Long-Term Efficacy of Insulin Glargine After Switching from NPH Insulin as Intensive Replacement of Basal Insulin in Japanese Diabetes Mellitus. Comparison of Efficacy between Type 1 and Type 2 diabetes (JUN-LAN Study 1.2)

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Abstract. To assess and compare the efficacy and safety of insulin glargine as intensive replacement of basal insulin in Japanese patients with type 1 (n = 72) and type 2 (n = 46) diabetes, we switched their intensive insulin regimen from NPH plus regular or rapid-acting insulin to glargine plus bolus insulin, which included regular and rapid-acting insulin, and recorded changes in glycemic control and frequency of hypoglycemia for 18 months. The dose titration of basal and bolus insulin was based on home self-monitored blood glucose measurements and monthly HbA_{1C}. Mean HbA_{1C} level was improved significantly at 3 months after switching to glargine plus bolus insulin regimen and these effects continued for 18 months in both type 1 and type 2 diabetes patients (HbA_{1C} level: type 1: baseline 8.9 ± 2.6%, 18 months 7.8 ± 1.5% (p<0.05), type 2: baseline 8.2 ± 2.6%, 18 months 7.7 ± 1.5%. Body weight was slightly but significantly increased at 18 months only in type 2 diabetes. Total daily bolus insulin doses were not changed but basal insulin could be increased significantly after switching regimens in both types diabetes compared with baseline. The frequency of mild to moderate hypoglycemia (self-assisted episodes, blood glucose <70 mg/dl) was marginally lower with glargine but not significantly. Self-monitored fasting blood glucose level was significantly improved after switching in type 2 diabetes. Patients with the worst HbA_{1C} level at baseline exhibited more than 10% improvement in HbA_{1C} level after switching both type 1 and type 2 diabetes. The HbA_{1C} levels of the effectively treated patients were comparable to those of ineffectively treated ones at 6 months and the same improvement was seen at 18 months. Our results suggested that insulin glargine is more effective than NPH insulin as intensive replacement of basal insulin, particularly in those Japanese patients with difficult glycemic control with NPH insulin, equally in both type 1 and type 2 diabetes.

Key words: Insulin analogue, Intensive insulin therapy, Hypoglycemia, Long-acting insulin.

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DEVELOPMENT of recombinant DNA technology has allowed the design of insulin analogues that pro-

vide more physiological insulin supplement therapy for both type 1 and type 2 diabetic patients. Regimens containing these insulin analogues are now expected to improve glycemic control and play an important role in preventing chronic complications of diabetes mellitus.

Glargine is a long-acting insulin analogue designed with long bioavailability and prolonged duration of action, which is based on modification of isoelectric

point, resulting in precipitation at neutral tissue pH and consequent delayed absorption. Consistent with these features of insulin glargine, it has been reported that this insulin has a 24-h time-action profile without a pronounced peak, resulting in enhanced stabilization of glycemic control and reduced chance of hypoglycemia in type 1 diabetes patients in American and European populations [1–9]. However, only a few studies have reported on the efficacy and safety of glargine as intensive replacement of basal insulin in patients with type 1 and type 2 diabetes mellitus in Asian ethnic populations [10]. In this 18-month study, we switched from using intensive insulin regimen from neutral protamine Hagedorn (NPH) insulin plus regular or rapid-acting insulin to using glargine plus regular or rapid-acting insulin in both type 1 and 2 diabetes Japanese patients and compared changes in glycemic control, frequency of hypoglycemic episodes over the 18-month period, and determined the clinical features of responders to this regimen.

Patients and Methods

This study was planned prospectively and we randomly chose 90 outpatients with type 1 and 60 with type 2 diabetes mellitus who received intensive insulin therapy using rapid-acting or regular insulin and NPH insulin for more than one year at Juntendo University School of Medicine or associated hospitals from 2003 to 2004 and were under fair to bad glycemic condition (HbA$_{1C}$ ≥6.5%) at least for more than three months even after appropriate diet and exercise therapies. We excluded patients with apparent liver or renal dysfunction, those with chronic inflammatory state, and those with who were seriously ill. All participants were on intensive insulin regimen using three times daily bolus insulin (rapid-acting or regular insulin) and once daily NPH insulin for more than one year. The characteristics of the enrolled type 1 and type 2 diabetes patients who were followed-up for 18 months are listed in Table 1. Eighteen of 90 type 1 and 14 of 60 type 2 diabetes patients dropped out during the 18-month study due to move to a different location, disability using the insulin device for administration of glargine, or hospital admission for treatment of diseases other than side effects of glargine. Clinical background of these dropped out patients including HbA$_{1c}$, total insulin dose, age, and body mass index were not significantly

Table 1. Baseline characteristics of type 1 and type 2 diabetes patients.

	Type 1 diabetes	Type 2 diabetes
Number (M/F)	72 (31/41)	46 (25/21)
Age (years)	43.6 ± 15.2	56.9 ± 1.6
Body weight (kg)	56.3 ± 9.4	62.4 ± 1.7
BMI (Kg/m^2)	22.1 ± 3.3	23.2 ± 0.5
Duration of diabetes (years)	11.2 ± 8.5	16.6 ± 2.1
Baseline HbA$_{1C}$ (%)	8.9 ± 2.6	8.2 ± 2.2
Baseline basal insulin dose (U/kg)	0.24 ± 0.13	0.20 ± 0.02
Baseline bolus insulin dose (U/kg)	0.49 ± 0.20	0.45 ± 0.03
Bolus insulin (rapid acting/regular)	50/22	35/11

different from those of included ones. Other laboratory tests were within normal limits or showed very small abnormalities. The switching dose of glargine from NPH insulin was similar to that of NPH insulin originally used in each patient. To confirm whether adequate dose of NPH or bolus insulin was used, the doses of those insulins were modified in response to self-monitored blood glucose level (capillary blood glucose before meals, 1–3 h after meals and at bedtime every week) and HbA$_{1c}$ levels for 3 months before switching to glargine. Total insulin dose and glycemic control for the period did not change significantly, indicating their glycemic control was stable. Also after switching from NPH to glargine, the doses of both glargine and/or bolus insulin were modified in the same way as before switching. Patients were advised to decrease or increase the dose of basal insulin if fasting blood glucose was reproducibly <100 mg/dl or >140 mg/dl, respectively, decrease or increase the dose of rapid-acting insulin at meals if the post-prandial blood glucose was reproducibly <140 mg/dl or >170 mg/dl, respectively, and adjust the doses of bolus insulin based on postprandial blood glucose level of previous days and episode of hypoglycemia, in addition to the composition and size of meals and physical activity. The doses of insulin glargine, NPH, and bolus insulin were increased or decreased by 1–2 units, if necessary, to meet the target fasting or post-prandial blood glucose level. Hypoglycemia was defined as episodes in which clinical symptoms were associated with self-monitoring confirmed blood glucose level of <60 mg/dl. Hypoglycemia was considered mild when the episodes were

self-treated by the patient and severe when the episode required any kind of others' help.

All data were expressed as mean ± SD. Differences between groups were examined for statistical significance using the unpaired Student's *t*-test. A *P* value less than 0.05 was regarded as statistically significant.

Results

Ninety type 1 and 60 type 2 diabetic outpatients who had been on appropriate diet regimen and intensive insulin therapy including three times daily premeal bolus insulin and once daily bedtime NPH insulin but whose glycemic control were fair to bad (mean HbA_{1C} 8.9 ± 2.6 for type 1, 8.2 ± 2.2% for type 2), were included in this study. Table 1 summarizes the clinical features of the patients who could complete this part of the study (type 1: n = 72, type 2: n = 46) before switching from NPH insulin to glargine. After three-month dose titration of NPH (see Methods) and steady glycemic control, the once daily NPH insulin injection was switched to insulin glargine using the same dose.

Fig. 1 shows changes in HbA_{1C} levels before and after switching of basal insulin. Baseline HbA_{1C} levels were 8.9 ± 2.6 in type 1 and 8.2 ± 2.2% in type 2 diabetes respectively. After 3 months of glargine treatment as basal insulin, HbA_{1C} levels improved significantly in both type 1 and type 2 diabetes patients and this improvement lasted up to 18 months. The mean body weight was slightly but significantly increased at the end of 18 months only in type 2 diabetes but not in type 1 diabetes (Fig. 2). Total daily bolus insulin dosage did not change significantly between before and after switching regimens in both type 1 and type 2 diabetes patients (Fig. 3). In both types of diabetes, the daily basal insulin dosage was increased significantly after switching regimens (Fig. 4). The frequency of mild to moderate hypoglycemia (self-assisted episodes, blood glucose <70 mg/dl) was a little lower with glargine but the difference was not significant (times per month at baseline and after 18 month: type 1: 5.65 ± 6.19 times/months to 3.33 ± 4.31 times/month, type 2: 3.43 ± 4.99 times/month to 1.66 ± 2.78 times per month). Fasting blood glucose level assessed by self-monitoring was significantly (p<0.01) improved after switching in type 2 diabetes (baseline; 152.3 ± 40.2 mg/dl, 6 months 134.6 ± 50.0 mg/dl, 12 months; 123.3 ± 31.4 mg/dl, 18 months; 128.8 ± 50.2 mg/dl) (those in type 1 diabetes were not analyzed).
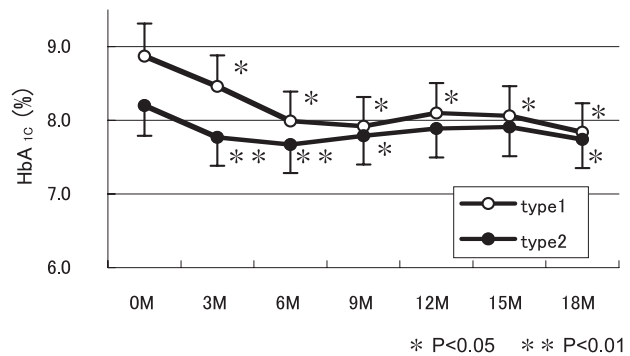
We then divided the patients into two groups: the effective group (defined as those patients with more than 10% improvement in HbA_{1C} at 18 months) and ineffective group (defined as those patients with less than 10% improvement in HbA_{1C} at 18 months). Twenty-eight (type 1) and 16 (type 2) patients showed effective response while the other 44 (type 1) and 30 (type 2) patients constituted the ineffective group. Fig. 5 shows

Fig. 1. HbA_{1C} levels before and after switching of basal insulin. Changes in HbA_{1C} over 18 months (mean ± SD) after switching from NPH insulin with bolus insulin to glargine with bolus insulin in type 1 (open circles) and type 2 diabetes patients (closed circles). The fall in HbA_{1C} at each time point (2–18 months) in both types of diabetes was significant relative to baseline HbA_{1C} (month 0) (p<0.01). The difference between the two types of diabetes at each time point was not significant.
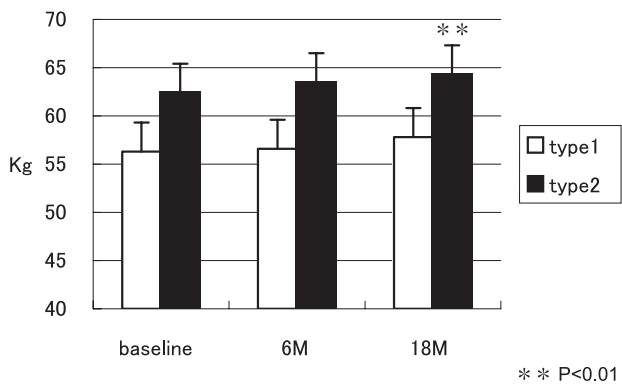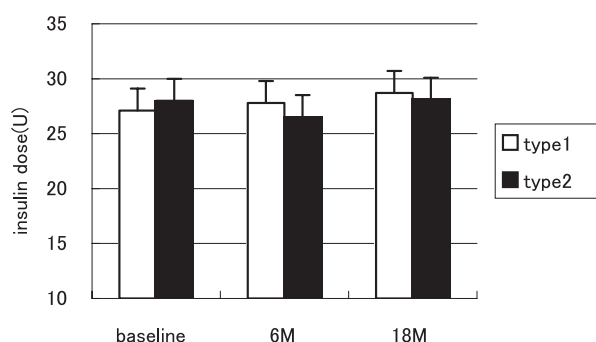

Fig. 2. Body weight before and after switching of basal insulin. Body weight at baseline, 6 and 18 months (mean ± SD) after switching from NPH insulin with bolus insulin to glargine with bolus insulin in type 1 and type 2 diabetes patients. The increase in body weight at 18 months in type 2 patients was statistically significant from baseline (month 0) (p<0.01). The difference between the two types of diabetes at each time point was not significant.

Fig. 3. Dosage of bolus insulin before and after switching of basal insulin.

Dosage of bolus insulin at baseline, 6 and 18 months (mean ± SD) after switching from NPH insulin with bolus insulin to glargine with bolus insulin in type 1 and type 2 diabetes patients. The dosages at 6 and 18 months were not significantly different from baseline (month 0) in both types of diabetes. The difference between the two types of diabetes at each time point was not significant.

Fig. 4. Dosage of basal insulin before and after switching of basal insulin.

Dosage of basal insulin at baseline, 6 and 18 months (mean ± SD) after switching from NPH insulin plus bolus insulin to glargine plus bolus insulin in type 1 and type 2 diabetes patients. The dosages at 6 and 18 months were significantly different from baseline (month 0) in both types of diabetes. The difference between the two types of diabetes at each time point was not significant.
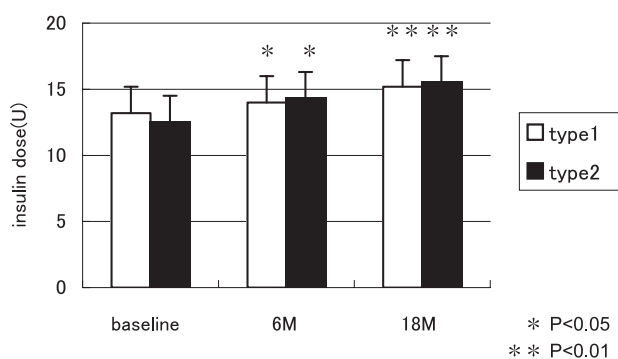

Fig. 5. Comparison of changes in HbA_{1C} before and after switching basal insulin in effective and ineffective patients with type 1 (a) and type 2 (b) diabetes.

Serial changes in HbA_{1C} over 18 months (mean ± SD) in type 1 (a) and type 2 (b) diabetes patients switched from NPH insulin with bolus insulin to glargine with bolus insulin. Open circles: effective group, including patients who showed >5% of improvement in HbA_{1C} at 6 months. Closed circles: ineffective group, including patients who showed <5% of improvement or worsening in HbA_{1C} at 6 months. Decreases of HbA_{1C} at all points (2–18 months) for effective groups of both diabetes types were significant relative to HbA_{1C} at baseline (month 0) (type 1: $p<0.05$ and type: $p<0.01$).

changes in HbA_{1C} levels of each group before and after switching of basal insulin in type 1 and type 2 diabetes.

Table 2 compares the clinical features of patients of the effective and ineffective groups. The baseline HbA_{1C} levels of patients (type 1 and type 2) of the effective groups were significantly worse than those of the ineffective groups. None of the other clinical parameters including sex, age, body mass index, annual
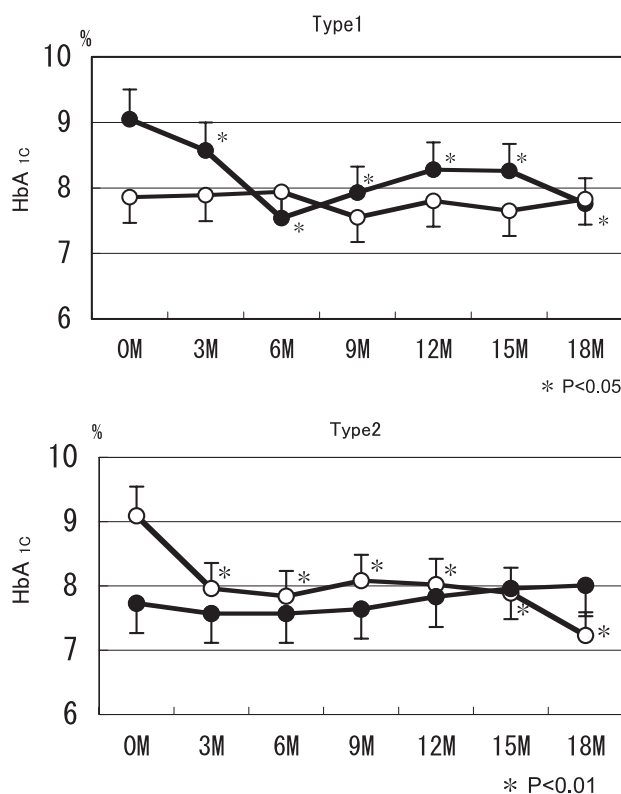
body weight change before switching glargine (data not shown), diabetic complications, ratio of rapid-acting insulin to regular insulin, and serum lipid (data not shown) was significantly different between the two groups, both in type 1 and type 2 diabetics. The duration of diabetes tended to be shorter in the effective group than ineffective group but the difference was not statistically significant. The baseline insulin doses, including bolus, basal, or total insulin, were not significantly different between the two groups. Frequencies of hypoglycemic attack before switching to glargine which may partially means instability of glycemic con-

Table 2. Comparison of baseline demographics and clinical characteristics between patients who responded well to glargine (*effective*) as basal insulin and those who did not (*ineffective*).

	Type 1		Type 2	
	effective	ineffective	effective	ineffective
Number (M/F)	28 (12/16)	44 (19/25)	16 (6/10)	30 (11/19)
Age (years)	44.5 ± 16.1	43.6 ± 14.8	55.3 ± 2.4	57.7 ± 2.2
Body weight (kg)	57.8 ± 10.6	57.7 ± 8.0	58.9 ± 2.4	64.3 ± 2.3
BMI (Kg/m^2)	22.1 ± 3.2	21.9 ± 3.4	22.4 ± 0.7	23.5 ± 0.7
Duration of diabetes (years)	9.4 ± 7.0	11.1 ± 7.4	10.0 ± 2.0	20.3 ± 2.7
FPG (mg/dl)	ND	ND	173.2 ± 14.2	143.1 ± 6.8
Baseline HbA_{1C} (%)	$9.04 \pm 1.97^*$	7.86 ± 1.74	$9.09 \pm 0.39^*$	7.73 ± 0.23
Baseline basal insulin dose (U/kg)	0.24 ± 0.18	0.22 ± 0.10	0.19 ± 0.04	0.26 ± 0.02
Baseline bolus insulin dose (U/kg)	0.47 ± 0.18	0.47 ± 0.20	0.45 ± 0.05	0.45 ± 0.03
Bolus insulin (rapid acting/regular)	18/10	32/12	10/6	24/6
Hypoglycemic attack before glargine (times/month)	3.7 ± 4.6	7.1 ± 6.9	2.5 ± 3.7	3.8 ± 5.5
Diabetic complications				
Retinopathy (%)	39	57	40	65
Nephropathy (%)	23	38	40	55
Neuropathy (%)	23	21	40	40

*$P<0.01$, compared with ineffective group of the same type of diabetes.
ND: not detected. Diabetic complications include simple diabetic retinopathy, microalbuminuria, sensory and sympathetic nerve disorder, and more severe stages of each complication.

trol in ineffective patients were a little more than those in effective groups both in type 1 and type 2 diabetics but differences were not significant (Table 2). Ratios of diabetic complications were not different between two groups both in type 1 and type 2 diabetics. Patients with severe unconsciousness of hypoglycemia were not included in this study. The data of fasting serum C-peptide were incomplete and no difference was observed between the groups (data not shown). The numbers of patients who were prescribed oral diabetic agents including metformin and alpha-glucosidase inhibitors were very few and no significance were observed between effective and ineffective groups in both type 1 and type 2 diabetics.

To examine whether the baseline HbA_{1C} level could predict the response to insulin glargine, we divided each of type 1 and type 2 diabetes patients into three groups based on the baseline HbA_{1C} level (≤ 7.5, >7.5 to 8.5, and $>8.5\%$) and compared the changes in HbA_{1C} levels before and 18 months after switching of basal insulin (Fig. 6). In both type 1 and type 2 diabetes patients, the worst HbA_{1C} tertile groups ($>8.5\%$) showed significant improvements while other groups (≤ 7.5 and >7.5 to 8.5%) did not. The dosages of basal insulin after switching were significantly increased in the worst tertile group for both type 1 and type 2 diabe-

tes (Fig. 7); but no such changes were noted in the other groups for both types of diabetes. Similar to bolus insulin, the dosage of bolus insulin or total insulin, ratio of rapid-acting insulin to regular insulin were not significantly different among the three groups based on HbA_{1C} level. These results suggest that one can consider switching the intensive insulin regimen to glargine plus bolus insulin at least when glycemic control is inadequate with NPH plus bolus insulin regimen, and increase the basal insulin dose relative to the baseline regardless of the type of diabetes mellitus.

Discussion

The basal and bolus insulin strategy as called "multiple daily insulin therapy" (MDI) is a regimen designed to prevent microvascular complications associated with type 1 [11] and type 2 diabetes [12]. It was reported recently that such intensive diabetes treatment program prevents cardiovascular disease in type 1 diabetes [13].

Previous studies reported that supplementation of basal insulin is best replaced with continuous subcutaneous insulin infusion (CSII) using an external minipump, compared with NPH insulin or ultralente
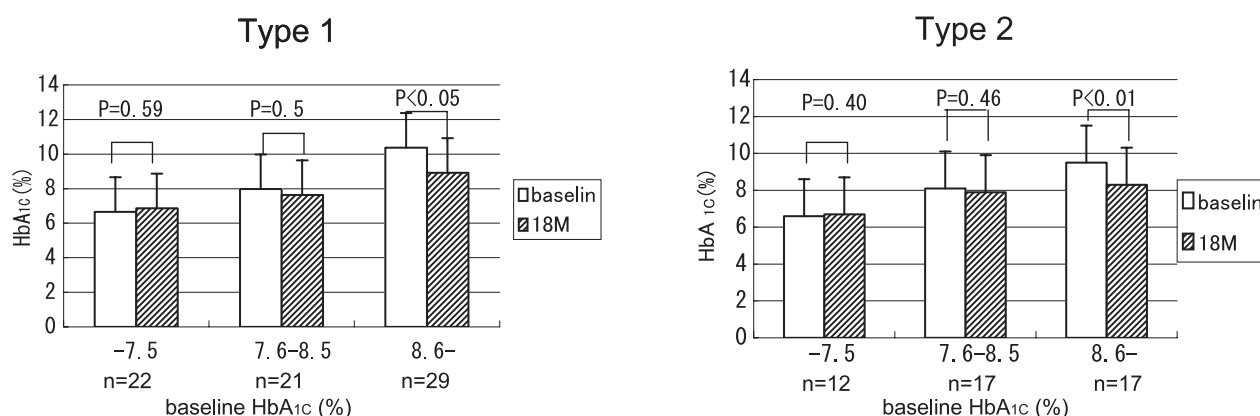
Type 1

Type 2

Fig. 6. Changes in HbA$_{1C}$ levels before and after switching of basal insulin in trisected groups based on baseline HbA$_{1C}$ level.
HbA$_{1C}$ at baseline and at 18 months (mean ± SD) in type 1 and type 2 diabetes patients switched from NPH insulin plus bolus insulin to glargine plus bolus insulin. Each group of diabetics was trisected into three groups based on baseline HbA$_{1C}$ level (≤7.5, >7.5 to 8.5, >8.5%). In both type 1 and type 2 diabetes patients, the worst HbA$_{1C}$ tertile groups (>8.5% HbA$_{1C}$) showed significant improvement at 18 months (type 1: p<0.05, type 2: p<0.01). Dosages of basal, bolus, or total insulin did not change after switching and were not different among three the groups of both type 1 and type 2 diabetes The difference in HbA$_{1C}$ between the two types at each time point was not significant.
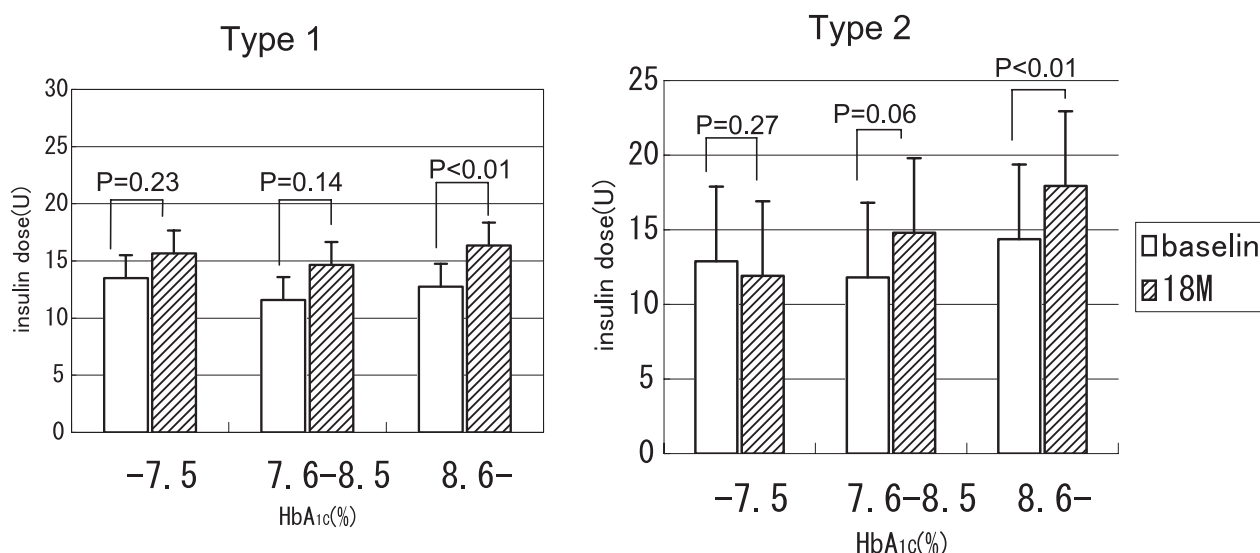
Type 1

Type 2

Fig. 7. Changes in dosage of basal insulin before and after switching of basal insulin in the trisected groups based on baseline HbA$_{1C}$ level.
Dosage of basal insulin at baseline and at 18 months (mean ± SD) in type 1 and type 2 diabetes patients switched from NPH insulin plus bolus insulin to glargine plus bolus insulin. Each type of diabetes patients was trisected into three groups based on baseline HbA$_{1C}$ level (≤7.5, >7.5 to 8.5, >8.5%) and changes dosage of basal insulin were compared. In both type 1 and type 2 diabetes patients, the worst HbA$_{1C}$ tertile groups (>8.5% HbA$_{1C}$) showed significant increase (type 1: p<0.01, type 2: p<0.01). Dosages of basal, bolus, and total insulin did not change after switching and did not differ among the three groups of both type 1 and type 2 diabetes. HbA$_{1C}$ at baseline and 18 months in both types were not significant at each time point.

human insulin [14–15]. However, in practice, subcutaneous injection of the intermediate-acting NPH insulin is the most commonly used replacement of basal insulin in both type 1 and type 2 diabetes mellitus.

Insulin glargine has a 24-h time-action profile with no pronounced peak, and thus produces a stable glycemic control and can reduce the likelihood of hypoglycemic episodes in type 1 diabetics, as reported in USA

and Europe [1–2]. In addition to reports on the efficacy and safety of insulin glargine as an intensive replacement of basal insulin in patients with type 1 and type 2 diabetes mellitus, this insulin has been also used in conjunction with oral hypoglycemic drugs such as sulfonylurea [16–17] and mitiglinide [18–19].

In the present study, we showed that insulin glargine is more effective than NPH as an intensive replacement of basal insulin in both type 1 and 2 Japanese diabetes patients, especially in those whose glycemic control was difficult with NPH. Formulation of NPH insulin fails to provide stable and predictable 24-h basal insulin levels because the duration of action is too short following once-daily administration. Moreover, the absorption is too variable and the non-physiological peak of insulin levels leaves patients at high risk of hypoglycemia, especially at midnight. On the other hand, insulin glargine has a 24-h time-action profile with no pronounced peak, and thus provides better stability of glycemic control and reduced chance of hypoglycemia in type 1 diabetes patients. Several recent studies compared the efficacy of CSII and multiple daily insulin injection (MDI) using glargine in conjunction with premeal rapid-acting insulin in type 1 and type 2 diabetes patients. In type 1 diabetes, some reports showed that lower HbA_{1C} and premeal glucose levels were more achievable in CSII groups [20–21] but others have reported CSII and MDI were equally effective [22]. On the other hand, the frequency of hypoglycemic episodes in these two regimens was not different in all reports. In other studies, both CSII and MDI were reported to achieve excellent glycemic control with good safety and patients' satisfaction in type 2 diabetes [23–24]. Thus, our results are consistent with these previous reports that supplementation of basal insulin with glargine was superior to that with NPH insulin but as equally effective as continuous preprogrammed basal supplement with CSII, at least in Japanese type 2 diabetes.

We also examined the long-term efficacy of insulin glargine after switching from NPH insulin, as an intensive replacement of basal insulin in both type 1 and type 2 diabetes. To our knowledge, only a few studies examined the long-term efficacy of glargine in type 1 diabetes and virtually none in type 2 diabetes (24 weeks was the longest duration of treatment). The usefulness of glargine in MDI was evident in the third tertile of baseline HbA_{1C} both in type 1 and type 2 diabetes patients. The reason for the superior efficacy of glargine in MDI therapy in patients with the worst HbA_{1C}, is not clear at present. However, we postulate the following mechanisms: 1) Ample supplementation of basic insulin was necessary in these patients. The dosage of glargine could be increased in these patients without hypoglycemic shock, compared with NPH insulin at baseline. Dose escalation of NPH insulin may not be appropriate or adequate dose modification could not be done by risk of hypoglycemia. 2) Longer or ubiquitous supplement of basic insulin was necessary in these patients. The half life of NPH insulin was too short to provide adequate cover throughout the 24 hours. Patients of the first and second tertiles may require a sufficient dose and duration of NPH insulin as the basal insulin, and thus one would expect no differences between such treatment regimen and glargine.

In conclusion, our results suggested that insulin glargine is more effective than NPH insulin as an intensive replacement of basal insulin in Japanese type 1 and 2 diabetes patients, especially in those patients with difficult glycemic control using NPH insulin.

Appendix

References

1. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB (2000) Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous

infusion of insulin lispro. *Diabetes* 49: 2142–2148.

2. Heinemann L, Linkeschova R Rave K, Hompesch B, Sedlak M, Heise T (2000) Time-action profiles of the long-acting insulin analogue glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 23: 644–649.

3. Murphy NP, Keane SM, Ong KK, Ford-Adams M, Edge JA, Acerini CL, Dunger DB (2003) Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care* 26: 799–804.

4. Rossetti P, Pampanelli S, Fanelli C, Porcellati F, Costa E, Torlone E, Scionti L, Bolli GB (2003) Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: A 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. *Diabetes Care* 26: 1490–1496.

5. Albright ES, Desmond R, Bell DS (2004) Efficacy of conversion from NPH insulin injection to once- or twice-daily injections of insulin glargine in type 1 diabetic patients using basal/bolus therapy. *Diabetes Care* 27: 632–633.

6. Porcellati F, Rossetti P, Pampanelli S, Fanelli CG, Torlone E, Scionti L, Perriello G, Bolli GB (2004) Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med* 21: 1213–1220.

7. Fulcher GR, Gilbert RE, Yue DK (2005) Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. *Intern Med J* 35: 536–542.

8. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA (2000) Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care* 23: 639–643.

9. Porcellati F, Rossetti P, Pampanelli S, Fanelli CG, Torlone E, Scionti L, Perriello G, Bolli GB (2004) Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med* 21: 1213–1220.

10. Yokoyama H, Tada J, Kamikawa F, Kanno S, Yokota Y, Kuramitsu S (2006) Efficacy of conversion from bedtime NPH insulin to morning insulin glargine in type 2 diabetic patients on basal-prandial insulin therapy. *Diabetes Res Clin Pract* 73: 35–40.

11. The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329: 977–986.

12. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M (1995) Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28: 103–117.

13. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B (2005) Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/ EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353: 2707–2709.

14. Renner R, Pfutzner A, Trautmann M, Harzer O, Santer K, Landgraf R (1999) Use of insulin lipro in continuous subcutaneous insulin infusion treatment. *Diabetes Care* 22: 784–788.

15. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB (2000) Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49: 2142–2148.

16. Yki-Jarvinen H, Dressler A, Ziemen M. The HOE 901/ 3002 Study Group (2000) Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 23: 1130–1136.

17. Goto H, Hirose T, Shimizu T, Mita T, Igarashi Y, Fujitani Y, Tanaka Y, Watada H, Kawamori R (2007) The effectiveness of combination therapy with sulfonylurea and once daily insulin glargine in Japanese type 2 diabetic patients. Evaluation of long-term (18 months) treatment with the combination therapy. *J Japan Diab Soc* 50: 591–597.

18. Yoshihara Y, Kumashiro N, Kanazawa Y, Mita T, Sakurai Y, Kawai J, Abe M, Motojima K, Hara K, Yamazaki K, Kanazawa A, Miwa S, Sato F, Kanno R, Shimizu T, Sakai T, Uchino H, Watada H, Tanaka Y, Kawamori R, Hirose T (2006) Therapeutic efficacy of mitiglinide combined with once daily insulin glargine after switching from multiple daily insulin regimen of aspart insulin and glargine in patients with type 2 diabetes mellitus. *Endocr J* 53: 67–72.

19. Kumashiro N, Yoshihara T, Kanazawa Y, Shimizu T, Watada H, Tanaka Y, Fujitani Y, Kawamori R, Hirose T (2007) Long-term effect of combination therapy with mitiglinide and once daily insulin glargine in patients who were successfully switched from intensive insulin therapy in short-term study. *Endocr J* 54: 163–166.

20. Hirsch IB, Bode BW, Garg S, Lane WS, Sussman A, Hu P, Santiago OM, Kolaczynski JW; Insulin Aspart

CSII/MDI Comparison Study Group (2005) Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. *Diabetes Care* 28: 533–538.

21. Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV (2004) A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 27: 1554–1558.

22. Harmel AP, Mathur R (2004) Similar HbA1C outcomes in type 1 diabetic patients undergoing intensive diabetes management with preprandial rapid-acting insulin and either CSII or glargine. *Diabetes Care* 27: 272–273.

23. Raskin P, Bode BW, Marks JB, Hirsch IB, Weinstein RL, McGill JB, Peterson GE, Mudaliar SR, Reinhardt RR (2003) Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. *Diabetes Care* 26: 2598–2603.

24. Herman WH, Ilag LL, Johnson SL, Martin CL, Sinding J, Al Harthi A, Plunkett CD, LaPorte FB, Burke R, Brown MB, Halter JB, Raskin P (2005) A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care* 28: 1568–1573.