Lispro Is Superior to Regular Insulin in Transient Intensive Insulin Therapy in Type 2 Diabetes

Yuko MURASE, Kunimasa YAGI*, Masako SUGIHARA, Daisuke CHUJO*, Michio OTSUJI*, Hiroaki MURAMOTO and Hiroshi MABUCHI*

Abstract

Objective **The optimal approach to relatively recent onset type 2 diabetes patients is still unknown. We speculated that the use of short-acting insulin analogs might be of particular benefit in this context.**

Patients and Methods **To explore this possibility, we compared the effect on β- and α-cell function of transient intensive insulin therapy using lispro versus human regular insulin in a total of 21 type 2 diabetic patients who were randomly assigned to 14-days intensive insulin therapy consisting of bedtime NPH insulin plus three injections of mealtime lispro (n=11) or regular insulin (n=10). The dosages of both types of insulin were adjusted to attain preprandial glucose levels of <6.1 mmol/*l* within 1 week with similar rates of glucose decline. An oral glucose tolerance test (OGTT) was performed at day 0 (baseline), 7, and 14; plasma glucose, serum insulin, and plasma glucagon responses over 0–120 minutes were measured, and calculated as the area under the curve (AUC).**

Results **Lispro led to a significant reduction in glucose-AUC and also an increase in insulin-AUC versus regular insulin on day 7. Glucagon secretion following OGTT was well suppressed with lispro on day 14 compared to regular insulin.**

Conclusion **Two-week intensive insulin therapy with lispro appeared to be more effective than that with regular insulin in type 2 diabetes in attaining both more rapid β-cell rest and greater suppression of glucagon. These changes may provide significant long-term benefits.**
(Internal Medicine 43: 779–786, 2004)

Key words: transient intensive insulin therapy, insulin lispro, diabetes mellitus

Introduction

Obesity is recognized to be a major risk factor for the development of type 2 diabetes, and is becoming an increasingly dire health and social problem worldwide (1–3). There is, however, an important subset of non-obese type 2 diabetes, whose insulin secretion is usually lower than that of obese diabetics, and to which relatively less attention has been paid. The optimal therapeutic approach for this non-obese subset has not yet been established and continues to be an important clinical concern, especially in Japan where such cases comprise a much greater proportion of the total type 2 diabetic population than in most Western countries (4–6).

In Japan, insulin therapy for patients with type 2 diabetes is resorted to earlier and used more frequently, partly because its use is associated with less weight gain than in Western countries (6). Evidence suggests that early insulin therapy can help correct the underlying β-cell dysfunction, at least some of which is reversible in relatively recent onset type 2 diabetes, and improve long-term glycemic control (7–9). For instance, it has been shown that, in newly diagnosed patients with type 2 diabetes, only 2 weeks of insulin therapy was sufficient to achieve satisfactory metabolic control for up to 3 years (10). For these reasons, some diabetologists advocate the initiation of insulin therapy earlier in the course of non-obese type 2 diabetes than has been common in the past (11, 12).

In addition to disordered β-cell function, α-cell dysfunction is also seen in individuals with type 2 diabetes (13–15), with glucagon concentrations after carbohydrate ingestion either not suppressed or, paradoxically, even increasing, contributing to postprandial hyperglycemia (16–18). The deleterious effects of hyperglycemia per se, however, on α-cell function are not as well understood as those on β-cell function and insulin action (19–21). Intensive glycemic regulation, if achieved early, might promote both α-cell and β-cell

From the Department of Internal Medicine, Kanazawa Social Insurance Hospital and *the Molecular Genetics of Cardiovascular Disorders, Graduate School of Medical Science, Kanazawa University, Ishikawa

Received for publication November 28, 2003; Accepted for publication April 20, 2004

Reprint requests should be addressed to Dr. Yuko Murase, the Department of Internal Medicine, Kanazawa Social Insurance Hospital, Ha-15, Oki-machi, Kanazawa 920-8610

Table 1. Baseline Characteristics of Lispro and Regular Insulin Randomization Groups

	Lispro	Regular	p value
No.	11	10	–
Sex (M/F)	6/5	5/5	–
Age (years)	57.9±1.6	56.0±3.4	0.64
Diabetes duration (years)	2.1±0.3	2.1±0.2	0.78
Diabetes treatment (diet/voglibose)	11/2	10/1	–
HbA_{1c} (%)	9.9±0.3	10.6±0.7	0.39
BMI (kg/m^2)	24.4±0.9	24.0±0.9	0.76
Fasting glucose (mmol/*l*)	11.2±0.6	11.7±0.9	0.65
Fasting IRI (pmol/*l*)	34.1±3.8	28.8±4.3	0.38

Data are mean±SEM.

recovery and preservation.

Transient intensive insulin therapy (TIIT) designed to achieve this is a reasonable goal that may be associated with major clinical benefit in recent onset uncontrolled type 2 diabetes patients. Two rapidly acting insulin analogs, insulin lispro and aspart, are currently available in Japan and other countries, and both insulin analogs are shown to be equally effective for the control of postprandial blood glucose excursions (22, 23). The use of short-acting insulin analogs might be particularly suited to approximate this ideal because they provide more physiological postprandial glucose control compared with human regular insulin (24), although until now a comparison of the two insulins in transient intensive insulin therapy has not been performed in recent onset type 2 diabetes.

With this in mind, we undertook this study to compare the effect on β- and α-cell function of TIIT using lispro versus human regular insulin in a group of poorly controlled relatively recent onset type 2 diabetes patients.

Methods

Subjects

The study subjects consisted of 21 patients with type 2 diabetes who were randomly recruited from August 2002 to March 2003 among patients consecutively referred to our department. The criteria for participation were: diagnosis of type 2 diabetes with endogenous insulin production (fasting C-peptide concentration ≥0.8 ng/ml at screening) and glutamic acid decarboxylase antibody negative, body mass index (BMI) less than 27 kg/m^2, aged 35–70 years, diabetes duration within 3 years, no β-cell stimulating agents, fasting plasma glucose levels of 10–13.9 mmol/*l*, no renal, hepatic, or cardiac dysfunction, and no diabetic complications. Three patients had taken voglibose and discontinued at least 3 days before the study. The clinical characteristics of the subjects are shown in Table 1.

All 21 subjects (aged 37 to 70 years) who met the inclusion criteria were randomly assigned in an unmasked fashion to 14-day intensive insulin therapy consisting of one injection of bedtime NPH (Humulin N; Eli Lilly, Indianapolis, IN, USA) insulin plus three injections of lispro 10 minutes prior to each meal (n=11) (Humalog; Eli Lilly) or human regular insulin 30 minutes prior to meal (n=10) (Humulin R; Eli Lilly). Insulin therapy was started from day 0, i.e. after the oral glucose tolerance test (OGTT) for baseline on the morning following admission. The study period was 20 days; all subjects were admitted to the hospital for intensification of diabetes control, which is standard clinical practice in Japan, and had all fasting/preprandial blood glucose levels checked using a portable and calibrated blood glucose meter (Medisafe; Terumo, Tokyo, Japan) for the entire period of the study. Diets of 30 kcal/kg ideal body weight containing at least 200 g (50% of total calories per day) carbohydrate were consumed during the study period. The dosages of both types of insulin were started from 0.3–0.4 U/kg, and adjusted to attain preprandial blood glucose levels of <6.1 mmol/*l* within 1 week with similar rates of glucose decline.

After 2 weeks of the optimal insulin therapy, insulin treatment was stopped. Seven-point plasma glucose levels before and 120 minutes after each of three meals and at bedtime were measured on 5 days after the cessation of insulin therapy. Good plasma glucose control was defined as fasting levels <7.8 mmol/*l*, with postprandial levels <11.1 mmol/*l*. If mean preprandial glucose levels ≥7.8 mmol/*l* or mean 2-h postprandial glucose levels ≥11.1 mmol/*l* were noted in seven-point plasma glucose, the patients were judged to be insufficiently treated and glimepiride was added to maintain better glycemic control thereafter.

Written informed consent was obtained from all subjects after they were given a complete description of the study, with local ethics committee approval.

OGTT

Two-h 50 g OGTTs were performed to observe β- and α-cell function during the study period. We considered that the 50 g OGTT was more appropriate than the 75 g OGTT from the standpoint of ethical consideration because the initial fasting glucose levels of the patients were 180–250 mg/dl. Patients did not inject NPH insulin in the evening pre-

ceding the test which was performed in an overnight 10-h fasted state on the day following admission (day 0 as baseline), after 7 days of treatment (day 7), and at the end of insulin therapy (day 14). After ingesting an oral glucose load of 50 g glucose, venous blood samples were obtained at 0, 30, 60, 90, and 120 minutes for determination of plasma glucose, serum insulin, and plasma glucagon. The test procedures were identical for the groups which received lispro and regular insulin.

Assays and calculations

HbA_{1c} was assessed by ion-exchange high-performance liquid chromatography with a cation exchange column. The normal reference limits of HbA_{1c} measured by this method are 4.3–5.8%. Plasma glucose was measured with the glucose hexokinase method (Shino-Test, Tokyo, Japan). Serum insulin was measured using an immunoradiometric assay (Dainabot, Tokyo, Japan). The intra-assay variation was 3.3%, and the inter-assay variation was 1.9%. This insulin assay did not cross-react with proinsulin. The samples for glucagon were collected in tubes containing EDTA and 1,500 KIU of aprotinin (Trasylol; Bayer, Leverkusen, Germany), and were analyzed by radioimmunoassay using OAL-123, C-terminal-region-specific antiserum of pancreatic glucagon (Daiichi Radioisotope Rabs, Tokyo, Japan). The intra-assay variation was 5.3%, and the inter-assay variation was 3.6%. The insulinogenic index was calculated as [(serum insulin t=30 min-serum insulin t=0 minute)/(plasma glucose t=30 min-plasma glucose t=0 minute)] (25). Plasma glucose, serum insulin, and plasma glucagon levels during the OGTT were calculated as the area under the curve (AUC) using a trapezoidal method in each case.

Statistical analysis

All calculations were performed with Statview software (version 5.0; SAS Institute, Inc., Cary, NC, USA). Data were shown as the mean±SEM. Differences between the different variables in two groups were analyzed using Student's t-test. The repeated measurements analysis of variance test was used when analyzing the results of the OGTT. Values of $p<0.05$ were considered statistically significant.

Results

Average 3-meal preprandial blood glucose levels decreased identically in both the insulin lispro and regular insulin groups to attain the target level of under 6.1 mmol/*l*, reaching a plateau after day 7 (Fig. 1A). No patient experienced severe hypoglycemia, defined as a blood glucose reading <3.5 mmol/*l*, or body weight gain during the study period. The maximum doses of insulin were similar for the groups with lispro versus regular insulin (0.65 vs. 0.72 U/kg/day, p=NS), while the insulin dosages began to decrease on day 7 with lispro, preceding day 8 with regular insulin (Fig. 1B). The dosages of NPH insulin were similar on day 6 for both the groups with lispro and regular insulin (10.0±1.9 vs. 11.2±7.3 U, p=NS), tended to be decreased in the lispro group on day 13 compared to that in the regular insulin group (6.7±1.3 vs. 10.0±1.1 U, p=0.07). All the patients needed NPH insulin for the 2 weeks to keep fasting blood glucose levels of <6.1 mmol/*l*.

Figure 2 shows the profiles of glucose, insulin, and glucagon concentrations after the ingestion of 50 g-glucose in the subjects using lispro or regular insulin at day 0, 7, and 14. No significant difference in any profile after oral glucose load could be detected between the two treatments at baseline. Plasma glucose response to the OGTT was significantly lower over 120 minutes comparing day 0 to day 7 ($p<0.05$) or to day 14 ($p<0.05$) with both lispro (Fig. 2A) and regular insulin (Fig. 2B). By contrast, the calculation of the AUC of glucose levels confirms better glucose tolerance with lispro than with regular insulin on day 7 (26.9±0.9 vs. 30.5±1.1 $mmol \cdot h \cdot l^{-1}$, $p<0.05$), whereas it reached the equivalent levels on day 14 (Fig. 3A). Significant improvement in insulin secretion was observed on day 14 compared to baseline in both the groups treated with lispro (AUC: 130.3±22.3 vs. 371.2±36.8 $pmol \cdot h \cdot l^{-1}$, $p<0.001$) (Fig. 2C) and with regular insulin (133.6±23.1 vs. 336.5±49.7 $pmol \cdot h \cdot l^{-1}$, $p<0.01$) (Fig. 2D). Figure 2D also shows a significant increase in fasting insulin levels on days 7 and 14 compared to baseline, which might be due to the delay of insulin clearance. The increase of post-OGTT serum insulin release was faster with lispro than with regular insulin; the insulin AUC was significantly higher with lispro than with regular insulin on day 7 (303.1±26.7 vs. 250.2±32.4 $pmol \cdot h \cdot l^{-1}$, $p<0.05$) (Fig. 3B). Differences between the groups were also notable when the insulinogenic index of the lispro group versus the regular insulin group was calculated on day 7 (20.6±3.3 vs. 5.8±1.2 pmol/mmol, $p<0.001$) and again on day 14 (25.5±3.4 vs. 13.2±2.7 pmol/mmol, $p<0.01$). Glucagon response to the OGTT showed a paradoxical rise at baseline, and began to be suppressed on day 7 only with lispro (Fig. 2E). Suppression of plasma glucagon concentrations after the ingestion of glucose was not found in the subjects using regular insulin either on day 7 or 14 (Fig. 2F). Glucagon secretion following the OGTT was well suppressed in the lispro group on day 14 compared to the regular insulin one (AUC: 216.4±13.6 vs. 273.7±35.8 $ng \cdot h \cdot l^{-1}$, $p<0.05$) (Fig. 3C).

Subsequent seven-point plasma glucose profiles 5 days after stopping 2-week intensive insulin treatment were shown in Fig. 4. Postprandial plasma glucose levels at breakfast and dinner, and before-lunch were significantly lower for the subjects taking lispro compared with those taking regular insulin. Plasma glucose levels before breakfast and dinner, after lunch, and at bedtime were not significantly different between the treatment groups. Both the average preprandial and postprandial plasma glucose levels were significantly lower in the lispro group than in the regular insulin group (6.7±0.4 vs. 8.0±0.4 mmol/*l*, $p<0.05$ and 10.1±0.6 vs. 12.1±0.5 mmol/*l*, $p<0.05$, respectively). Six of 11 patients (54.5%) treated with lispro were well controlled with preprandial blood glucose levels <7.8 mmol/*l* and

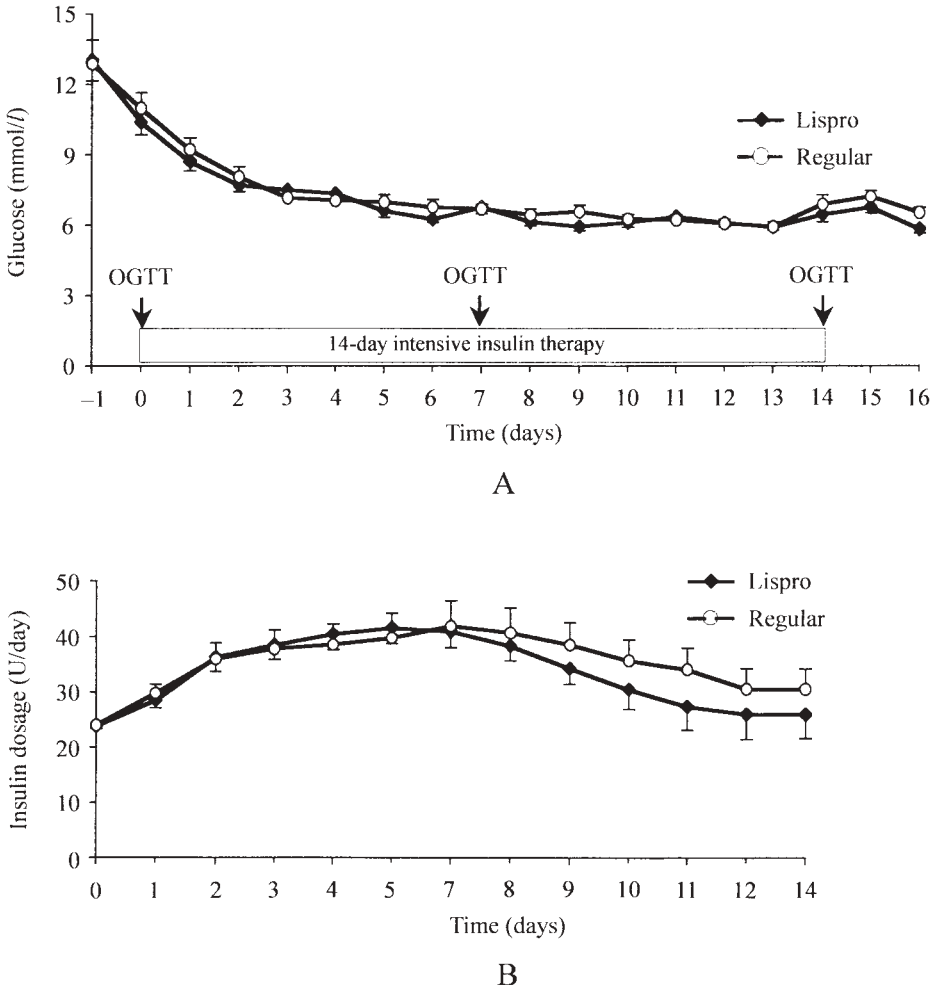

Figure 1. Mean±SEM daily average of 3-meal preprandial blood glucose levels (A) and insulin dosage during the 2-week intensive insulin therapy for lispro and regular insulin groups (B). Days 6, 13 were excluded from analysis for insulin dosage because NPH insulin was omitted for the next day's OGTT on these days. OGTT: oral glucose tolerance test.

postprandial glucose levels <11.1 mmol/*l* at the time the study was ended in contrast to only 2 of 10 patients (20%) treated with regular insulin. The remaining 13 patients who were judged to show insufficient glycemic control after the TIIT course tended to have a longer diabetes duration compared with the 8 well-controlled subjects (2.3±0.2 vs. 1.9± 0.3 years, p=0.08). Figure 4B shows the relationship between the mean values of seven-point plasma glucose levels of Fig. 4A and diabetes duration in each patient. Other discernible factors such as BMI, age, and HbA_{1c} were not associated with the glucose control after TIIT.

Discussion

In relatively recent onset type 2 diabetes, mitigation of glucose toxicity which aggravates the insulin secretory defect should be an important goal of therapy; to achieve that TIIT would seem to be a reasonable approach. The present evidence suggested that β- and α-cell functions showed greater improvement in uncontrolled type 2 diabetic patients following 14 days of TIIT using insulin lispro compared with regular insulin. The view, however, that multiple insulin injections are desirable for type 2 diabetes is not common in Western countries (26, 27), because among other reasons, it is feared that exogenous insulin will promote weight gain. In Japanese, however, weight gain is less of a concern, and diminished insulin secretion appears to be the pivotal event, making this population particularly vulnerable to the deleterious effects of insulin resistance (28–30). In other words, Japanese subjects may be more prone to develop 'insulinopenia' with less provocation than Westerners. For this reason, we consider it reasonable to select short-term intensive insulin therapy as first-line insulin therapy to achieve β-cell rest in the early course of the disease. In this study, we showed

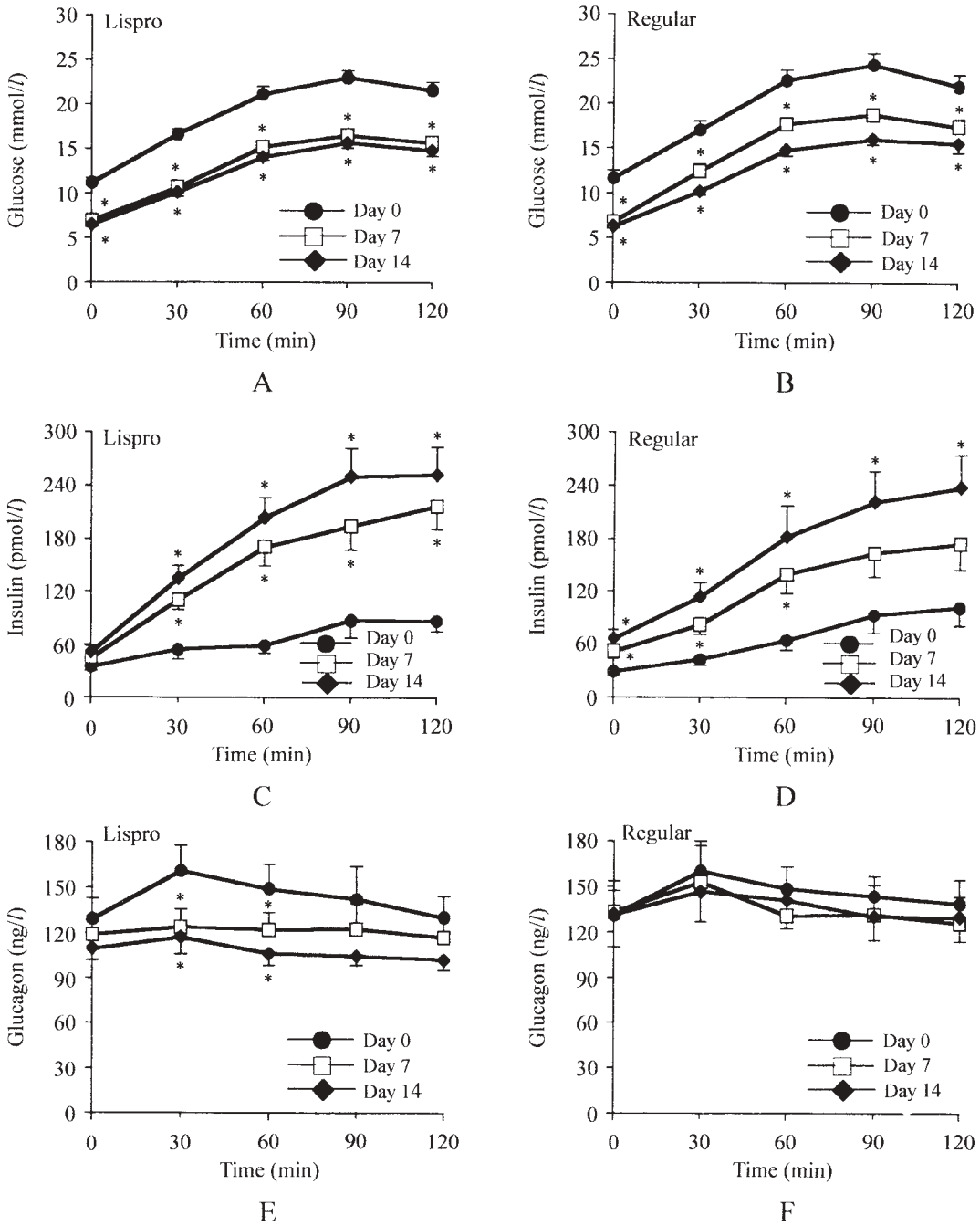

Figure 2. Mean±SEM plasma glucose (A, B), serum insulin (C, D), and plasma glucagon (E, F) concentrations during the OGTT for lispro and regular insulin groups at baseline (day 0), day 7, and day 14. *Statistically significant ($p<0.05$) difference from baseline (day 0). OGTT: oral glucose tolerance test.

that 2-week intensive insulin therapy, especially with lispro, improved insulin secretion and glucose kinetics in our subjects without any undesirable effects. Our findings are in agreement with several lines of evidence, which noted that the effect of transient tight glycemic control with insulin in type 2 diabetic subjects uniformly enhanced insulin secretion and alleviated glucose toxicity (31–34).

Using insulin lispro in TIIT resulted in significantly more rapid β-cell rest compared with regular insulin. In the lispro-treated subjects, the required dosage of daily insulin decreased earlier and serum insulin concentrations following OGTT increased significantly faster compared with the regular insulin-treated subjects. Insulinogenic index, which represents early phase insulin secretion (25), was significantly

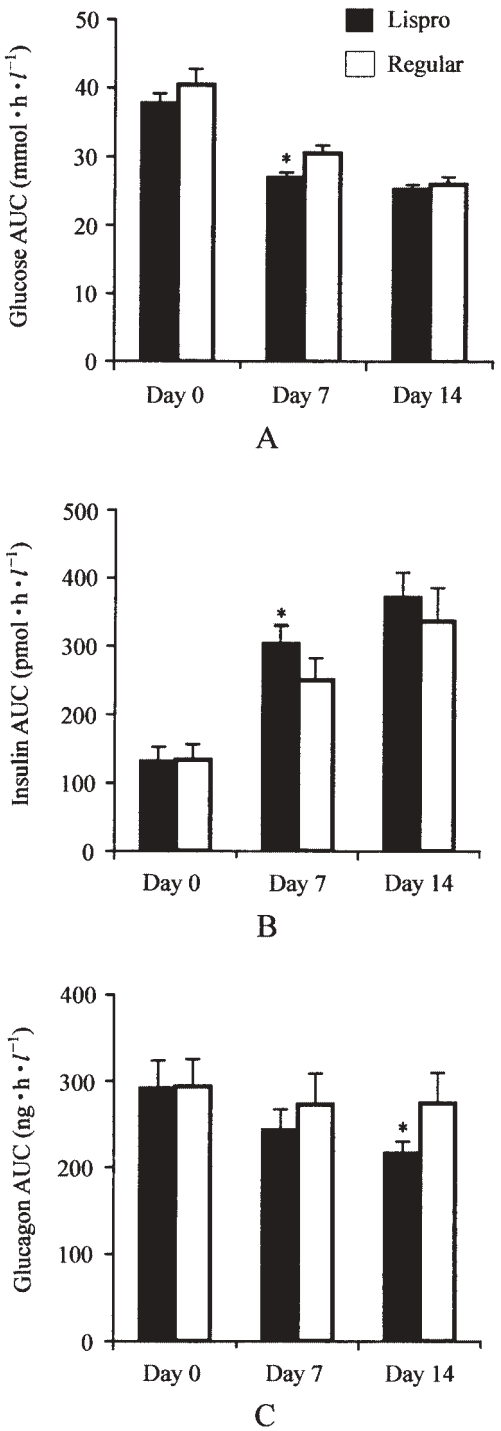

Figure 3. Mean±SEM area under the curve (AUC) of plasma glucose, serum insulin, and plasma glucagon during the OGTT for lispro and regular insulin groups at baseline (day 0), day 7, and day 14. *Statistically significant ($p<0.05$) difference between treatment groups. OGTT: oral glucose tolerance test.

higher for the lispro-treated group than the regular insulin-treated group after at least 1-week of TIIT. These results may support a report by Bruttomesso et al (35) which described that restoration of the early phase in prandial insulin concentration by lispro injection inhibits early prandial glucose output and ameliorates post-prandial hyperglycemia, which may have a β-cell sparing effect.

An important finding in this study is that the subjects who used lispro benefited from the greater suppression of glucagon achieved by TIIT. The postprandial secretion of glucagon is not suppressed or is even elevated in type 2 diabetes, thereby aggravating postprandial hyperglycemia (13–18). This might be due to loss of paracrine inhibition of α-cell function by intra-islet insulin and/or chronic hyperglycemia (36, 37). Sufficient β-cell recovery or reversal of glucose desensitization itself might possibly have restored the meal-stimulated suppression of glucagon in our lispro group. In contrast, the group receiving regular insulin did not show any improvement in abnormal glucagon secretion. Thus, our study suggests that TIIT using lispro may improve α-cell function in addition to β-cell function in type 2 diabetes facilitating tighter glycemic control. Although it is not concluded whether a 2-week period of euglycemia is adequate or appropriate, a 2-week TIIT using lispro appeared to succeed in reestablishing satisfactory islet metabolic control.

The current study showed that lispro provided significantly better glycemic control than regular insulin in subsequent daily glucose profiles after cessation of TIIT. Moreover, 54.5% of the patients treated with lispro attained good control versus only 20% with regular insulin. The patients whose glycemic control was insufficient after TIIT tended to show a longer duration of diabetes, implying worsening β-cell function over time in type 2 diabetes (38).

There are some limitations in this study. First, we did not measure insulin sensitivity using clamp studies, as glucose toxicity can impair insulin sensitivity as well as secretion. However, previous studies have shown that tight glycemic control with insulin caused no major rise in insulin sensitivity in type 2 diabetic individuals (19, 30–32). In addition, Kawamori et al (39) reported that after short-term intensive insulin therapy, glucose disposal by peripheral tissue using a euglycemic hyperinsulin clamp was not altered in Japanese type 2 diabetes. Thus, we focused on observing the time course of β-cell secretory function by TIIT. Secondly, we did not examine the incretin hormones such as GIP and GLP-1 which could potentiate insulin action during OGTT (40, 41). A third limitation was the lack of a control group. A fourth limitation is the fact that the follow-up period is still short, however, a follow-up study of these subjects is in progress and will be reported in the future.

In conclusion, transient intensive glycemic regulation by insulin may promote β-cell recovery and preservation. A 2-week intensive insulin therapy with lispro appeared to be more effective than that with human regular insulin in Japanese non-obese type 2 diabetes in attaining both more rapid β-cell rest and greater suppression of glucagon, possibly providing significant long-term benefits. The benefit of this approach suggested by these limited data needs to be established by larger scale and longer term controlled studies,

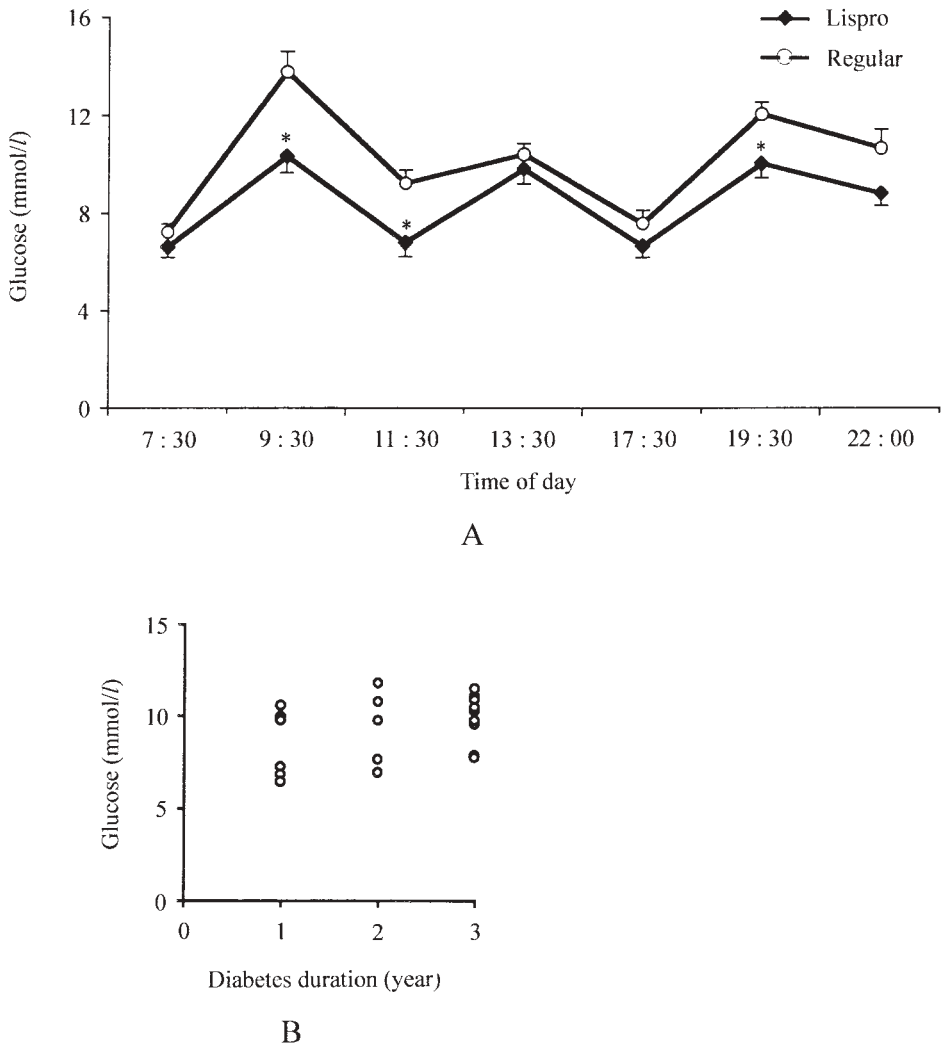

Figure 4. Comparison of 7-point mean plasma glucose profiles (mean±SEM) for lispro and regular insulin groups 5 days after the cessation of the 2-week intensive insulin therapy (A), and the relationship between mean values of the 7-point plasma glucose levels and diabetes duration in each patient (B). *Statistically significant ($p<0.05$) difference between treatment groups.

and if confirmed may provide another option to treat this important subset of patients.

References

1) Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. Arch Intern Med **159**: 1450–1456, 1999.
2) Center for Disease Control and Prevention. Trends in the prevalence and incidence of self reported diabetes mellitus: United States, 1980–1994. MMWR Morb Mortal Wkly Rep **46**: 1014–1018, 1997.
3) Burke JP, Williams K, Narayan KM, Leibson C, Haffner SM, Stern MP. A population perspective on diabetes prevention: Whom should we target for preventing weight gain? Diabetes Care **26**: 1999–2004, 2003.
4) Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N, Japan Diabetes Complication Study Group. Obesity and type 2 diabetes in Japanese patients. Lancet **361**: 85, 2003.
5) Deurenberg P, Yap M, van Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. Int J Obes Relat Metab Disord **22**: 1164–1171, 1998.
6) Yoshiike N, Matsumura Y, Zaman MM, Yamaguchi M. Descriptive epidemiology of body mass index in Japanese adults in a representative sample from the National Nutrition Survey 1990-1994. Int J Obes Relat Metab Disord **22**: 684–687, 1998.
7) Samanta A, Burden AC, Jones GR, Clarkson L. The effect of short term intensive insulin therapy in non-insulin-dependent diabetics who had failed on sulfonylurea therapy. Diabetes Res **3**: 269–271, 1986.
8) Kayashima T, Yamaguchi K, Konno Y, Namimatsu H, Aragaki S, Shichiri M. Effects of early introduction of intensive insulin therapy on

the clinical course in non-obese NIDDM patients. Diab Res Clin Prac **28**: 119–125, 1995.
9) McFarlane SI, Chaiken RL, Hirsch S, Harrington P, Lebovitz HE, Banerji MA. Near-normoglycaemic remission in African-Americans with type 2 diabetes mellitus is associated with recovery of beta cell function. Diabet Med **18**: 10–16, 2001.
10) Ilkova H, Glaser B, Tunckale A, Bagriacik N, Cerasi E. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. Diabetes Care **20**: 1353–1356, 1997.
11) Campbell RK, White JR Jr. Insulin therapy in type 2 diabetes. J Am Pharm Assoc (Wash) **42**: 602–611, 2002.
12) Nathan DM. Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. N Engl J Med **347**: 1342–1349, 2002.
13) Butler PC, Rizza RA. Contribution to postprandial hyperglycemia and effect on initial splanchnic glucose clearance of hepatic glucose cycling in glucose-intolerant or NIDDM patients. Diabetes **40**: 73–81, 1991.
14) Shah P, Basu A, Basu R, Rizza R. Impact of lack of suppression of glucagon on glucose tolerance in humans. Am J Physiol **277**: E283–E290, 1999.
15) Banerji MA. Impaired beta-cell and alpha-cell function in African-American children with type 2 diabetes mellitus-"Flatbush diabetes". J Pediatr Endocrinol Metab **15**: 493–501, 2002.
16) Shah P, Vella A, Basu A, Basu R, Schwenk WF, Rizza RA. Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. J Clin Endocrinol Metab **85**: 4053–4059, 2000.
17) Gin H, Rigalleau V. Post-prandial hyperglycemia. Post-prandial hyperglycemia and diabetes. Diabetes Metab **26**: 265–272, 2000.
18) Jiang G, Zhang BB. Glucagon and regulation of glucose metabolism. Am J Physiol Endocrinol Metab **284**: E671–E678, 2003.
19) Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. Diabetes Care **13**: 610–630, 1990.
20) Yki-Jarvinen H. Glucose toxicity. Endocr Rev **13**: 415–431, 1992.
21) Kaiser N, Leibowitz G, Nesher R. Glucotoxicity and beta-cell failure in type 2 diabetes mellitus. J Pediatr Endocrinol Metab **16**: 5–22, 2003.
22) Plank J, Wutte A, Brunner G, et al. A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. Diabetes Care **25**: 2053–2057, 2002.
23) Homko C, Deluzio A, Jimenez C, Kolaczynski JW, Boden G. Comparison of insulin aspart and lispro: pharmacokinetic and metabolic effects. Diabetes Care **26**: 2027–2031, 2003.
24) Gerich JE. Novel insulins: expanding options in diabetes management. Am J Med **113**: 308–316, 2002.
25) Phillips DI, Clark PM, Hales CN, Osmond C. Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. Diabet Med **11**: 286–292, 1994.
26) Genuth S. Insulin use in NIDDM. Diabetes Dare **13**: 1240–1264, 1990.
27) Riddle MC. The underuse of insulin therapy in North America. Diabetes Metab Res Rev **18**: S42–S49, 2002.
28) Sakamaki H, Yamasaki H, Matsumoto K, et al. No deterioration in insulin sensitivity, but impairment of both pancreatic β-cell function and glucose sensitivity, in Japanese women with former gestational diabetes mellitus. Diabet Med **15**: 1039–1044, 1998.
29) Sato Y, Komatsu M, Katakura M, et al. Diminution of early insulin response to glucose in subjects with normal but minimally elevated fasting plasma glucose. Evidence for early beta-cell dysfunction. Diabet Med **19**: 566–571, 2002.
30) Kanauchi M. A new index of insulin sensitivity obtained from the oral glucose tolerance test applicable to advanced type 2 diabetes. Diabetes Care **25**: 1891–1892, 2002.
31) Kosaka K, Kuzuya T, Akanuma Y, Hagura R. Increase in insulin response after treatment of overt maturity-onset diabetes is independent of the mode of treatment. Diabetologia **18**: 23–28, 1980.
32) Gormley MJ, Hadden DR, Woods R, Sheridan B, Andrews WJ. One month's insulin treatment of type II diabetes: the early and medium-term effects following insulin withdrawal. Metabolism **35**: 1029–1036, 1986
33) Hidaka H, Nagulesparan M, Klimes I, et al. Improvement of insulin secretion but not insulin resistance after short term control of plasma glucose in obese type II diabetics. J Clin Endocrinol Metab **54**: 217–222, 1982.
34) Laakso M, Uusitupa M, Takala J, Majander H, Reijonen T, Penttila I. Effects of hypocaloric diet and insulin therapy on metabolic control and mechanisms of hyperglycemia in obese non-insulin-dependent diabetic subjects. Metabolism **37**: 1092–1100, 1988.
35) Bruttomesso D, Pianta A, Mari A, et al. Restoration of early rise in plasma insulin levels improves the glucose tolerance of type 2 diabetic patients. Diabetes **48**: 99–105, 1999.
36) Samols E, Tyler J, Marks V. Glucagon-insulin interrelationships. in: Glucagon. Molecular Physiology, Clinical and Therapeutic Implications. Lefebvre PJ, Unger RH, et al Eds. Pergamon Press, New York, 1972: 151–172.
37) Asplin CM, Paquette TL, Palmer JP. In vivo inhibition of glucagon secretion by paracrine beta cell activity in man. J Clin Invest **68**: 314–318, 1981.
38) U.K. Prospective Diabetes Study 16. Overview of 6 year's therapy of type II diabetes: a progressive disease. Diabetes **44**: 1249–1258, 1995 (Erratum in: Diabetes **45**: 1655, 1996).
39) Kawamori R, Morishima T, Ikeda M, et al. Effect of strict metabolic control on glucose handling by the liver and peripheral tissues in non-insulin-dependent diabetes mellitus. Diabetes Res Clin Pract **23**: 155–161, 1994.
40) Fritsche A, Stefan N, Hardt E, Haring H, Stumvoll M. Characterisation of beta-cell dysfunction of impaired glucose tolerance: evidence for impairment of incretin-induced insulin secretion. Diabetologia **43**: 852–858, 2000.
41) Greenbaum CJ, Prigeon RL, D'Alessio DA. Impaired beta-cell function, incretin effect, and glucagon suppression in patients with type 1 diabetes who have normal fasting glucose. Diabetes **51**: 951–957, 2002.