir is characterized by a consistent pharmacokinetic profile across age - groups in children, adolescents and adults in type 1 diabetes. *Diabetes care* 2003; 26: 3087-3092.
8. The Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: Outcomes after the conclusion of the Diabetes Control and Complications Trial. *The Journal of Pediatrics* 2001; 139: 804-812.
9. Hermansen K, Fontaine P, Kukolja KK et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal - bolus therapy for patients with Type 1 diabetes. *Diabetologia.* 2004; 47: 622-629.
10. Vague P, Selam JL, Skeie S et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with Type 1 diabetes on a basal - bolus regimen with premeal insulin aspart. *Diabetes Care* 2003; 26: 590-596.
11. Standl E, Lang H, Roberts A. The 12 - month efficacy and safety of insulin detemir and NPH insulin in basal

- bolus therapy for the treatment of Type 1 diabetes. *Diabetes Technology and Therapeutics* 2004; 6: 579-588.
12. Leeuw ID, Vague P, Selam JL et al. Insulin detemir used in basal – bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes, Obesity and Metabolism* 2005; 7: 73-82.
 13. Brunner GA, Sendlhofer G, Wutte A et al. Pharmacokinetic and pharmacodynamic properties of long – acting insulin analogue NN304 in comparison to NPH insulin in humans.
 14. Robertson KJ, Schönle E, Gucev Z et al. Benefits of insulin detemir over NPH insulin in children and adolescents with Type 1 diabetes: Lower and more predictable fasting plasma glucose and lower risk of nocturnal hypoglycemia. *Diabetologia* 2004; 47: supplement 1.
 15. Home P, Bartley P, Russel – Jones D et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes. *Diabetes Care* 2004; 27: 1081-1087.
 16. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: Meta analysis of randomised controlled trials. *BMJ* 2002; 324: 1-6.
 17. Hermansen K, Madsbad S, Perrild H et al. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin. *Diabetes Care* 2001; 24: 296-301.
 18. Russel – Jones D, Simpson R, Hylleberg B et al. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type 1 diabetes mellitus using a basal – bolus regimen. *Clinical Therapeutics* 2004; 26: 724-736.
 19. Haak T, Tiengo A, Draeger et al. Lower within – subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism* 2005; 7: 56-64.
 20. Purnell JQ, Hokanson JE, Marcovina SM et al. Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure. *JAMA* 1998; 280: 140-146.