

Oral glucose-stimulated serum C-peptide predicts successful switching from insulin therapy to liraglutide monotherapy in Japanese patients with type 2 diabetes and renal impairment

Hisazumi Araki*, Yuki Tanaka, Syohei Yoshida, Yoshikata Morita, Shinji Kume, Keiji Isshiki, Shin-ichi Araki, Takashi Uzu, Atsunori Kashiwagi, Hiroshi Maegawa

Department of Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan

Keywords

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*Correspondence

Hisazumi Araki
Tel.: +81-775-48-2222
Fax: +81-775-43-3858
E-mail address: haraki@belle.shiga-med.ac.jp

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ABSTRACT

Aims/Introduction: In Japan, liraglutide was recently approved for patients with type 2 diabetes. To our knowledge, there are no markers predicting successful switching from insulin therapy to liraglutide monotherapy in Japanese patients with type 2 diabetes and renal impairment. We therefore assessed clinical characteristics predicting successful switching.

Materials and Methods: We analyzed 21 patients with type 2 diabetes and estimated glomerular filtration rates <60 mL/min/1.73 m² receiving long-term insulin in Shiga University of Medical Science Hospital, Otsu, Shiga, Japan. Their β -cell function was assessed by measuring urinary C-peptide and C-peptide immunoreactivity (CPR) index, along with glucagon loading and oral glucose tolerance tests. Blood glucose concentration and blood pressure were measured daily before and after switching from insulin to liraglutide, and glycated hemoglobin (HbA1c; National Glycohemoglobin Standardization Program) was assessed 12 weeks after switching to liraglutide.

Results: Baseline HbA1c was significantly lower in successfully switched than in unsuccessfully switched patients. CPR index, urinary C-peptide concentration and 6-min post-glucagon increment in CPR (Δ CPR) did not differ significantly in the two groups. Δ CPR 120 min after 75 g oral glucose was significantly higher in successfully than unsuccessfully switched patients. Mean blood glucose concentrations before breakfast, after breakfast, before lunch and after dinner were significantly lower in successfully switched patients. HbA1c did not change significantly in either group.

Conclusions: Measurement of oral glucose-stimulated Δ CPR120 min is recommended when considering switching Japanese type 2 diabetes patients with renal impairment from insulin to liraglutide monotherapy.

INTRODUCTION

Type 2 diabetes mellitus is a progressive, multifactorial, debilitating disease marked by a gradual decrease in pancreatic β -cell

function and concomitant deterioration in insulin secretion against a background of increased insulin resistance. Many patients with type 2 diabetes have renal impairment, a late complication of inadequate glycemic control¹. Microalbuminuria, the earliest indicator of nephropathy attributable to diabetes,

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affects 25% of patients with type 2 diabetes within 10 years of diagnosis². Diabetic nephropathy develops in 5–10% of patients with both type 2 diabetes and microalbuminuria each year^{3–7}. Therefore, there is a need for therapies that can achieve glyce-mic control in type 2 diabetes, and that are also safe and effec-tive in patients with renal dysfunction. The glucose-lowering actions of glucagon-like peptide-1 (GLP-1), an incretin hor-mone, are glucose-dependent, which limits the risk of hypogly-cemia^{8,9}. GLP-1 induces insulin secretion and reduces glucagon secretion, resulting in potent reduction of blood glucose con-centrations.

Because the pharmacokinetics of exenatide (exendin-4), an incretin mimetic, are significantly affected by renal dysfunction, this agent is not recommended for patients with severe renal impairment or end-stage renal disease (ESRD)^{10,11}.

Liraglutide is a once-daily human GLP-1 analog under devel-opment for the treatment of hyperglycemia in patients with type 2 diabetes. Liraglutide has a high degree of sequence iden-tity to human GLP-1, but differs in having an Arg34Lys substi-tution and a glutamic acid and 16-C free fatty acid addition to Lys26¹². Its half-life in humans after subcutaneous injection is approximately 13 h¹³, allowing once-daily administration. The metabolism of liraglutide is similar to that of large peptides, in that it is fully degraded¹⁴. There is no evidence that the kidney is the main organ for its elimination.

Liraglutide monotherapy in patients with type 2 diabetes was found to significantly improve glyce-mic control and to reduce bodyweight with a small risk of hypoglycemia^{15,16}. Liraglutide also has favorable effects on several indicators of β -cell func-tion^{17–21}, and improves early markers of cardiovascular dis-ease²². Regression analysis of log (area under the curve) for subjects with normal renal function and mild-to-severe renal impairment showed that decreasing creatinine clearance did not significantly affect the pharmacokinetics of liraglutide²³.

Japanese authorities recently approved liraglutide for glyce-mic control in patients with type 2 diabetes. Most patients with type 2 diabetes and moderate-to-severe renal impairment receive insulin. Switching from insulin to liraglutide adversely affects glyce-mic control in patients with type 2 diabetes and poor β -cell function. A recent study reported that postprandial serum C-peptide is useful in selecting those patients with type 2 diabetes without renal impairment who can be safely switched from insulin to liraglutide²⁴. To our knowledge, however, no guidelines to date have been formulated that predict which Japanese patients with type 2 diabetes and renal impairment can be safely and successfully switched from insulin to liraglutide monotherapy. We therefore assessed the clinical characteristics of patients predicting successful switching.

MATERIALS AND METHODS

Patients, Liraglutide Dosage and Assessment of β -Cell Function

A total of 21 patients (18 males and 3 females), ranging in age from 29 to 85 years (median age 61 years) with type 2 diabetes

receiving long-term (more than 1 year) complex insulin therapy in Shiga University of Medical Science Hospital, Otsu, Shiga, Japan were studied. Pregnant patients and those with liver cir-rhosis were excluded. All patients had an estimated glomerular filtration rate (eGFR), as assessed by the Modification of Diet in Renal Disease study equation modified for Japanese patients²⁵, less than 60 mL/min/1.73 m². While still receiving insulin, and before being switched to liraglutide, β -cell function in each patient was assessed and urinary C-peptide in 24-h urine was measured by a chemiluminescence immunoassay. Glucagon tests were carried out after overnight fasting. Venous blood samples for measurement of blood glucose and serum C-peptide concentrations were obtained immediately before and 6 min after an intravenous bolus injection of 1 mg gluca-gon (Novo Industries, Copenhagen, Denmark). Increments of C-peptide immunoreactivity (Δ CPR) after 6 min were calcu-lated according to the formula:

$$\Delta\text{CPR at 6 min} = \text{concentration of C-peptide at 6 min (ng/mL)} \\ - \text{C-peptide at 0 min (ng/mL)}$$

Oral glucose tolerance tests were carried out in the same way after overnight fasting. Venous blood samples for measurement of blood glucose and serum C-peptide concentrations were obtained immediately before and 30 and 120 min after a 75-g glucose load, with immunoreactive insulin (IRI) measured before and 30 min after the 75-g glucose load. Δ CPRs at 120 min were calculated according to the formula:

$$\Delta\text{CPR at 120 min} = \text{CPR concentration at 120 min (ng/mL)} \\ - \text{CPR at 0 min (ng/mL)}$$

CPR indexes were calculated according to the formula:

$$\text{CPR index} = \text{fasting C-peptide concentration (ng/mL)} \\ \times 100/\text{fasting blood glucose concentration (mg/dL)}$$

Insulinogenic indexes (II) were calculated according to the formula:

$$\text{II} = (\text{IRI at 30 min } [\mu\text{U/mL}]) \\ - (\text{IRI at 0 min } [\mu\text{U/mL}]) / (\text{blood glucose at 30 min } [\text{mg/dL}]) \\ - (\text{blood glucose at 0 min } [\text{mg/dL}])$$

Blood glucose concentrations were monitored daily in all patients before and after switching to liraglutide monotherapy. Patients were started on 0.3 mg liraglutide (Novo Nordisk, Bagsvaerd, Denmark) once daily for 3 days; if there was no nausea or vomiting, patients were increased to 0.6 mg/day for 3 days, and finally increased to 0.9 mg. Once adequate glyce-mic control was achieved, the dose of liraglutide was main-tained.

Successful switching from insulin to liraglutide was defined as a mean blood glucose concentration <200 mg/dL 120 min

after breakfast (AB), lunch (AL) and dinner (AD) on three consecutive days after reaching the final dose of liraglutide. Unsuccessfully switched patients resumed insulin therapy.

The present study was approved by the local institutional review board, and was carried out in accordance with the Declaration of Helsinki. All patients received full explanations of the study and the use of liraglutide, and provided informed consent.

Follow up of Patients Switched to Liraglutide

Blood glucose was measured daily before and after switching to liraglutide monotherapy. Glycated hemoglobin (HbA1c) was measured in 10 successfully-switched patients at baseline and 4, 8, 12, and 24 weeks after starting liraglutide monotherapy using high-performance liquid chromatography and an assay certified by the Japan Diabetes Society (JDS). HbA1c (%) was estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) and calculated according to the formula:

$$\text{HbA1c (\%)} = \text{HbA1c (JDS; \%)} + 0.4\%$$

This equation converts the HbA1c (JDS) (%), measured using the previous standard Japanese method, to the HbA1c (NGSP) (%)^{26,27}.

Blood pressure was measured daily before breakfast (BB) during hospitalization. Mean blood pressure over three consecutive days before and after switching to liraglutide in successfully switched patients, or before switching to liraglutide and after resuming insulin therapy in unsuccessfully switched patients, was calculated.

Statistical Analysis

Data were analyzed using SPSS version 17.0 (SPSS, Tokyo, Japan). The distribution of variables was analyzed by checking histograms and normal plots of the data, and normality was tested using Kolmogorov–Smirnov and Shapiro–Wilk tests. Student's *t*-test was used to compare parameters at different time-points, and the χ^2 -test was used to compare proportions between variables. Pearson's or Spearman's rank correlation coefficients were calculated to determine correlations between variables. To evaluate the predictive factors of the model, Logistic regression was carried out. Values are expressed as means \pm standard deviation, with $P < 0.05$ considered statistically significant.

RESULTS

Patient Characteristics

Of the 21 patients, 16 were successfully switched from insulin to liraglutide, and five were unsuccessful. There were no significant differences between these two groups in age, sex, bodyweight, body mass index; total cholesterol, triglyceride and high-density lipoprotein cholesterol concentrations; and eGFR. Interestingly, the doses of insulin also did not differ significantly in these two groups. HbA1c was significantly lower in success-

Table 1 | Baseline characteristics of patients

	Successfully switched (n = 16)	Unsuccessfully switched (n = 5)	P-value
Age (years)	59.7 \pm 12.5	62.6 \pm 13.4	0.66
Sex (male/female)	15/1	3/2	0.13
Bodyweight (kg)	72.5 \pm 16.4	60.0 \pm 15.3	0.15
Body mass index	26.4 \pm 8.4	24.0 \pm 3.9	0.55
Insulin (units)	25.9 \pm 26.9	33.8 \pm 11.0	0.54
Duration (years)	21.9 \pm 10.6	20.2 \pm 12.5	0.77
T-cho (mg/dL)	200.8 \pm 67.8	222.0 \pm 35.9	0.52
TG (mg/dL)	197.4 \pm 138.9	190.2 \pm 124.5	0.92
HDL (mg/dL)	45.7 \pm 21.0	51.4 \pm 11.6	0.57
eGFR (mL/min/1.73 m ²)	26.1 \pm 14.6	19.8 \pm 8.1	0.38
HbA1c (%)	7.1 \pm 1.6	9.0 \pm 1.6	0.03*

Paired Student's *t*-tests were used to compare values at different time-points. *Values are expressed as means \pm standard deviation, with $P < 0.05$ considered statistically significant. eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; T-cho, total cholesterol; TG, triglyceride.

fully switched than in unsuccessfully switched patients (7.1 \pm 1.6 vs 9.0 \pm 1.6%, $P = 0.03$; Table 1).

β -Cell Function

Comparisons of successfully and unsuccessfully switched patients showed no significant differences in CPR index (2.20 \pm 1.48 vs 0.9 \pm 0.65, $P = 0.074$), urinary C-peptide (47.8 \pm 36.4 vs 44.1 \pm 40.2 μ g/day, $P = 0.85$), Δ CPR 6 min after glucagon load (2.0 \pm 1.25 vs 0.9 \pm 0.72 ng/mL, $P = 0.07$) and II (0.1 \pm 0.12 vs 0.04 \pm 0.04, $P = 0.21$). Δ CPR 120 min after a 75-g oral glucose load was significantly greater in successfully than unsuccessfully switched patients (5.2 \pm 2.81 vs 1.2 \pm 0.65 ng/mL, $P = 0.006$). The lowest 120 min Δ CPR in successfully switched patients was 2.4 ng/mL, and the highest in unsuccessfully switched patients was 1.6 ng/mL (Figure 1).

Follow up of Successful and Unsuccessful Switching to Liraglutide Monotherapy

In successfully switched patients, the mean blood glucose concentrations over three consecutive days after reaching the final dose of liraglutide were lower than before switching to liraglutide. In particular, mean blood glucose concentrations were significantly lower BB (123.9 \pm 25.4 vs 109.6 \pm 20.0 mg/dL, $P = 0.010$), AB (210.0 \pm 53.3 vs 157.6 \pm 26.7 mg/dL, $P = 0.001$), before lunch (BL; 178.9 \pm 60.4 vs 119.5 \pm 23.1 mg/dL, $P = 0.001$) and after dinner (AD; 200.4 \pm 42.7 vs 159.9 \pm 22.8 mg/dL, $P = 0.002$). In unsuccessfully switched patients, however, blood glucose concentrations BD increased significantly (188.4 \pm 32.1 vs 301.6 \pm 95.7 mg/dL, $P = 0.038$). Before switching to liraglutide, blood glucose concentrations in successfully and unsuccessfully switched patients did not differ

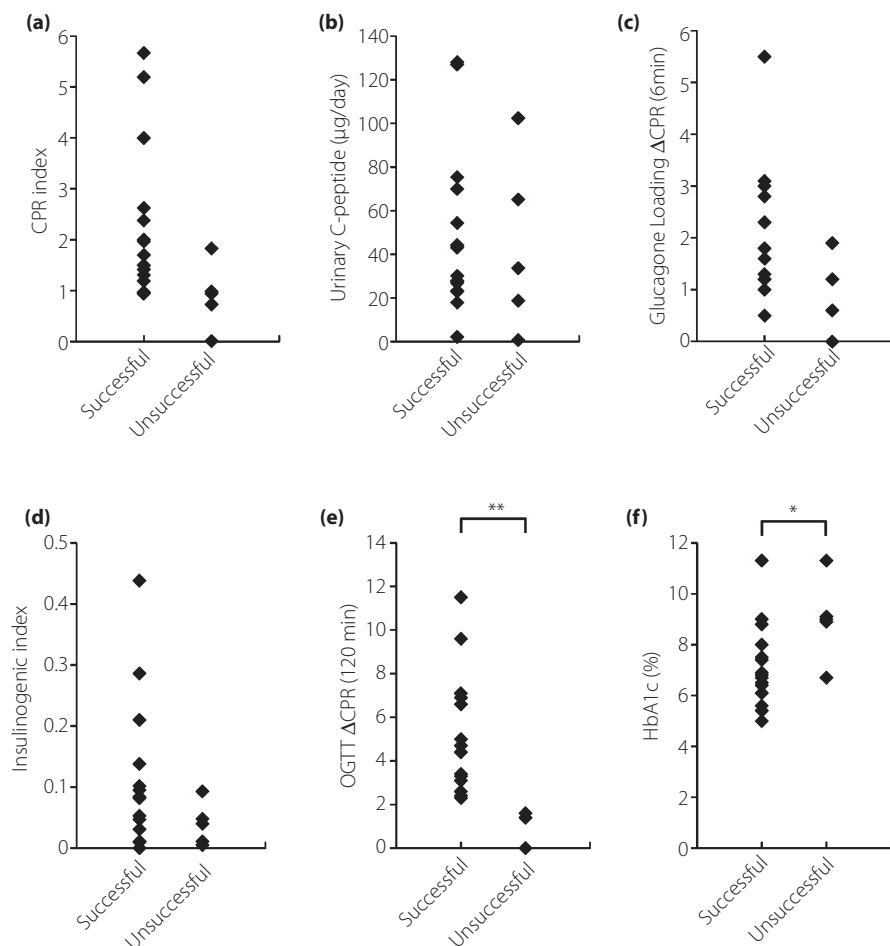


Figure 1 | Baseline β-cell function and glycated hemoglobin (HbA1c) in patients successfully and unsuccessfully switched from insulin to liraglutide. (a) C-peptide immunoreactivity (CPR) index. (b) 24-h urinary C-peptide. (c) ΔCPR 6 min after a 1-g glucagon load. (d) Insulinogenic index at 30 min. (e) ΔCPR 120 min after a 75-g glucose load. (f) HbA1c (National Glycohemoglobin Standardization Program). * $P < 0.05$, ** $P < 0.01$. OGTT, oral glucose tolerance test.

significantly BB (123.9 ± 25.4 vs 119.0 ± 13.5 mg/dL, $P = 0.69$) AB (210.0 ± 53.3 vs 245 ± 32.8 mg/dL, $P = 0.18$), AL (181.7 ± 77.9 vs 240.4 ± 54.2 mg/dL, $P = 0.14$) and AD (200.4 ± 42.7 vs 231.4 ± 57.0 mg/dL, $P = 0.20$). However, blood glucose concentrations BL (178.9 ± 60.4 vs 259.6 ± 50.6 mg/dL, $P = 0.01$) and BD (121.1 ± 48.1 vs 188.4 ± 32.1 mg/dL, $P = 0.01$) differed significantly in the two groups (Figure 2).

HbA1c did not differ significantly before and 24 weeks after successful switching in the 10 patients who were switched successfully (Figure 3).

Successfully switched patients showed clinically significant reductions in systolic (142.0 ± 19.2 vs 123.6 ± 13.2 mmHg, $P = 0.001$) and diastolic (79.6 ± 13.4 vs 71.8 ± 9.8 mmHg, $P = 0.036$) blood pressure (BP) after switching. No significant changes in systolic or diastolic blood BP were observed in unsuccessfully switched patients. Before switching to liraglutide, systolic BP (142.0 ± 19.2 vs 143.2 ± 15.0 mmHg, $P = 0.95$)

and diastolic BP (79.6 ± 13.4 vs 71.4 ± 16.7 mmHg, $P = 0.28$) did not differ significantly between successfully and unsuccessfully switched patients.

DISCUSSION

The UK Prospective Diabetes Study showed that intensive glycaemic control prevents microangiopathy in patients with type 2 diabetes²⁸. However, the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) and the Advance Collaborative Group reported that intensive glycaemic control does not reduce major macrovascular complications. Surprisingly, in the ACCORD trial, the mortality rate was significantly higher in the intensive than in the standard therapy group^{29,30}. Therefore, treatments that less frequently induce hypoglycemia while improving glycaemic control are more desirable, especially for type 2 diabetic patients with diabetic complications. The present study showed that liraglutide improves glycaemic control without serious adverse effects, including hypoglycemia, in dia-

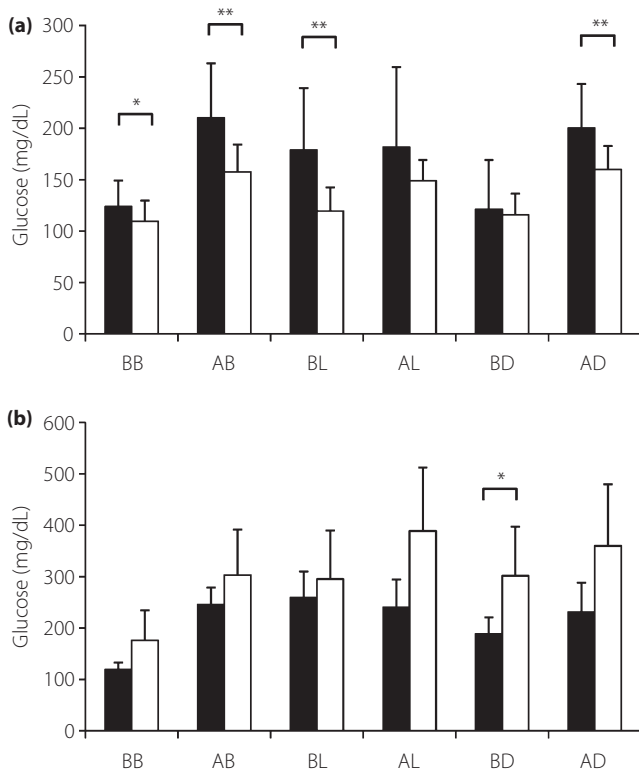


Figure 2 | Daily blood glucose monitoring before (black bars) and after (white bars) switching from insulin to liraglutide monotherapy. (a) Successfully switched patients. (b) Unsuccessfully switched patients. Measurement times were 2 h after meals. * $P < 0.05$, ** $P < 0.01$. AB, after breakfast; AD, after dinner; AL, after lunch; BB, before breakfast; BD, before dinner; BL, before lunch.

betic patients with renal impairment. Furthermore, switching to liraglutide from insulin worsened glycemic control in just five of 21 patients. These results suggest that liraglutide is an effective antidiabetic agent for type 2 diabetic patients with renal impairment.

The five patients who were unsuccessfully switched to liraglutide all had a long duration of diabetes mellitus and had received oral antidiabetic therapy immediately after diagnosis. Furthermore, all five were negative for anti-glutamic acid decarboxylase and anti-islet antigen 2 antibodies, indicating that none had type 1 diabetes.

Serum C-peptide concentration has been reported to be a poor indicator of β -cell function in type 2 diabetic patients with nephropathy, because the kidneys are the major sites of C-peptide catabolism³¹. We found that CPR index and urinary C-peptide were not useful predictors of successful switching from insulin to liraglutide in patients with renal impairment. In addition, CPR index and urinary C-peptide have also been reported to be unrelated to β -cell function in patients receiving complex insulin therapy. In such patients, glucagon or glucose load tests are more useful in evaluating insulin secretion. Although we observed no difference in glucagon test results

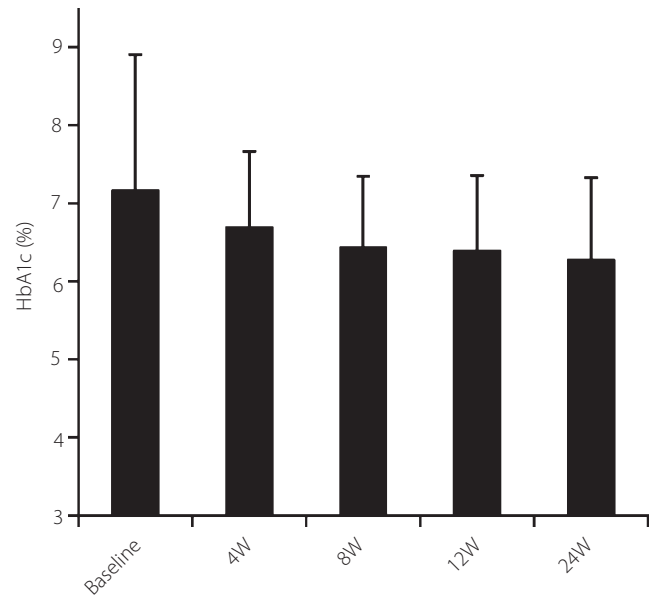


Figure 3 | Glycated hemoglobin (HbA1c; National Glycohemoglobin Standardization Program) in successfully-switched patients. W, weeks.

between patients successfully and unsuccessfully switched to liraglutide, we found that oral glucose tolerance tests were useful in distinguishing between these two groups. Δ CPRs at 120 min were greater than 2.4 ng/mL in successfully switched patients, but lower than 1.6 ng/mL in unsuccessfully switched patients, suggesting that the cut-off between the two is probably close to these concentrations. No significant correlations were observed between eGFR and Δ CPR at 120 min (data not shown). Interestingly, II did not differ significantly between successfully and unsuccessfully switched patients, suggesting that early insulin secretion is not important in switching to liraglutide. In contrast, although mean HbA1c differed significantly between these two groups, logistic regression analyses before and after adjustment for age and sex found that HbA1c concentration was not an independent predictor of successfully switched patients; the crude odds ratio was 0.59 (95% confidence interval 0.25–1.03, $P = 0.06$) and the age- and sex-adjusted odds ratio was 0.38 (95% confidence interval 0.13–1.15, $P = 0.09$). Furthermore, CPR120 min was not correlated with HbA1c concentration ($r = -0.115$, $P = 0.64$), indicating that CPR120 min was a marker that independently predicted 'successful switching' independent of HbA1c concentration. Patients with impaired renal function generally require less insulin, mainly because their insulin clearance is prolonged³². We observed a very high rate of successful switching from insulin to liraglutide (76%, 16/21 patients). In patients without renal impairment, the rate of successful switching was reported to be 56%, although these patients had a shorter duration of diabetes than ours²⁴. Thus, patients with renal impairment might require less autosecreted insulin to maintain good glycemic control than do patients without renal impairment, sug-

gesting that liraglutide is appropriate for patients with renal impairment.

Clinical trials have shown that patients treated with 1.8 mg liraglutide experience decreases in systolic BP from baseline to 26 weeks of 2–5.6 mmHg, compared with decreases of 0.9–1.8 mmHg in patients receiving placebo^{33–37}. The mechanism by which liraglutide reduces BP is unclear, but it might be through increased natriuresis³⁸. It is difficult to assess the effect of natriuresis in patients with renal impairment, because almost all of these patients take diuretics. We found that patients who successfully switched from insulin to liraglutide experienced significant decreases in systolic and diastolic BP, suggesting that liraglutide monotherapy also reduces BP in patients with renal impairment.

In conclusion, the present findings showed that oral glucose-stimulated serum C-peptide should be measured when considering switching from insulin therapy to liraglutide monotherapy in Japanese type 2 diabetes patients with renal impairment. The distribution of CPR 120 min in the successfully switched group was completely separated from that in the unsuccessfully switched group, precluding receiver operating characteristic analysis. The highest CPR 120 min in the 'unsuccessful' group was 2.4 ng/mL, whereas the lowest CPR 120 min in the 'successful' group was 1.6 ng/mL, making the cut-off somewhere between these two concentrations. Receiver operating characteristic curve analysis showed that a cut-off value for CPR 120 min of 1.95 could optimally distinguish between successfully and unsuccessfully switched patients. Clinically, we recommended a cut-off of 1.95 ng/mL. However, the present study was limited by the small number of patients. Larger studies are required to confirm the cut-off value. In addition, the relationship between oral glucose-stimulated C-peptide and postprandial C-peptide is unknown. Further studies are required to clarify the most useful predictor of successful switching.

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