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The Effect of Basal Analog Insulin on the Glycemic Variability in Type 2 Diabetics

Tip 2 Diyabetiklerde Bazal Analog İnsulinlerin Glisemik Dalgalanmalar Üzerine Etkisi

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Abstract

Purpose: The aim of this study was to investigate the effect of insulin detemir and glargine on glycemic variability as determined by capillary blood glucose measurements in Type 2 diabetics treated with oral antidiabetic drugs.
Material and Method: A total of 64 insulin-naive type 2 diabetics with a HbA1c level of 7.5%-10% were included in the study. The patients were randomized into 3 groups according to the basal insulin analog started; Group 1 (n=22) was started on once-daily detemir, Group 2 (n=22) twice-daily detemir, and Group 3 (n=20) insulin glargine. Basal insulin doses were titrated according to the morning/evening fasting capillary blood glucose levels. Standard deviations of the 8-point intraday fasting and postprandial blood glucose values were compared.
Results: The fasting blood glucose intraday standard deviation values showed an improvement of 22.4% in Group 1, 21.4% in Group 2, and 26.4% in Group 3, while the intraday standard deviation for the postprandial values showed an improvement of 14.4%, 15.2%, and 38.7%, respectively (p>0.05). The standard deviation values did not show statistical significance when the groups were compared with each other. Baseline HbA1c values and insulin doses negatively correlated with the glycemic variability.
Dicussion: Basal insulin added to treatment in Type 2 diabetics provided an improvement of 14.4% to 38.7% in glycemic variability. There was no significant difference between insulin glargine and detemir regarding this effect. *Turk Jem 2014; 2: 33-38*

Key words: Type 2 Diabetes, glycemic variability, basal insulin therapy

Özet

Amaç: Bu çalışmanın amacı, oral antidiyabetik ilaçlar ile tedavi edilen Tip 2 diyabet hastalarında insülin detemir ve glarjinin, kapiller kan glukoz ölçümleri ile tespit edilen glisemik dalgalanmalar üzerine etkilerinin incelenmesidir.
Gereç ve Yöntem: Daha önce hiç insulin kullanmamış ve HbA1c düzeyi %7,5-%10 arasında olan toplam 64 Tip 2 diyabetik hasta çalışmaya dahil edilmiştir. Hastalar başlanan bazal insulin analoguna göre 3 gruba randomize edildi; Grup 1'deki (n=22) hastalara günde tek doz insülin detemir, Grup 2'deki (n=22) hastalara günde iki doz detemir ve Grup 3'deki (n=20) hastalara insulin glarjin başlandı. Bazal insulin dozları sabah/akşam açlık kapiller glukoz ölçüm düzeylerine göre titre edildi. Gün içi 8 nokta açlık ve öğün sonrası kan glukoz ölçümlerinin standart deviasyon değerleri karşılaştırıldı.
Bulgular: Gün içi açlık kan glukoz ölçümlerinin gün içi standart sapma değerlerinde Grup 1'de %22,4, Grup 2'de %21,4 ve Grup 3'te %26,4 düzelme gözlenirken, öğün sonrası değerlerin standart sapma değerlerinde ise sırası ile %14,4, %15,2 ve %38,7 (p>0,05) düzelme tesbit edildi. Standart sapma değerleri her üç grup birebir karşılaştırıldığında istatistiksel olarak anlamlı fark tesbit edilmedi. Başlangıç HbA1c değerleri ve insulin dozları ile glisemik değişkenlik arasında negatif korelasyon tesbit edildi.
Tartışma: Tip 2 diayebtiklerde tedaviye bazal insulin eklenmesi, glisemik dalgalanmalarda %14,4'ten %38,7'ye kadar iyileşme sağlamaktadır. Bu etki açısından insulin detemir ve glargjin arasında istatistiksel olarak anlamlı bir fark tesbit edilmemiştir. *Turk Jem 2014; 2: 33-38*

Anahtar kelimeler: Tip 2 diyabet, glisemik dalgalanma, bazal insulin tedavisi

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Introduction

Glycemic control is essential for the prevention of cardiovascular disease and related complications in Type 2 diabetes (T2D) patients. HbA1c remains the best parameter reflecting average blood glucose levels over a 3-month period of time together with fasting and postprandial 2-hour glycemic levels. Studies have shown that decreased HbA1c levels caused reduction in micro and macrovascular complications (1,2,3). However, many studies have also shown that, besides increased fasting blood glucose and HbA1c levels, postprandial hyperglycemia is an independent risk factor for macrovascular complications in Type 2 diabetics (4,5,6). The Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) study has also shown a higher relationship of postprandial glycemic levels with increased mortality than that of higher levels of fasting blood glucose in more than 25000 patients followed up for more than 7 years (7). The Framingham Offspring Study has reported that an elevated glucose level 2 hours after an oral challenge increased the relative risk for cardiovascular disease by up to 40%, independent of fasting hyperglycemia in nondiabetic subjects (8).

Many studies indicated that diabetes complications in T2D are the result of excessive glycation and the generation of oxidative stress as a consequence of the three main glycemic disorders: Fasting hyperglycemia, postprandial hyperglycemia, and acute glucose fluctuations (9). Excessive fasting and postprandial glucose levels activate the glycation process, which can be evaluated by HbA1c measurements. Fasting hyperglycemia, acute or sustained postprandial hyperglycemia, and more generally, acute glucose fluctuations lead to oxidative stress. The resulting effect is the increased risk of complications as depicted by the diagonal arrow of a geometric cube consisting of fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and glucose fluctuations for the three axes The resulting effect is the risk of complications depicted by the diagonal arrow of a geometric cube for which three-dimensional coordinates on the three axes are fasting plasma glucose, postprandial glucose, and glucose fluctuations (10,11). This suggests that therapy for patients with T2DM should not only target HbA1c as a long-term goal, also should aim to avoid acute glucose fluctuations as an immediate goal.

Glycemic variability is a complex phenomenon that includes both intraday and interday variability. The intraday component corresponds to the within-day vertical glycemic fluctuations. The interday component is defined as day-to-day glucose variations, i.e., glycemic variability along a time-dependent horizontal axis. From a statistical point of view, the standard deviation (SD) around a mean glucose value measured over a 24-hour period using a continuous glucose monitoring system is probably the most appropriate tool for assessing intraday glycemic variability. The mean of daily differences is still the only index for estimating intraday glycemic variability. This parameter is calculated as the mean of the absolute differences between glucose values at the same time on two consecutive days (10).

The pharmacodynamic and pharmacokinetic properties of the long-acting insulin analogues provide less nocturnal and overall hypoglycemia than do NPH and this benefit has been observed in several comparative clinical trials evaluating glycemic variability. Both long-acting analogues have shown lower within-subject variability in blood and plasma glucose measurements when compared with NPH (12,13). Insulin detemir demonstrated less within-subject variability of blood glucose levels than insulin glargine in patients with Type 1 diabetes (T1D) or T2D in head-to-head comparisons of the analogues in glucose clamp studies (13,14). However, observational findings following the use of the two insulin analogues in clinical practice vary from patient to patient. Our aim in this study was to determine the effect detemir and glargine added to the treatment on glycemic variability according to capiallary blood glucose measurements of insulin in Type 2 diabetics treated with oral antidiabetics but without adequate glycemic control and to compare these two analogues with extended effect durations regarding glycemic variability in clinical practice.

Materials and Methods

A total of 64 Type 2 diabetic patients, who were treated with oral antidiabetics, had not received insulin treatment, and had inadequate glycemic, control were included in the study. The age range was 35-65 years and the HbA1c value was 7.5%-10%. Patients with a known malignant disease, chronic renal failure or chronic liver disease as well as pregnant patients, and those with a body mass index (BMI) >40 kg/m^2 were excluded from the study. The patients were using sulphonylurea (gliclazide) and/or metformin at the optimal dose for their body weight. Basal insulin treatment at a daily dose of 0.12 U/kg was added without changing the oral antidiabetic regiment. Following randomization, 22 patients received once-daily insulin detemir, 22 received twice-daily insulin detemir and 20 patients once daily insulin glargine. The patients were grouped as once-daily insulin detemir (Group 1), twice-daily insulin detemir (Group 2) and insulin glargine (Group 3) patients. Insulin doses were titrated every two weeks according to the morning preprandial glucose levels in the once-daily groups and the morning and evening preprandial glucose levels for the twice-daily group. A standard titration plan was used as follows: If the blood glucose (mg/dl) level is <80: →reduce 2 U - 80-120: →no change - 120-140: →increase 2U - 140-160: →increase 4U - 160-180: →increase 6U - >180: →increase 8U, while the plan for twice-daily users was: if the blood glucose level is <80: →reduce 1U - 80-120: →no change - 120-140: →increase 1U - 140-160: →increase 2U - 160-180: →increase 3U - >180: →increase 4U for each morning and evening doses. The patients were followed up for 12 weeks.

The trial was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice, and was approved by the local ethics committee. All the subjects were recruited in the study after they provided written informed consent. The demographic data of the patients, the baseline fasting insulin and C-peptide levels, and the baseline and 12th week HbA1c levels were recorded. The patients were asked to check their blood glucose 8 times a day (before breakfast, after breakfast, before lunch, after lunch, before dinner, after dinner, at 11:00 p.m, and at 02:00 a.m). The patients were given a glucometer

and its sensors (Freestyle Optium TM, Abbott) at the beginning of the study and, the relevant training was provided. The patients' self-blood glucose measurements were recorded during the telephone calls and clinic visits for dose titration once every two weeks. Body weight was measured at the beginning and end of the study and any hypoglycemic events were recorded according to patient information and blood glucose measurements. The capillary blood glucose values recorded to evaluate glycemic variability were evaluated in detail. The fasting and postprandial blood glucose averages of the 4th and 12th week 8-point measurements were calculated for each patient and the standard deviation values were recorded as another variable. The pre-meals and capillary blood glucose values at 02:00 p.m were used for the fasting blood glucose while the values after meals and at 11:00 p.m were used for the postprandial blood glucose mean value calculation.

Statistics

Demographic characteristics, HbA1c levels, age (years), diabetes duration (years), daily insulin dose at the end of the 12th week (U/kg), baseline insulin (U/mL) and C-peptide (ng/dL) levels, and BMI (kg/m^2) were summarized with descriptive statistics, including median and minimum-maximum values (given in parentheses) for continuous variables and frequency and percentages for categorical variables. Insulin dose data were given as units per kilogram. Statistical analysis was performed using a chi-square test for comparison of the categorical data, while the Kruskal-Wallis test and Mann-Whitney U test were used for comparison of the continuous data between the groups where appropriate. The Wilcoxon signed-rank test was used for analysis of the differences in standard error values and change ratios at the beginning and the end of the 12th week. Spearman's correlation coefficients were calculated to assess the associations between variables. All analyses were performed using IBM SPSS 20™ (SPSS Inc., Chicago, IL, USA) and a p value of less than 0.05 was considered statistically significant.

Results

The median age of the 64 patients, who completed the study, was 57(41-70) years and the mean diabetes duration was 6.5 (1-10) years. The starting dose of insulin was 0.12 units/kg/day in all the three groups. The HbA1c values were mildly elevated in Group 1 and Group 3 compared to that in Group 2, although the difference was not statistically significant. Baseline insulin and C-peptide levels were mildly elevated in Group 3 compared to Group 1 and Group 2 (p=0.04). We did not divide the patients into groups according to body measurements as the subjects were chosen randomly. The body mass index (BMI) and waist to hip ratio values were mildly higher in Group 3 than in the other two groups (p=0.19 for BMI, p<0.01 for waist to hip ratio). The basal characteristics of the groups are presented in (Table 1).

The glycemic control values of the 64 patients completing the study were similar between the groups. In Group 1, a median insulin dose increase of 0.19 (0.0-0.4) U/kg led to a median change of -1.9% [(-4.5)-(-1.4)] in HbA1c levels in 12 weeks. In Group 2, a median insulin dose increase of 0.22 (0.0-0.6) U/kg led to a median change of -1.2% [(-4.4)-(-0.4)] in HbA1c levels. In Group 3, a median insulin dose increase of 0.25 (0.0-0.5) U/kg led to median change of 1.35% [(-7.0)-1.5] in HbA1c levels (Table 2). There was a decrease of 7.4% in fasting blood glucose levels (the mean value of the 4 fasting values among the 8-point intra-day capillary blood glucose values) and 1.9% in postprandial blood glucose values (the mean value of the 4 postprandial values among the 8 point intra-day capillary blood glucose values). These values were 4.3 and 9.9% in Group 2, and 6.9 and 1.8% in Group 3. Comparison of the groups showed no statistically significant difference in changes in FBG and PBG levels (Table 3). Weight changes and hypoglycemic events are summarized also in Table 2 and there were no difference between the groups.

Standard deviations calculated from the 8-point capillary blood glucose measurements of the intraday mean FBG and PBG values at the 4th and 12th weeks were compared to evaluate the glycemic variability. The standard deviation of FBG values had decreased from a median value of 37.0 at 4 weeks to 28.7 at 12 weeks in group I while the values were 40.5 to 31.8 for Group 2 and 38.5 to 28.3 for Group 3, respectively. Standard deviation of PBG values had decreased from 43.6 at 4 weeks to 37.73 at 12 weeks in group I while the values were 45.9 to 38.9 in Group 2 and 44.9 to 27.5 in Group 3, respectively. When the groups were compared, no statistically significant difference was found

Table 1. Baseline characteristics according to the groups

	Group 1 (n=22)	Group 2 (n=22)	Group 3 (n=20)	p
Age (year)	57 (41-70)	54 (39-73)	59 (40-69)	0.38
Diabetes duration (year)	6.5 (1-10)	7.0 (2-10)	7.0 (1-10)	0.72
Male/female (%/%)	32/68	68/32	35/65	0.03
Starting insulin dose (U/kg/day)	0.12	0.12	0.12	
Basal insulin level (U/mL)	12.1 (2-35)	9.8 (2-58)	12.7 (3-49)	0.25
Basal c peptide level (ng/dL)	2.7 (1.0-9.4)	2.5 (0.3-8.4)	3.4 (1.7-10.8)	0.04
HbA1c (%)	9.9 (7.7-12.0)	9.3 (7.5-12.0)	9.6 (7.3-12.0)	0.35
Weight Kg	75.5 (50-130)	84.5 (67-117)	79.5 (61-113)	0.19
Body Mass Index kg/m^2	28.7 (22-40)	27.6 (21-36)	30.1 (21-37)	0.19
Waist to Hip Ratio cm/cm	0.94 (0.8-1.0)	0.91 (0.8-1.0)	1.02 (0.8-1.1)	<0.01

regarding the 4- and 12-week standard deviation values between Group 1 and 2, Group 1 and 3, and Group 2 and 3 (Table 4). An improvement of 22.4%, 21.4% and 26.4% was seen in Group 1, 2 and 3, respectively in FBG fluctuation with basal insulin treatment according to the standard deviation values while the values for PBG fluctuation were 14.4%, 15.2% and 38.7%, respectively. These changes in standard deviations were not statistically significant, probably due to small sample size (Figure 1).

The correlation analysis of patient characteristics and mean standard deviations was conducted by evaluating all parameters together. Baseline A1c values, insulin dose per body weight and insulin dose change in the 12-week period significantly positively correlated with the standard deviation values. We demonstrated that high baseline A1c level and high insulin dose were the most important factors for increased glycemic fluctuation (Figure 2).

Discussion

The aim of our study was to determine the effects of long-acting insulin analog treatment on glycemic fluctuation in Type 2 diabetic patients. This study has demonstrated that both insulin analogues (detemir once or twice-daily and glargine) had positive effect on glycemic fluctuation although it is not significant.

Studies comparing the two insulin analogues with NPH insulin have shown that they are much better than NPH insulin regarding glycemic variability (12,13,15). However, the LANMET study using HbA1c and 8-point capillary glucose measurement as marker of glucose control has reported similar improvement with insulin glargine and NPH insulin added to the treatment of Type 2 diabetic patients who had not used insulin. An equal decrease in capillary blood glucose measurement values was found in different periods of the day and the glycemic variability was not affected (11,16). The Study of Once Daily Levemir (SOLVE) evaluating the effectiveness of single-dose insulin detemir in 1671 patients have demonstrated a significant improvement in HbA1c, fasting plasma glucose, hypoglycemic events and glycemic variability when once-daily insulin detemir was added (17). In a Turkish

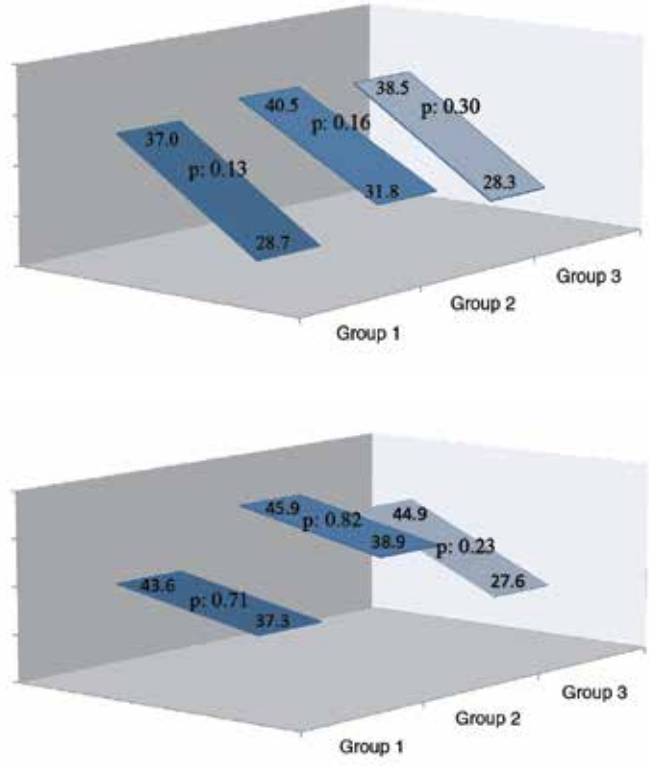

Figure 1. Changes in standard deviation values of within-day fasting and postprandial capillary blood glucose levels at the fourth week and the end of the study

Table 2. The markers of the diabetes control in once-daily insulin detemir, twice daily insulin detemir and insulin glargine groups

	Change in insulin dose (U/kg)	Change in HbA1c (%)	Weight change (kg)	BMI change (kg/m^2)	Hypoglycemic events Per week/patient
Group 1	+0.19 (0.0-0.4)	-1.9 [(-4.5)-1.4]	+1.0 [(-8)-9]	+0.34 [(-3.3)-2.6]	0.0 (0-4)
Group 2	+0.22 (0.0-0.6)	-1.2 [(-4.4)-0.4]	+0.0 [(-5)-3]	+0.00 [(-1.6)-1.1]	0.5 (0-4)
Group 3	+0.25 (0.0-0.5)	-1.35 [(-7.0)-1.5]	+1.1 [(-5)-3]	+0.42 [(-2.0)-1.1]	0.0 (0-2)
p (Group 1-2)	0.51	0.74	0.32	0.34	0.82
p (Group 1-3)	0.32	0.78	0.73	0.73	0.26
p (Group 2-3)	0.73	0.84	0.31	0.35	0.13

Table 3. Medians of fasting and postprandial capillary blood glucose levels at the fourth week and the end of the study, after the addition of insulin to OAD therapy

	FBG 4th week	FBG 12th week	PBG 4th week	PBG 12th week
Group 1	147 (82-352)	133 (102-281)	191 (136-313)	191 (136-313)
Group 2	152 (85-316)	142 (86-260)	200 (150-325)	190 (111-257)
Group 3	179 (89-301)	162 (107-230)	204 (122-342)	195 (144-295)
p (Group 1-2)	0.95	0.74	0.34	0.78
p (Group 1-3)	0.18	0.04	0.40	0.61
p (Group 2-3)	0.16	0.23	0.89	0.32

cohort of the Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE) study where the effectiveness of once-daily dose insulin detemir was evaluated in T2D patients found a significant improvement in HbA1c and glycemic variability 12 weeks after the switching from NPH or glargine insulin (18).

There are only a few studies with a small number of patients comparing head to head the two long-acting insulin analogues. Heinse et al. evaluated the pharmacokinetic and pharmacodynamic features of NPH insulin, insulin glargine and insulin detemir in 54 Type 1 diabetic patients and concluded that insulin detemir was associated with significantly less within-subject variability than both NPH insulin and insulin glargine, as assessed by coefficient of variation (CV) for the pharmacodynamic end points studied and also provided less within-subject variability in the pharmacokinetic end points (19). Klein et al. evaluated the pharmacokinetic features of insulin detemir and glargine in 27 Type 2 diabetic patients by the euglycemic clamp test and found lower within-subject variability with insulin detemir than insulin glargine although the metabolic effects were similar. The authors concluded that better predictability may be an important characteristic of the albumin-bound analogues as insulin detemir has already been shown to improve hypoglycemia (14).

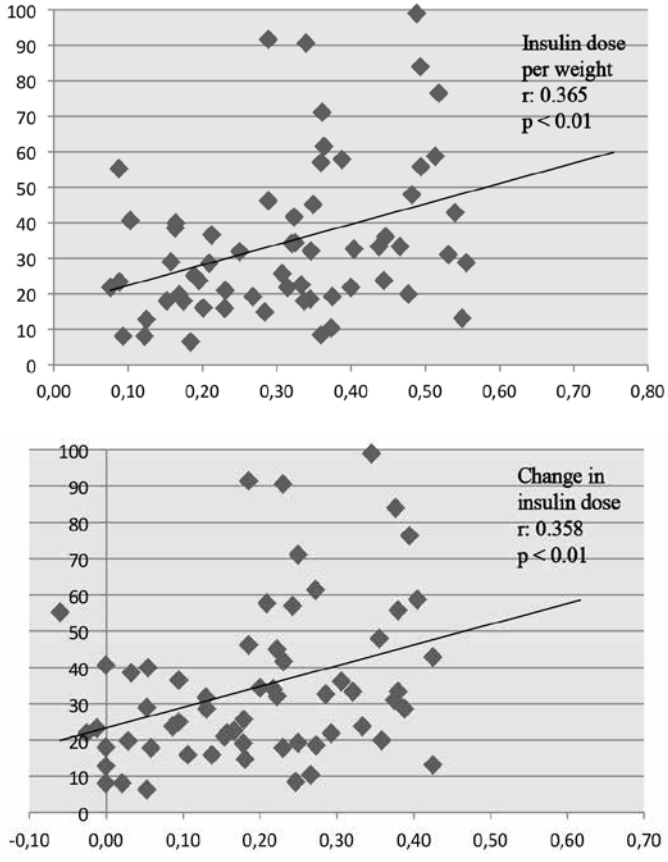

Figure 2. Correlations of 12th week intraday standard deviation of fasting blood glucose with insulin dose, change of insulin dose and HbA1c

Two clinical studies reported different results than did the two previous experimental studies. In a cross-over study, Tone et al. had 15 Type 1 diabetic and 14 Type 2 diabetic patients on intensive insulin treatment who were switched from insulin detemir to insulin glargine or from insulin glargine to insulin detemir as the basal insulin and evaluated changes in glycemic variability with standard deviation and coefficient of variance of capillary glucose values. They found a beneficial effect of switching insulin glargine to insulin detemir in Type 1 diabetic patients who had high glycemic variability (20). However, Renard et al. reported that insulin glargine had not weaker effect than did insulin determir according to the coefficient of variation and fasting blood glucose levels in their multicenter, randomized study with a 16-week crossover period on 78 Type 1 diabetic patients (21). We also evaluated glycemic variability with standard deviation using the fasting and postprandial capillary blood glucose levels as the basis and found no difference between insulin glargine treatment and insulin detemir in regards to glycemic variability in Type 2 diabetic patients.

As in the previously mentioned studies, we were unable to show a definitive and significant beneficial effect of basal insulin treatment on glycemic variability when added to OAD treatment in Type 2 diabetics. We demonstrated an improvement of 15 to 20% in all patients after initiating OAD + basal insulin treatment when the standard deviations of the mean fasting and postprandial blood glucose values were evaluated, but this result was not statistically significant. The small sample size is probably a factor and studies with larger numbers of patients are therefore required. Our results are important as they reflect a therapeutic window designed to demonstrate clinical practice. It is widely accepted that one of the treatment targets in Type 2 diabetic patients is to decrease glycemic variability. We therefore believe that glycemic variability is an

Table 4. Standard deviation (SD) values of within-day fasting and postprandial capillary blood glucose levels at the fourth week and the end of the study

	4th week within-day FBG levels SD	12th week within-day FBG levels SD	4th week within-day PBG levels SD	12th week within-day PBG levels SD
Group 1	37.0 (8.5-99.7)	28.7 (8.0-91.5)	43.6 (12.5-77.3)	37.3 (5.3-72.4)
Group 2	40.5 (15.1-92.7)	31.8 (7.9-98.9)	45.9 (17.2-89.0)	38.9 (11.2-85.5)
Group 3	38.5 (5.6-90.6)	28.3 (6.4-83.9)	44.9 (8.6-78.1)	27.5 (14.0-98.4)
p (Group 1-2)	0.60	1.00	0.37	0.75
p (Group 1-3)	0.92	0.85	0.36	0.62
p (Group 2-3)	0.56	0.78	0.92	0.33

important factor for starting insulin treatment in T2D patients, who have not reached treatment targets, and insulin treatment should be started without delay in patients with high glycemic variability.

Conclusion

We found that adding basal insulin analogues to treatment in Type 2 diabetics, who have not achieved adequate glycemic control with OADs, had positive effect on glycemic fluctuation. However, this effect was not statistically significant in our study and it should be verified with large sample sized studies. The effects of insulin detemir and insulin glargine on glycemic variability are not different.

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Conflicts of Interest

There are no conflicts of interest.

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